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**Traditional Indian Therapies in Type 2 Diabetes:
Strengthening the Scientific Evidence Base**

Dr. Kaushik Chattopadhyay

**Associate Professor in Evidence Based Healthcare
School of Medicine, University of Nottingham, UK**

Adviser: Prof. Jo Leonardi-Bee

Professor of Medical Statistics and Epidemiology

**Work Submitted to the University of Nottingham for
PhD by Publication**

2024

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Introduction

Diabetes mellitus is a group of metabolic disorders in which persistent hyperglycaemia is caused by deficient insulin secretion, resistance to the action of insulin, or both.¹ Insulin deficiency and insulin resistance lead to the abnormalities of carbohydrates, fat, and protein metabolism that are characteristic of diabetes mellitus.¹ Diabetes mellitus is mainly classified into type 1 diabetes mellitus (i.e., an absolute insulin deficiency causes persistent hyperglycaemia, and insulin activity is normal) and type 2 diabetes mellitus (T2DM).¹ T2DM is caused by a combination of insulin resistance/insensitivity (where the body is unable to respond to normal levels of insulin) and insulin deficiency (where the pancreas is unable to secrete enough insulin to compensate for this resistance), resulting in persistent hyperglycaemia.¹ T2DM is one of the most common chronic diseases, and about 90% of adults currently diagnosed with diabetes mellitus have T2DM.¹ T2DM has replaced the terms 'non-insulin-dependent diabetes mellitus (NIDDM)' and 'adult-onset diabetes', as people with T2DM may require insulin, and T2DM can occur in all age groups and is increasingly being diagnosed in children.¹ Some of the major risk factors for T2DM are non-modifiable such as age, family history of diabetes, and certain ethnicities and some are modifiable such as unhealthy lifestyle (e.g., lack of physical activity and low-fibre, high glycaemic index diet) and overweight/obesity.¹

Many people with T2DM are asymptomatic.¹ T2DM is suspected if a person presents with persistent hyperglycaemia that may be accompanied by some of the most common symptoms like polydipsia, polyuria, and polyphagia.¹ Some of the well-recognised tests for the diagnosis of T2DM are fasting blood glucose (i.e., ≥ 126 mg/dL) or glycated haemoglobin (HbA1c; i.e., $\geq 6.5\%$).² People at high risk of T2DM (also known as prediabetes) have higher blood glucose levels than normal, but lower than the established threshold for T2DM (e.g., fasting blood glucose 100 to 125 mg/dL or HbA1c 5.7 to 6.4%).² T2DM has major health and socioeconomic consequences.³ People living with T2DM are at risk of developing microvascular complications (such as diabetic retinopathy, nephropathy, and neuropathy/foot), macrovascular complications (such as coronary heart disease, stroke, and peripheral arterial disease), leading to an increased need for healthcare services, poor quality of life, and even death.³

Indians are at greater risk of developing T2DM compared to other ethnicities.^{4,5} They rapidly develop T2DM from the high-risk state, one of the highest rates across many ethnicities.^{5,6} Currently, India has the world's second-largest diabetes population and will remain so in 2045.³ In India, the prevalence of diabetes and prediabetes is considerably higher than

previously estimated - 21.1% (95% confidence interval (CI) 17.6 to 24.5) and 26.6% (95% CI 22.8–30.4), respectively.⁷ In other words, it is estimated that 101.3 million (95% CI 90.7 to 111.1) and 136 million (95% CI 123.5 to 147.5) adults in India are living with diabetes and prediabetes, respectively.⁷ Many cases of diabetes and prediabetes remain undetected in India.³ India has the third highest annual number of deaths from diabetes, at approximately 0.6 million.³ In terms of disability-adjusted life years (DALYs), which combine morbidity and mortality information, diabetes is the 13th leading cause in India and has dramatically increased from the 35th place in 1990 (i.e., from 0.7% in 1990 to 2.2% in 2016).⁸ In India, the diabetes-related expenditure is US \$114.4 per person with diabetes.³

Considering the burden of chronic conditions such as T2DM in India, there is a need to move beyond the one-size-fits-all model. Complex interventions, such as Yoga and Ayurveda, can contribute here to prevent and manage such diseases in India.⁹ Yoga, a mind-body discipline, incorporates a healthy lifestyle.¹⁰ Similarly, Ayurveda incorporates a healthy lifestyle, and Ayurvedic medicines are used for treating diseases.¹¹ People in India prefer these traditional Indian therapies as they align with their health beliefs and culture. Other reasons are satisfaction and perceived benefit, accessibility, and preference for avoiding Western medicines' side effects, costs, and administration modes like injections. Yoga and Ayurveda share a deep-rooted and interrelated relationship as both originated in ancient India and have been in practice for thousands of years. The exact age of Yoga and Ayurveda is difficult to determine precisely, as these have evolved over thousands of years through oral tradition and written texts. The earliest written references can be found in the Vedas, the foundational scriptures of Hinduism, especially Rigveda (1500-1200 BCE) for Yoga and Atharvaveda (1200–900 BCE) for Ayurveda. Classical Yoga and Ayurveda texts are available, also written in Sanskrit, such as the Yoga Sutras of Patanjali (around 400 BCE) and Charaka Samhita (400–200 BCE), Sushruta Samhita (400–200 BCE), and Astanga Hridaya (around 200 CE) for Ayurveda. Emerging within the broader context of Hindu philosophy and spiritual practices, Yoga and Ayurveda have long been recognised as complementary disciplines. These two systems are based on the principle of holistic health and well-being. They view human beings as a complex interplay of body, mind, and spirit, emphasising the significance of balance and harmony for optimal health and well-being. Traditionally, the primary focus of these two systems is on preventive healthcare, promoting a healthy lifestyle to prevent diseases before they manifest, and for this, complementary practices are used. In modern times, there is a growing trend towards integrating Yoga and Ayurveda into holistic interventions that address the physical, mental, and emotional aspects of health. Ayurvedic interventions often therefore incorporate specific Yogic practices to enhance their effectiveness, while Yoga-based

interventions may integrate Ayurvedic principles such as dietary recommendations and lifestyle modifications.

The focus of my written guest editorials and invited book chapters is on strengthening the scientific evidence base of traditional Indian therapies like Ayurveda. These therapies come with both popularity and problems in India, especially issues related to the scientific evidence base. Hence, the emphasis is on how to move forward to strengthen the scientific evidence base by conducting high-quality studies and then using these research findings to bring changes in real practice. In continuation, there is a need to follow a systematic process, starting from the development of interventions based on these traditional therapies, followed by their evaluations, and finally, implementation of evidence-based interventions to promote the health and safety of people and reduce the disease burden on people, their families, the health system, and economy. The work presented in this thesis therefore addresses this important issue and contributes to strengthening the scientific evidence base of traditional Indian therapies, specifically through the development and evaluation of such interventions to prevent and manage T2DM in the four empirical chapters. I have been working in this area for over a decade. I started this work at the London School of Hygiene and Tropical Medicine and was able to fully develop and become a research leader in this area after I joined the University of Nottingham. I secured two highly competitive external research grants as a Principal Investigator, and the projects were funded by the UK's FCDO, MRC, NIHR, and Wellcome Trust Joint Global Health Trials. All the included publications are the result of work conducted at the University of Nottingham.

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Overarching Research Question and Objectives

The overarching research question is whether interventions based on traditional Indian therapies are effective in T2DM prevention and management, which will be evaluated in definitive randomised controlled trials (RCTs) in the future. This thesis therefore aimed at strengthening the scientific evidence base by contributing to the initial stages of complex interventions i.e., development of interventions and conducting feasibility studies.

The specific objectives of the work were:

1. To develop a Yoga programme for T2DM prevention (YOGA-DP). (Empirical chapter 1)
2. To determine the feasibility of undertaking the definitive RCT that will evaluate YOGA-DP's effectiveness. (Empirical chapter 2)
3. To synthesise evidence on the effectiveness and safety of Ayurvedic medicines for managing T2DM. (Empirical chapter 3)
4. To develop a clinical guideline for Ayurvedic practitioners to manage T2DM. (Empirical chapter 4)

In other words, the first and second empirical chapters are on developing and evaluating (feasibility study) a Yoga-based intervention for preventing T2DM. The third and fourth empirical studies are on developing an Ayurveda-based intervention (clinical guideline) for managing T2DM. These innovative projects were guided by the MRC/NIHR's framework for developing and evaluating complex interventions,¹ and the detailed methodologies of each of these empirical studies are presented in individual chapters.

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List of Publications and Contributions

Guest editorials

1. **Chattopadhyay K**, Leonardi-Bee J. Type 2 diabetes mellitus: answering the call for need-sensitive, evidence-based interventions. *JBIM Evid Synth.* 2021;19(5):909-10.
My contribution: I wrote the first draft of the manuscript and revised it based on the feedback received from the other author and editors.
2. **Chattopadhyay K**. Ayurveda and lifestyle modification: research to practice. *Int J Med Public Health.* 2017;7(3):132-3.
My contribution: I wrote the first draft of the manuscript and revised it based on the feedback received from the editors.

Invited book chapters

1. **Chattopadhyay K**. Ayurveda, longevity and aging. In: Gu D and Dupre ME, eds., *Encyclopedia of Gerontology and Population Aging*. Cham: Springer. 2020.
My contribution: I wrote the first draft of the book chapter and revised it based on the feedback received from the editors.
2. **Chattopadhyay K**. Globalisation of Ayurveda: importance of scientific evidence base. In: Sen S and Chakraborty R, eds., *Herbal Medicine in India: Indigenous Knowledge, Practice, Innovation and its Value*. Singapore: Springer. 2020.
My contribution: I wrote the first draft of the book chapter and revised it based on the feedback received from the editors.

Empirical studies

1. **Chattopadhyay K**, Mishra P, Manjunath NK, Harris T, Hamer M, Greenfield SM, Wang H, Singh K, Lewis SA, Tandon N, Kinra S, Prabhakaran D. Development of a yoga program for type-2 diabetes prevention (YOGA-DP) among high-risk people in India. *Front Public Health.* 2020;8:548674.
My contribution: I was the Principal Investigator of the project, funded by the UK's FCDO, MRC, NIHR, and Wellcome Trust Joint Global Health Trials. I conceptualised and designed the study. The Co-Investigators gave me feedback during the grant application stage. I conducted the study, and more specifically, I developed the

intervention. The other authors helped me in the process e.g., acted as a second independent systematic reviewer and provided access to experts, Yoga practitioners and laypeople. I wrote the first draft of the manuscript and revised it based on the feedback received from other authors, reviewers, and editors.

2. **Chattopadhyay K**, Mishra P, Singh K, Singh K, Harris T, Hamer M, Greenfield SM, Manjunath NK, Nair R, Mukherjee S, Tandon N, Lewis SA, Kinra S, Prabhakaran D. Yoga programme for type 2 diabetes prevention (YOGA-DP) among high-risk people in India: a multicenter feasibility randomized controlled trial. *Diabetes Ther.* 2023.

My contribution: I was the Principal Investigator of the project, funded by the UK's FCDO, MRC, NIHR, and Wellcome Trust Joint Global Health Trials. I conceptualised and designed the study. The Co-Investigators gave me feedback during the grant application stage. I led and supervised this multicentre randomised controlled trial. The other authors helped me in conducting the trial e.g., as a trial manager. I wrote the first draft of the manuscript and revised it based on the feedback received from other authors, reviewers, and editors.

This work was also presented at the International Diabetes Federation Congress, in 2021.

3. **Chattopadhyay K**, Wang H, Kaur J, Nalbant G, Almqahawi A, Kundakci B, Panniyammakal J, Heinrich M, Lewis SA, Greenfield SM, Tandon N, Biswas TK, Kinra S, Leonardi-Bee J. Effectiveness and safety of Ayurvedic medicines in type 2 diabetes mellitus management: a systematic review and meta-analysis. *Front Pharmacol.* 2022;13:821810.

My contribution: I was the Principal Investigator of the project, funded by the UK's FCDO, MRC, NIHR, and Wellcome Trust Joint Global Health Trials. I conceptualised and designed the study. The Co-Investigators gave me feedback during the grant application stage. I conducted the systematic review. The other authors helped me in the process e.g., acted as other independent systematic reviewers. I wrote the first draft of the manuscript and revised it based on the feedback received from other authors, reviewers, and editors.

This work was also presented at the International Diabetes Federation Congress, in 2021, and was widely covered in the international media, including The Independent.

4. **Chattopadhyay K**, Kapoor N, Heinrich M, Mitra A, Mittal M, Lewis SA, Greenfield SM, Mukherjee S, Pischel I, Jeemon P, Tandon N, Kinra S, Biswas TK, Leonardi-Bee J.

Development process of a clinical guideline to manage type 2 diabetes in adults by Ayurvedic practitioners. *Front Med.* 2023;10:1043715.

My contribution: I was the Principal Investigator of the project, funded by the UK's FCDO, MRC, NIHR, and Wellcome Trust Joint Global Health Trials. I conceptualised and designed the study. The Co-Investigators gave me feedback during the grant application stage. I conducted the study, and more specifically, I developed the clinical guideline. The other authors helped me by being part of the Guideline Development Group or by providing access to people with type 2 diabetes. I wrote the first draft of the manuscript and revised it based on the feedback received from other authors, reviewers, and editors.

This work was also presented at the World Congress on Public Health, in 2023, and as an invited speaker at national government conferences in India and Nepal.

Publications

Type 2 diabetes mellitus: answering the call for need-sensitive, evidence-based interventions

Type 2 diabetes mellitus (T2DM) is a major global health issue with socioeconomic consequences. It is associated with macro- and micro-vascular complications, and increases mortality.¹ Globally, it is estimated that around 463 million adults (aged 20 to 79 years) are living with diabetes.¹ Type 2 diabetes mellitus is the most common type of diabetes, accounting for approximately 90% of all diabetes cases worldwide.¹ Some ethnic groups are at greater risk of developing T2DM, for example, Asian, African-Caribbean, and Black African-origin people.¹ There is unacceptable variation in the prevention and management of T2DM, with poor national economic and health systems worsening the situation.^{2,3} The countries with the highest number of people with diabetes are China and India.¹ This is likely an underestimation of the burden in low- and middle-income countries (LMICs) because it is estimated that more than three out of four adults have diabetes and four out of five adults have undiagnosed diabetes.¹ Around 87% of diabetes-related deaths occur in LMICs, but only one-third of health expenditure in these countries is related to diabetes.¹

The management of T2DM across the world centers on using evidence-based interventions, which are recommended in good-quality clinical guidelines for controlling blood glucose levels in people with T2DM. This mainly includes pharmacological interventions, including Western medicines, and complex non-pharmacological interventions, such as diet and physical activity for self-management.⁴ However, the assumption of a one-size-fits-all model made by many health care providers is too restrictive in controlling blood glucose levels in people with T2DM. It is likely that there are people whose needs are unmet, and other approaches for preventing and managing T2DM, such as evidence-based regional diets and physical activities and indigenous therapies, should be considered. The content, structure, and delivery methods of such interventions should also be need-sensitive and evidence-based. These approaches should go beyond the biomedical model and take into account individual- and country-level factors known to influence the needs, such as culture, religion, and psychological factors (eg, anxiety, stress), which are addressed in the qualitative review by Nixon *et al.* in this issue.⁵

In many parts of the world, people use traditional therapies, such as Ayurveda, traditional Chinese medicine, and yoga, for preventing and managing a range of short- and longer-term conditions, including T2DM.⁶⁻⁹ One of the main reasons for the widespread use of traditional therapies is their alignment with people's respective health beliefs and culture.⁶ Also, the popularity of traditional therapies may be because Western medicines, including those for T2DM management, are perceived to have concerning side effects and are costly, and there may be a fear of the mode of administration (eg, injections).⁶ Thus, there is a need to consider these issues when developing, evaluating, and implementing interventions for T2DM prevention and management.

It should be noted that many traditional therapies are not evidence-based and may have serious adverse effects.¹⁰ Unfortunately, in many parts of the world, the scaling up of such need-sensitive interventions is typically conducted with no or inadequate evaluation of the intervention, which is likely to lead to inefficient use of scarce resources and, most importantly, could lead to harm.¹⁰ Therefore, the intervention must be need-sensitive as well as evidence-based.

In continuation with the global effort to tackle diabetes, the need of the hour is to move beyond the one-size-fits-all biomedical model and to develop, evaluate, and implement need-sensitive, evidence-based interventions to prevent and manage T2DM among different population groups.

Kaushik Chattopadhyay^{1,2} • Jo Leonardi-Bee^{1,2}

¹*The Nottingham Centre for Evidence-Based Healthcare: A JBI Centre of Excellence, University of Nottingham, UK,* ²*Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, UK*

JL-B is a senior associate editor for JBI Evidence Synthesis and was not involved in the decision-making process for this editorial.

KC declares no conflict of interest.

DOI: 10.11124/JBIES-21-00113

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Ayurveda and Lifestyle Modification: Research to Practice

Kaushik Chattopadhyay

ABSTRACT

The global burden of non-communicable diseases is rapidly increasing, and the essential management strategy is to follow a healthy lifestyle. Ayurveda can play a major role in this aspect, as the primary aim of Ayurveda is to prevent diseases by following a healthy lifestyle. However, in order to implement such classical knowledge (that is, healthy lifestyle based on Ayurvedic principles) into real practice, a systematic process needs to be followed. This systematic process must include robust research studies (that is, development and evaluation of Ayurveda-based lifestyle intervention) and behaviour change of people. This paper describes these two important steps in detail. In conclusion, there is a huge scope of implementing classical Ayurvedic knowledge into real practice, which will be beneficial to all of the society.

Key words: Ayurveda, Healthy lifestyle, Research, Evidence-based, Behaviour change.

INTRODUCTION

Globally, there is a huge burden of non-communicable diseases (NCDs), such as cardiovascular diseases, cancers, respiratory diseases and diabetes. Around 55% of all cause disability-adjusted life years (DALYs),^{1a} a summary measure to indicate the overall burden of disease and includes mortality as well as morbidity, are due to NCDs.¹ Modifiable lifestyle factors, such as physical inactivity and unhealthy diets, are some of the important risk factors of NCDs and thus, the essential management strategy is to follow a healthy lifestyle, including diet.² However, the conventional or western care model has its own limitations in terms of its effectiveness, safety, affordability and acceptability.³ Ayurveda, a system of medicine that originated in the Indian subcontinent, can play a major role in this aspect. The primary aim of Ayurveda is to prevent diseases by following a healthy lifestyle.⁴ Ayurvedic approach to a healthy lifestyle includes dinacharya (day-time regimen), ratricharya (night-time regimen) and ritucharya (seasonal regimen), and these have been described in detail in various classical Ayurvedic texts (such as texts written by Charaka (400-200 BC), Sushruta (400-200 BC) and Vagbhatt (600-500 BC)).⁴⁻⁶ However, in order to implement such classical knowledge (that is, healthy lifestyle based on Ayurvedic principles) into real practice, a systematic process needs to be followed. This systematic process must include robust research studies and behaviour change of people.

STEP ONE: DEVELOPMENT AND EVALUATION OF AYURVEDA-BASED LIFESTYLE INTERVENTION

The evidence-base of Ayurveda related studies is extremely poor, which is either due to the non-existence of research studies or poorly conducted research studies.⁷ The first step should be to develop an Ayurveda-based lifestyle intervention and then, to evaluate its effectiveness, safety, affordability and acceptability. Globally, the United Kingdom Medical Research Council's guideline is used for development and evaluation of complex interventions.⁸ This guideline should be used to develop and evaluate Ayurveda-based lifestyle interventions, which are considered to be complex. It should be noted that this is an iterative process, as shown in Figure 1, and mixed methods approach (quantitative (including economic evaluation) as well as qualitative) should be used.⁸ Apart from this guideline, many internationally recognised checklists, to report research studies, are available which could be used to design such studies, such as the Consolidated Standards of Reporting Trials (CONSORT) 2010 (includes a specific checklist for herbal medicines) and Drummond's checklist for assessing economic evaluation studies.⁹⁻¹⁴

STEP TWO: BEHAVIOUR CHANGE

The availability of a lifestyle intervention and providing health education are not enough to bring the desired outcomes in people.^{15,16} Once the Ayurveda-

Kaushik Chattopadhyay

Assistant Professor (Evidence-based Healthcare),
Division of Epidemiology and Public Health, School
of Medicine, The University of Nottingham, Nottingham, UK.

Correspondence

Dr. Kaushik Chattopadhyay

Assistant Professor (Evidence-based Healthcare), Division of Epidemiology and Public Health, School of Medicine, The University of Nottingham, Nottingham, UK.

Email: kaushik.chattopadhyay@nottingham.ac.uk

History

- Submission Date: 05-06-2017
- Accepted Date: 15-06-2017

DOI : 10.5530/ijmedph.2017.3.27

Article Available online

<http://www.ijmedph.org/v7/i3>

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Cite this article : Chattopadhyay K. Ayurveda and Lifestyle Modification: Research to Practice. Int J Med Public Health. 2017;7(3):132-3.

^{1a} One DALY represents the loss of the equivalent of one year of full health.¹

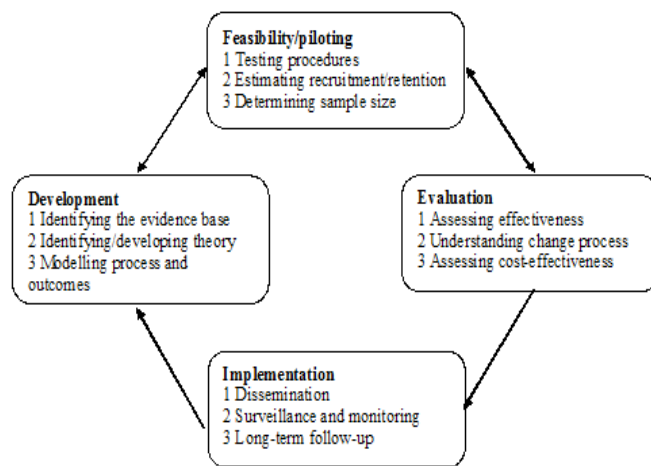


Figure 1: Key elements of the development and evaluation process⁸

based lifestyle intervention is developed and is found to be effective, safe, affordable and acceptable, then this intervention needs to be implemented in real practice through the behaviour change of people. A behaviour emerges from the interaction between three necessary conditions: capability (psychological or physical ability to enact the behaviour), motivation (reflective and automatic mechanisms that activate or inhibit the behaviour) and opportunity (a physical and social environment that enables the behaviour).^{17,18} The behaviour change process helps an individual to transit from an unhealthy lifestyle to a healthy lifestyle and to adhere to the healthy lifestyle in the longer term.^{15,16} The established behaviour change techniques (BCTs), such as information provision, exploration and reinforcement of motivation to change, goal setting, action planning, coping plans, and relapse prevention, should be used for this purpose.¹⁶ The selection and application of any additional BCT should be based on the behavioural analysis, that is, by understanding the target behaviour.^{17,18} The main questions involved in this process are: why the desired behaviour is not occurring and what needs to change for the desired behaviour to occur? The theoretical domains framework (TDF), as shown in Figure 2, can help to understand the target behaviour and answer these questions.^{17,18}

CONCLUSION

There is a huge scope of implementing classical knowledge (that is, healthy lifestyle based on Ayurvedic principles) into real practice, which will be beneficial to all of the society. This implementation of classical Ayurvedic knowledge should follow a systematic process, which must include robust research studies and behaviour change of people.

CONFLICT OF INTEREST

None

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Soc	Social influences
Env	Environmental context and resources
Id	Social/professional role and identity
Bel Cap	Beliefs about capabilities
Opt	Optimism
Int	Intentions
Goals	Goals
Bel Cons	Beliefs about consequences
Reinf	Reinforcement
Em	Emotion
Know	Knowledge
Cog	Cognitive and interpersonal skills
Mem	Memory, attention and decision processes
Beh Reg	Behavioural regulation
Phys	Physical skills

Figure 2: Theoretical domains framework¹⁸



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Cite this article : Chattopadhyay K. Ayurveda and Lifestyle Modification: Research to Practice. Int J Med Public Health. 2017;7(3):132-3.

Globalisation of Ayurveda: Importance of Scientific Evidence Base

1

Kaushik Chattopadhyay

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1.1 Introduction

This chapter is written from an evidence-based perspective, which is needed for the globalisation of Ayurveda. The author is a qualified Ayurveda practitioner and an evidence-based healthcare academic in a world-class university. This chapter is divided into sections like Ayurveda and its popularity, problems associated with Ayurveda, scientific evidence base of Ayurveda—the way

forward, pathways to impact and communication plans and beneficiaries and impacts.

1.2 Ayurveda and its Popularity

Ayurveda is one of the world's oldest medical systems, which originated in the Indian subcontinent more than 5000 years ago. Ayurveda can be considered as a complex intervention, which includes maintaining a healthy lifestyle and using Ayurvedic therapies and medicines (such as herbal and herbo-mineral formulations). Ayurvedic interventions are written in Sanskrit, in the form of classical texts, such as Charaka Samhita (400–200 BC), Sushruta Samhita (400–200 BC) and Astanga Hridaya (around 200 AD) (Sharma 1981; Bhishagratna 1991; Murthy 1991).

K. Chattopadhyay (✉)
Division of Epidemiology and Public Health, School
of Medicine, The University of Nottingham,
Nottingham, UK
e-mail: kaushik.chattopadhyay@nottingham.ac.uk

© Springer Nature Singapore Pte Ltd. 2020
S. Sen, R. Chakraborty (eds.), *Herbal Medicine in India*,
https://doi.org/10.1007/978-981-13-7248-3_1

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Ayurvedic interventions are particularly used for the prevention and management of chronic diseases (Sharma et al. 2007a, b; Rudra et al. 2017). In India, the Ministry of AYUSH is dedicated exclusively towards traditional therapies, including Ayurveda (Katoch et al. 2017). Globally, different rules and regulations are in place, which may change over time. Many countries had less stringent laws but have now implemented well-defined and well-enforced laws. Some countries consider Ayurvedic medicines as conventional pharmaceuticals and some as dietary supplements (Barnes et al. 2016; Job et al. 2016; Sammons et al. 2016; Teng et al. 2016).

In general, the acceptability of and faith in Ayurveda are high among South Asians, especially among older, women, rural, poor and tribal populations. Ayurveda fits their health beliefs and is compatible with their social and cultural expectations. Many of them do not prefer Western medicines—to avoid the associated side effects and costs (Roy et al. 2015; Rudra et al. 2017; Srinivasan and Sugumar 2017). In fact, Western medicine is facing new challenges arising from its limitations when applied to chronic diseases and ageing (Warrell et al. 2010). Globally, Ayurveda is gaining popularity due to its holistic approach (Patwardhan 2014). Ayurvedic therapies like Panchakarma (i.e. detoxification of the body) are popular among people, especially among foreign tourists who travel to Indian states like Kerala (Ramesh et al. 2010).

1.3 Problems Associated with Ayurveda

Many times, Ayurvedic medicines are either prescribed by an unqualified practitioner or used as self-medication. One of the major reasons behind self-medication is the easy availability of these medicines over-the-counter (which includes online shopping). Many people blindly follow the claims made by others or use a ‘trial and error’ approach in deciding the medication (Bhamra et al. 2017; Rao et al. 2016; Rudra et al. 2017; Srinivasan and Sugumar 2017). A wide

range of non-evidence-based Ayurvedic medicines are used by people, which can have serious negative health and socio-economic consequences. Globally, many cases of heavy metal poisoning (such as lead and mercury) have been reported among people using Ayurvedic medicines (Ernst 2002; Lynch and Braithwaite 2005; Karri et al. 2008; Kales and Saper 2009). Although many Ayurveda practitioners claim that heavy metal poisoning occurs due to the inadequate processing of heavy metals before they are used in Ayurvedic medicines (i.e. if the exact processing methods, as mentioned in Ayurvedic classical texts, are not followed), but robustly designed scientific studies are still lacking on this issue. In addition, many people simultaneously use multiple Western and/or traditional medicines (i.e. polypharmacy)—many times without any evidence of effectiveness and safety and can lead to harmful drug-drug interactions (Aslam and Shaw 1995; Bhamra et al. 2017; Bush et al. 2007; Sarkar et al. 2013). Thus, strong concerns remain about the suboptimal management and care of many people, arising from the unacceptable usage of non-evidence-based Ayurvedic interventions. It is important to use only effective and safe Ayurvedic interventions and minimise the use of interventions that are of no, minimal, or questionable value.

One of the major hurdles in the globalisation of Ayurveda is its poor scientific evidence base. Unfortunately, the interest of commercial pharmaceutical companies in conducting research studies is not always strong, as it is not possible to patent prior published knowledge (Chaudhary and Singh 2012). In most cases, the scientific evidence base does not exist. Even if it does, it is of poor quality. Most of them are short-term studies and are often associated with considerable methodological limitations, such as small sample sizes in treatment groups, resulting in lack of statistical power for outcome assessment and poor concealment of treatment allocation, leading to potential analysis bias. In addition, most of them have evaluated Ayurvedic medicines but not Ayurveda as a system of care or complex intervention (Patwardhan 2014).

1.4 Scientific Evidence Base of Ayurveda: The Way Forward

In the case of Ayurveda, there is a strong need for robustly designed pragmatic studies. One of the major research areas should be the evaluation of effectiveness and safety of Ayurvedic interventions through randomised controlled trials. The World Health Organization says that a traditional therapy (including Ayurveda) with an established history of use can proceed directly from basic animal toxicity studies to a phase III clinical trial (Chaudhury 1992). The UK Medical Research Council's guideline for developing and evaluating complex interventions can be used for designing such studies (MRC 2006). Many internationally recognised checklists for reporting research studies are available, which should be used to design such studies, such as the Consolidated Standards of Reporting Trials (CONSORT) 2010 (includes a specific checklist for herbal medicines) (Gagnier et al. 2006a, b, c; Moher et al. 2010; Schulz et al. 2010). However, research studies on Ayurvedic interventions should not be restricted to randomised controlled trials and should also include basic pharmacological studies, observational (epidemiological) studies, qualitative studies, economic evaluations and systematic reviews (and meta-analysis). Some other important research topics are Ayurveda related education, health services and systems and diagnostic methodologies. These studies will provide a complete picture of the situation and have the potential to make the scientific evidence base of Ayurveda strong.

1.5 Pathways to Impact and Communication Plans

User involvement (patient and public involvement) in research studies is a major pathway to impact (Staley 2009; Bagley et al. 2016). It should also be the backbone of research studies on Ayurvedic interventions. Such studies need to be carried out with patients and the public, to meet their needs and preferences. Research top-

ics should be identified and discussed with users and user groups. They should agree and acknowledge the importance of the research topic. The issues identified during these discussions should be taken into consideration while designing and developing such studies. These users and user groups should regularly take part in discussions and give feedback on different aspects of the project, including research tools, data analyses and interpretation, research updates and reports and different mediums for communicating results. These collaborations should build relationships within the research community and should extend beyond the life of such projects. It is highly recommended to produce reports on user involvement and disseminate such reports.

In order to ensure the translation of research outputs into actions, key stakeholders should be continuously engaged from the beginning of any study. A range of key stakeholders, representing health policymakers and managers (of public and private healthcare providers), healthcare professionals (including Ayurveda practitioners), patient and public groups, non-profit organisations, non-governmental organisations and international organisations, should be involved. Public-friendly research updates and brief final reports should be produced and disseminated through various avenues, including meetings, study and institutional websites and online forums (e.g. Facebook, Twitter). The press offices of host institutions should also advise on how best to present and disseminate the findings. They usually have good contacts with the media. Press releases should be sent to the media in advance of newsworthy publications. The host institutions can release MP3 podcasts of topical research, an additional medium for dissemination.

The findings of research studies should be widely disseminated in the scientific community through publications in high-impact peer-reviewed open-access journals and presentations at national and international conferences. Both general and specialist conferences should be targeted for a wider coverage. The data (anonymised) on which a journal paper is based should be made available to the readers as an additional supporting file. Publications and

additional supporting files should also be made available on the study and institutional websites. These dissemination strategies also have the potential to attract researchers for further collaborative research studies.

1.6 Beneficiaries and Impacts

Research studies on Ayurvedic interventions have the potential to directly benefit people (patients and the public), health policymakers and managers (of public and private healthcare providers), Ayurveda practitioners and academics.

If Ayurvedic interventions are found to be clinically and cost effective, the clinical, personal and economic burden of diseases on people and their families/carers will be prevented or reduced. They will be provided with more evidence-based choices to prevent and manage diseases. These interventions may simultaneously empower people to manage their health. These interventions may reduce health inequalities and be beneficial to all of the society.

Health policymakers and managers will benefit from the availability of low-cost and acceptable evidence-based solutions to prevent and manage diseases, since more expensive disease prevention and management models are in use. The economic burden of diseases on the health systems and the economies will be prevented or reduced.

Ayurveda practitioners will have access to evidence-based Ayurvedic interventions. They may potentially get a boost due to greater interest in their services, which may also enhance their job opportunities. These interventions may close the gap between what they do for preventing and managing diseases and what scientific evidence supports. These interventions may reinforce their position in prevention and management of diseases and offer them medico-legal protection.

The scientific research on Ayurvedic interventions has the potential to directly benefit academics working in at least two research disciplines—specific diseases and traditional therapies (including Ayurveda). Such projects can bring together Western medicine and Ayurveda experts. There will be mutual academic benefit and capacity building by

cross-sharing of expertise and experience within the groups. A good-quality cross-country project should be a collaboration between academics with complementary strengths, such as the UK's methodological expertise and India's large clinical networks. Such projects have the potential to improve scientific links between countries and more broadly through wider collaborative links and networking. Greater use of these interventions has the potential to highlight the gaps in evidence, which may stimulate further research activities. Funding opportunities for research on Ayurvedic interventions are growing but are still limited. Conclusive evidence of the beneficial effects and safety of some of these interventions may lead to greater funding opportunities and conduct of robust studies. All these may greatly enhance the acceptance of Ayurveda by the scientific and wider communities.

Given that chronic diseases and ageing are global concerns and the cost is a concern everywhere, low-cost Ayurvedic interventions will be of interest to many countries, particularly South Asian countries and in countries with South Asian ethnic minorities. Such projects will involve collaborative research work to evaluate and implement these interventions in a range of settings and populations. Thus, research studies on Ayurvedic interventions have the potential to impact the world.

1.7 Conclusion

Globally, the scope of Ayurveda is huge and has the potential to benefit a range of beneficiaries. In order to achieve this, the scientific evidence base of Ayurveda must be made strong.

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Ayurveda, Longevity, and Aging



Kaushik Chattopadhyay

Division of Epidemiology and Public Health,
School of Medicine, University of Nottingham,
Nottingham, UK

Synonyms

Rasayana, longevity, and aging; Traditional Indian medicine, longevity, and aging

Definition

Ayurveda is a Sanskrit word and is made up of two words, Ayuh meaning life and Veda meaning knowledge. So, Ayurveda means knowledge of life. The main aims of Ayurveda are to maintain the health of healthy individuals and to manage the disease conditions. Ayurveda has its unique and comprehensive concepts based on philosophy such as anatomy, physiology, disease pathology, diagnosis and prognosis, and pharmacology and therapeutics. Briefly, similar to the universe, people are considered to be made up of Panchamahabhuta (five elements, namely, Prithvi (earth), Jal (water), Agni (fire), Vayu (air), and Aakash (aether)). Health is defined as a state of equilibrium of Dosha (humors, namely, Vata (air), Pitta (fire), and Kapha (water)), Agni (such as

digestive juices, enzymes, and hormones involved in the digestion and metabolism), Dhatu (tissues, namely, Rasa (lymph), Rakta (blood), Mamsa (muscle), Meda (fat), Asthi (bone), Majja (marrow), and Shukra (semen)), and Mala (excretion of waste products, namely, Purisha (feces), Mutra (urine), and Sweda (sweat)) along with a happy state of Atma (soul), Indriya (sensory and motor organs), and Manas (mind). An imbalance of these brings disease, and the aim is to bring back normalcy. It should be noted that Kapha dominates during childhood, Pitta during adulthood, and Vata during old age. Agni, Dhatu, and Indriya rise during childhood, mature during adulthood, and finally, decline during old age. Prakriti refers to the general constitution of an individual, based on which an individualized approach is used in Ayurveda (Bhishagratna 2002; Sharma 2004; Srikantha Murthy 2014).

Overview

Ayurveda is one of the world's oldest health and medical systems. It originated in the Indian sub-continent more than 5,000 years ago (Sharma 1992). Some experts say that Ayurveda originated from the Vedas, the compendium of ancient Indian knowledge, and some say that it is an independent Veda (Sharma 1992). Many medicinal plants have been mentioned in the *Rig Veda* (around 2000 BC) and *Atharva Veda* (1500–1000 BC). *Atharva Veda* also introduces

many Ayurvedic concepts. Under the master-disciple system (Guru-Shishya Parampara), initially, Ayurveda was long conveyed verbally before being recorded in texts, written in an ancient language, Sanskrit. The most essential classical texts are (a) three major texts (Brhat Trayi): *Charaka Samhita* (400–200 BC), *Sushruta Samhita* (400–200 BC), and *Astanga Hridaya* (around 200 AD), and (b) three minor texts (Laghu Trayi): *Madhava Nidana* (around 700 AD), *Sharngadhara Samhita* (around 1400 AD), and *Bhavaprakash* (around 1600 AD). Over the years, these important classical texts are supplemented by many additions based on observation and experience, and translated into many foreign languages (Bhishagratna 2002; Sharma 1992, 2004; Srikantha Murthy 2004, 2012, 2014, 2015).

In South Asia (such as in India and Nepal), Ayurveda is the dominant traditional health and medical system. It fits their health beliefs and is compatible with their sociocultural expectations. Acceptability and satisfaction are usually high among people, especially among rural, poor, women, older, and tribal populations. In addition, many of them do not prefer the western medical system – to avoid the associated side effects and costs (Srinivasan and Sugumar 2017). Ayurveda is popular not only in South Asia and in countries with South Asian ethnic minorities, but it is also becoming increasingly popular in many high-income countries (Chattopadhyay 2019). Ayurvedic therapies like Panchakarma (five detoxifying and purifying therapies) are popular among people, especially among foreign tourists who travel to South Asia, for example, to Indian states like Kerala (Ramesh et al. 2010).

Ayurveda in Classical Texts for Enhancing Longevity and Delaying Aging

In general, people aspire to live a long and healthy life, and avoid aging. Ayurveda considers aging as a natural and unavoidable process, and mentions the total life span of an individual to be over a hundred years. In order to achieve this, Rasayana,

one of the eight clinical specialties of Ayurveda, was introduced. It is also known as Jarachikitsa. Similar to the Greek word Gerios, from which the term geriatrics has been derived, Jara means aging (Agarwal 2013). Rasayana focuses on enhancing longevity (in terms of both quantity and quality) and decelerating aging. Other benefits include immunity against diseases, memory, and intelligence. It is known to be a holistic therapy which rejuvenates physical as well as mental health. Rasayana enhances the digestive and metabolic process (Agni) which leads to improved bioavailability of nutrients, nutrients' microcirculation through the body channels (Srotas), and plasma's nutritive value that gets generated (Rasadhātu). Ayurveda recommends the usage of Rasayana throughout an individual's life, selecting the one after considering a number of factors, including, but not limited to, age and purpose. Rasayana usage in the early years is given more emphasis, as it may not be possible to reverse the change once it has occurred. In line with the aim of Ayurveda, Rasayana is used to maintain the health of healthy individuals (Kamya Rasayana) and in diseases (Naimittika Rasayana). Another special and complex intervention is Kuti Praveshika Rasayana, in which only an eligible individual enters a specially constructed house (build only for this purpose) and treated inside. The person has to follow a strict and rigorous regimen – before, during, and after the therapy (Agarwal 2013; Dwivedi et al. 1993; Rao 2018; Sharma 2004; Srikantha Murthy 2014).

It should be noted that Ayurveda is a complex intervention and includes components like a healthy lifestyle (including diet) and Ayurvedic medicines. The approach to a healthy lifestyle includes Dinacharya (daytime regimen), Ratricharya (nighttime regimen), and Ritucharya (seasonal regimen). Yoga (such as Asana (Yogic poses), Pranayama (breathing practices), and Dhyana (meditation) and relaxation practices) is another core component. Purvakarma (procedures done before Panchakarma, such as Snehana (oleation) and Swedan (fomentation)), Panchakarma (namely, Vamana (therapeutic emesis), Virechana (therapeutic purgation), Basti (medicated enema of decoction or oil), Nasya

(administration of medicine through nostrils), and Raktamokshana (therapeutic bloodletting)), and Paschatkarma (procedures done after Panchakarma) play an important role in the process. In order to gain the benefits of Rasayana, the individual also needs to follow a good behavioral code of conduct (Achara Rasayana). In Ayurvedic medicines, plant-, animal-, and mineral-origin ingredients are used. These are used either alone or in combination (Bhishagratna 2002; Sharma 2004; Srikantha Murthy 2014). In terms of enhancing a healthy and long life, and delaying aging, a range of herbs has been mentioned. Some of these herbs are Haritaki (*Terminalia chebula*), Amalaki (*Emblica officinalis*), Bibhitaki (*Terminalia bellirica*), Ashwagandha (*Withania somnifera*), Pippali (*Piper longum*), Guduchi (*Tinospora cordifolia*), Guggul (*Commiphora mukul*), Dadim (*Punica granatum*), Shankhapushpi (*Convolvulus pluricaulis*), and Brahmi (*Bacopa monnieri*) (Agarwal 2013; Balasubramani et al. 2011; Sharma 2004; Singh 2013; Srikantha Murthy 2014).

Research on and Practice of Ayurveda

In spite of the rich information written in classical Ayurvedic texts, the whole concept of enhancing longevity and delaying aging is limited to a conceptual model. Unfortunately, commercial pharmaceutical companies' interest in conducting studies is not always strong, as it is not possible to patent prior published knowledge (Chaudhary and Singh 2012). Many *in vitro* and *in vivo* studies have been conducted to explore the effectiveness of Ayurvedic medicines in promoting a healthy and long life, and delaying aging. Many of these medicines are found to have antioxidant, immunomodulating, anti-inflammatory, and anti-stress properties (Balasubramani et al. 2014; Kure et al. 2017; Pannakal et al. 2017; Priyadarshini et al. 2010). However, there is hardly any good methodological quality experimental or observational study conducted among human beings to determine the clinical effectiveness and safety of Ayurveda in promoting longevity or delaying aging (Choudhary et al. 2017; Gelderloos et al. 1990; Vishwanatha et al. 2016). Short-term

studies, with small sample sizes resulting in the lack of statistical power for outcome assessment and poor concealment of treatment allocation leading to potential analysis bias, are some of the limitations. Many times, the complexity of Ayurveda is not considered, and studies are conducted on Ayurvedic medicines by completely ignoring its other components like a healthy lifestyle. Most of the time, biomarkers are used in studies, but data on clinical outcomes are limited. It should be noted that not all biomarkers should be used as surrogate endpoints to assess clinical outcomes (Fleming and Powers 2012).

The lack of good quality studies leads to the prescription and usage of nonevidence-based Ayurveda. Many nonevidence-based Ayurvedic medicines are readily available over the counter (which includes online shopping as well) (Srinivasan and Sugumar 2017). Many people blindly follow the claims made by others or use a "trial and error" approach in deciding the regimen and therapy. All these can have serious adverse effects on health (as well as socioeconomic consequences). For example, heavy metal (such as lead and mercury) poisoning cases have been reported among people using Ayurvedic medicines (Ernst 2002). Although many Ayurvedic practitioners claim that heavy metal poisoning occurs due to the poor processing of heavy metals before they are used in Ayurvedic medicines (i.e., if the exact processing methods, as mentioned in the classical texts, are not followed), good quality research studies are still lacking on this issue. Inappropriate polypharmacy is another serious issue, as many people simultaneously use multiple medicines, which can lead to harmful drug-drug interactions. There is hardly any good quality research on this aspect from the safety point of view (Sarkar et al. 2013).

Prospects

The western medical system is facing challenges arising from its limitations when applied to longevity and aging. In this situation, evidence-based Ayurveda can play a major role. The scope of Ayurveda in enhancing people's longevity and delaying their aging is huge. It is important to

prescribe and use only effective and safe Ayurvedic interventions, and minimize the use of interventions that are of no, minimal, or questionable value. Therefore, one of the main research areas should be the effectiveness and safety evaluation of such interventions through robustly designed (and conducted and reported) randomized controlled trials. As per the World Health Organization (WHO), a traditional therapy like Ayurveda with an established history of use can proceed directly from basic animal toxicity studies to a phase III clinical trial (Chaudhury 1992). Given that Ayurveda is a complex intervention, the UK Medical Research Council (MRC) guideline for developing and evaluating complex interventions should be used for designing such studies (MRC 2006). Many internationally recognized checklists are available for reporting research studies, which can be used for designing as well, such as the Consolidated Standards of Reporting Trials (CONSORT) 2010 (includes a specific checklist for herbal medicines) (Gagnier et al. 2006; Moher et al. 2010). Research should not be restricted to randomized controlled trials and should also include basic pharmacological studies, observational (epidemiological) studies, qualitative studies, economic evaluations, and systematic reviews (and meta-analysis). All these studies will make scientific evidence base strong (Chattopadhyay and Bochenek 2008; Chattopadhyay 2017, 2019). It should be noted that to foster broad ownership and ensure the translation of research outputs into actions, the key stakeholders should be formally engaged from the beginning. Given that longevity and aging are global concerns, robust research studies have the potential to impact across the world and may greatly enhance the acceptance of Ayurveda by the scientific and wider communities.

Cross-References

- [Siddha Practice and Management of Geriatrics](#)
- [Unani Medicine and Healthy Living](#)
- [Yoga Practice and Health](#)

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Chattopadhyay K, Mishra P, Manjunath NK, Harris T, Hamer M, Greenfield SM, Wang H, Singh K, Lewis SA, Tandon N, Kinra S, Prabhakaran D. Development of a yoga program for type-2 diabetes prevention (YOGA-DP) among high-risk people in India. *Front Public Health*. 2020;8:548674.

In this first empirical chapter, a systematic iterative process was followed to develop a novel Yoga-based intervention for T2DM prevention (YOGA-DP), which included five steps, namely, a systematic review of the scientific literature to generate a list of Yogic practices that improves blood glucose levels among adults at high risk of or with T2DM; validation of identified Yogic practices by Yoga experts; drafting the intervention; consultation with Yoga, exercise, physical activity, diet, behaviour change, and/or diabetes experts about the intervention; and pretesting the intervention among Yoga practitioners and laypeople (those at risk of T2DM and had not practised Yoga before) in India.



Development of a Yoga Program for Type-2 Diabetes Prevention (YOGA-DP) Among High-Risk People in India

Kaushik Chattopadhyay^{1,2*}, Pallavi Mishra³, Nandi Krishnamurthy Manjunath⁴, Tess Harris⁵, Mark Hamer⁶, Sheila Margaret Greenfield⁷, Haiquan Wang^{1,2}, Kavita Singh³, Sarah Anne Lewis¹, Nikhil Tandon⁸, Sanjay Kinra⁹ and Dorairaj Prabhakaran³

¹ Division of Epidemiology and Public Health, University of Nottingham, Nottingham, United Kingdom, ² The Nottingham Centre for Evidence-Based Healthcare: A Joanna Briggs Institute Centre of Excellence, Nottingham, United Kingdom, ³ Centre for Chronic Disease Control, New Delhi, India, ⁴ Swami Vivekananda Yoga Anusandhana Samsthana, Bengaluru, India, ⁵ Population Health Research Institute, St. George's University of London, London, United Kingdom, ⁶ Division of Surgery and Interventional Science, Institute Sport Exercise and Health, University College London, London, United Kingdom, ⁷ Institute of Applied Health Research, University of Birmingham, Birmingham, United Kingdom, ⁸ Department of Endocrinology, Metabolism and Diabetes, All India Institute of Medical Sciences, New Delhi, India, ⁹ London School of Hygiene and Tropical Medicine, London, United Kingdom

OPEN ACCESS

Edited by:

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*Correspondence:

Kaushik Chattopadhyay
kaushik.chattopadhyay@
nottingham.ac.uk

Specialty section:

This article was submitted to
Public Health Education and
Promotion,
a section of the journal
Frontiers in Public Health

Received: 03 April 2020

Accepted: 02 October 2020

Published: 17 November 2020

Citation:

Chattopadhyay K, Mishra P, Manjunath NK, Harris T, Hamer M, Greenfield SM, Wang H, Singh K, Lewis SA, Tandon N, Kinra S and Prabhakaran D (2020) Development of a Yoga Program for Type-2 Diabetes Prevention (YOGA-DP) Among High-Risk People in India. *Front. Public Health* 8:548674. doi: 10.3389/fpubh.2020.548674

Introduction: Many Indians are at high-risk of type-2 diabetes mellitus (T2DM). Yoga is an ancient Indian mind-body discipline, that has been associated with improved glucose levels and can help to prevent T2DM. The study aimed to systematically develop a Yoga program for T2DM prevention (YOGA-DP) among high-risk people in India using a complex intervention development approach.

Materials and Methods: As part of the intervention, we developed a booklet and a high-definition video for participants and a manual for YOGA-DP instructors. A systematic iterative process was followed to develop the intervention and included five steps: (i) a systematic review of the literature to generate a list of Yogic practices that improves blood glucose levels among adults at high-risk of or with T2DM, (ii) validation of identified Yogic practices by Yoga experts, (iii) development of the intervention, (iv) consultation with Yoga, exercise, physical activity, diet, behavior change, and/or diabetes experts about the intervention, and (v) pretest the intervention among Yoga practitioners and lay people (those at risk of T2DM and had not practiced Yoga before) in India.

Results: YOGA-DP is a structured lifestyle education and exercise program, provided over a period of 24 weeks. The exercise part is based on Yoga and includes Shithilikarana Vyayama (loosening exercises), Surya Namaskar (sun salutation exercises), Asana (Yogic poses), Pranayama (breathing practices), and Dhyana (meditation) and relaxation practices. Once participants complete the program, they are strongly encouraged to maintain a healthy lifestyle in the long-term.

Conclusions: We systematically developed a novel Yoga program for T2DM prevention (YOGA-DP) among high-risk people in India. A multi-center feasibility randomized controlled trial is in progress in India.

Keywords: Yoga, prevention, prediabetes, lifestyle, physical activity, diet

INTRODUCTION

India has the second-largest type-2 diabetes mellitus (T2DM) population in the world, a disorder with major health and socioeconomic consequences (1). More than 77 million Indians are at high-risk of T2DM—their blood glucose levels are higher than normal but lower than the established threshold for T2DM itself (2). These people are more likely to develop T2DM and its complications than those with normal blood glucose levels (3). Unhealthy lifestyle (i.e., physical inactivity and unhealthy diet) is a major risk factor for T2DM (3). Physical activity levels are low among Indians (4). Similarly, unhealthy diets, high in fat (especially saturated fat) and low in fiber, are more prevalent among Indians (5, 6). Screening of people who are at high-risk of T2DM, followed by an effective lifestyle intervention is a cost-effective approach that can normalize blood glucose levels and has other health benefits (3, 7, 8).

Health interventions should be informed by and compatible with the sociocultural expectations of people and their health beliefs (9). The prevention and management of chronic diseases like T2DM using traditional Indian therapies have been prioritized by the Indian government (10). Yoga, an ancient Indian mind-body discipline, covers not only physical activity but also a healthy diet (11). Many different styles of Yoga are undertaken, focusing on similar core elements of physical, mental, and spiritual practices. No particular style of Yoga is necessarily better or more authentic than the others (12). Indians usually have high acceptability of Yoga because it fits their health beliefs and culture (13, 14). Generally, it uses a gentle approach, is easy to learn, is safe, requires a low to moderate level of guidance, is inexpensive to maintain, and can be practiced indoors and outdoors (13). It can be practiced by older adults and those with a wide range of comorbidities (12, 13). As a form of physical activity, some of the Yogic practices are of low-intensity (<3.5 kcal/min) and some are of moderate-intensity (3.5–7.0 kcal/min) (12, 15). For example, Surya Namaskar (sun salutation exercises) burns about 3.8–6.7 kcal/min (16, 17). Yoga is also a muscle-strengthening activity (12). Thus, it can contribute to the aim of routine lifestyle advice given to people at high-risk of T2DM to prevent it.

The beneficial effects of Yoga on T2DM-related risk profiles appear to occur via two main pathways. First, by reducing the activation and reactivity of the sympathoadrenal system and the hypothalamic-pituitary-adrenal axis and by promoting the feelings of well-being, Yoga may alleviate the effects of stress and foster multiple positive downstream effects on the neuroendocrine status, metabolic function, and related systemic inflammatory responses (18). Second, by directly stimulating the vagus nerve, Yoga may enhance the parasympathetic activity and lead to positive changes in the cardiovascular function, mood, energy state, and related neuroendocrine, metabolic, and inflammatory responses (18). In addition, Yoga may lead to weight loss, which itself lowers the risk of T2DM (18).

The beneficial effects of Yoga on T2DM-related outcomes in T2DM (as adjuvant therapy) and metabolic syndrome have been reported in several systematic reviews of clinical trials

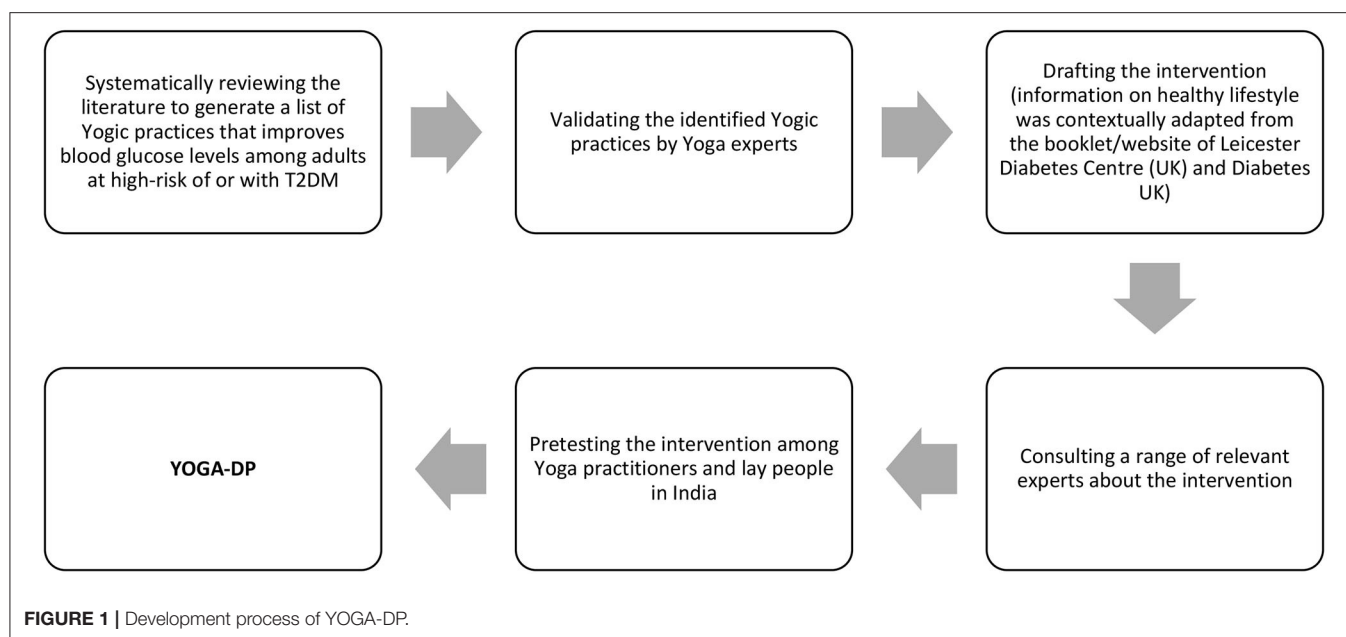
(19–22). For example, a review of 44 randomized controlled trials (RCTs), conducted among T2DM, metabolic syndrome, or healthy participants ($n = 3,168$), found that Yoga improves blood glucose levels compared to usual care or no intervention (mean difference = -0.45% ; 95% confidence interval = -0.87 to -0.02), without any major safety issues (19). However, most of the included studies were short-term (≤ 3 months) and were often associated with considerable methodological limitations, such as small sample sizes in treatment groups, resulting in lack of statistical power for outcome assessment, and lack of blinding of outcome assessors, leading to potential analysis bias. In addition, some of the relevant previous studies have not described the intervention in detail, and it is difficult to replicate successful interventions. Most studies have not reported the intervention development process. It is hard to know whether these interventions were carefully thought out (e.g., their safety and acceptability) and comprehensive in their development. Thus, it is difficult to select (and replicate) one successful intervention over the other. Another selection barrier is their heterogeneous contents (i.e., different Yogic practices were included in these interventions), which needed to be summarized for utilization in T2DM prevention. Thus, our study aimed to address these issues by systematically developing a Yoga program for T2DM prevention (YOGA-DP) among high-risk people in India.

MATERIALS AND METHODS

We followed a systematic iterative process to develop the intervention, guided by the UK's Medical Research Council (MRC) guidance on developing and evaluating complex interventions and Sherman's guideline for developing Yoga interventions for RCTs (9, 23). The template for intervention description and replication (TIDieR) checklist and guide were used to report the intervention (24). As part of the intervention, we developed a booklet and a high-definition video for participants and a manual for YOGA-DP instructors. An external filmmaking company was hired to convert the booklet (Yoga part) into a video to aid audio-visual learning. It was decided to use USB flash drives (having a compressed video—2.08 gigabyte (GB) in MPEG-4 Part 14 (MP4) file format) after discussing the technological advancements as well as accessibility issues in India with the relevant stakeholders (e.g., those in the field of film making). All these are available in English and two other Indian languages, Hindi and Kannada.

Figure 1 shows the development process of YOGA-DP, which consisted of five steps:

(1) We conducted a systematic review of scientific literature to generate a list of Yogic practices that improves blood glucose levels among adults at high-risk of or with T2DM. The PROSPERO protocol informed the systematic review process (PROSPERO registration number CRD42018097216) (25). The process was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) documents (26). Two Joanna Briggs Institute (JBI) accredited systematic reviewers (KC/HW) were involved in the process



and independently screened the titles and abstracts and full-text of studies, assessed the methodological quality of studies, and extracted data from the studies. Any disagreements between them were resolved through discussion.

Inclusion and Exclusion Criteria

Population, intervention, comparator, and outcome: Studies targeting adults (≥ 18 years) at high-risk of or with T2DM were eligible. The diagnosis was based on blood glucose levels. Studies comparing Yoga intervention to no or any intervention and reporting successful Yoga interventions were eligible i.e., Yogic practices which improved blood glucose levels. At least one of the following needed to be statistically significant in the Yoga intervention group as compared to the control group: fasting blood glucose (FBG), postprandial blood glucose (PPBG), or glycated hemoglobin (HbA1c). Studies reporting at least one Yogic practice (i.e., Asana (Yogic pose), Pranayama (breathing practice), or Dhyana (meditation) and relaxation practice), based on classical Yoga texts, were eligible. Studies were excluded if they did not report the Sanskrit name of the Yogic practice. No restrictions were made regarding the frequency or duration of the Yoga intervention. Studies on multimodal interventions that included Yoga amongst others were excluded. Studies allowing individual co-interventions were eligible i.e., studies allowing participants to continue their individual treatment were not excluded as long as all the study groups were allowed to do so.

Study design: Only RCTs were eligible.

Language of publication: No language restrictions were applied.

Search Strategy

(a) Using existing full-text peer-reviewed systematic reviews as a starting point for identifying the relevant RCTs (and

interventions), systematic reviews were searched on PubMed from its inception date to 7th May 2018. The systematic review authors (reviewers) searched a range of databases, the reference list of identified original and review articles, and the table of contents of relevant journals, trial registers, proceedings, and abstracts from relevant symposiums, conferences, and colloquiums. These systematic review authors also approached the relevant experts. The search strategy used was: (Yoga[MeSH] OR Yoga*[tiab] OR Yogi*[tiab] OR Asana*[tiab] OR Pranayam*[tiab] OR Dhyana*[tiab]) AND systematic[sb].

(b) To supplement the above step, we searched on PubMed to directly identify any full-text peer-reviewed RCTs that were published between 1st January 2015 and 7th May 2018. The search strategy used was: (Yoga[MeSH] OR Yoga*[tiab] OR Yogi*[tiab] OR Asana*[tiab] OR Pranayam*[tiab] OR Dhyana*[tiab]) AND random*[mp] NOT systematic[sb].

(c) We also searched IndMED and Google Scholar for additional systematic reviews and RCTs, using different words for Yoga, prediabetes, diabetes, systematic review, and RCT. For Google Scholar, the advanced search tool was used (with all of the words in the title of the article) and excluded patents and citations. The reference list of all the relevant RCTs was also screened for additional RCTs.

Screening and Full-Text Reading

Following the search, all identified citations were collated and uploaded into EndNote X8.2, a reference management software (27). Titles and abstracts were screened for eligibility using the inclusion and exclusion criteria. The full-texts of studies identified as potentially eligible or those without an abstract were retrieved and assessed against the inclusion and exclusion criteria. The full-texts of studies that did not meet the inclusion criteria were excluded, and the reasons for exclusion were reported (Supplementary Table 1).

Methodological Quality Assessment

In terms of methodological quality of the included RCTs, the following were assessed: randomization method, allocation concealment, blinding of outcome assessors, and withdrawals and dropouts. The Jadad score was also calculated. The Jadad score ranges from zero to five points—two points are given for randomization, two points for blinding, and one point for dropouts (28). A low-quality study receives a score of two points or less, and a high-quality study receives a score of at least three points (28). The Jadad score is easy to use, contains many of the important elements that have empirically been shown to correlate with bias, and has known reliability and external validity (29). Data were extracted and synthesized from all the included RCTs, regardless of their methodological quality.

Data Extraction

Study characteristics of the included RCTs and the intervention details were extracted using a standardized data extraction tool.

Data Synthesis

Narrative data synthesis was conducted as the aim of the systematic review was to generate a list of Yogic practices that improves blood glucose levels among adults at high-risk of or with T2DM.

(2) We required at least 40 Yoga experts (41 responders) to validate each of the identified Yogic practices, based on Lawshe's content validity ratio (CVR) formula (30). Highly qualified and experienced Yoga practitioners and/or Yoga researchers with an interest in diabetes (including those with high-level authority) were purposively selected in India for this purpose. One of the study authors (NKM) is a key person in the field of Yoga, and this helped us to gain access to these Yoga experts. A questionnaire with all the identified practices was administered electronically through email, and they marked the content validity of each practice on a three-point scale (zero = not necessary, one = useful but not essential, two = essential), taking into account the safety aspect. CVR was calculated for each practice but only those with $CVR \geq 0.29$ were included in the intervention (30, 31).

$$CVR = (ne - N/2)/(N/2)$$

Where,

ne = number of experts indicating "essential"

N = total number of experts.

(3) We drafted the intervention, with texts and pictorials. With permission, the information on being at high-risk of T2DM and how to prevent T2DM by being more physically active, keeping a healthy weight, eating less fat (especially saturated fat), and eating more fiber was extracted from an existing booklet of Leicester Diabetes Centre (UK) and the Diabetes UK website and adapted to the Indian context (32, 33). Any traditional advice which is based on anecdotal (or contradictory) evidence was not included in the intervention e.g., dietary advice to consume ghee, a type of clarified butter composed almost entirely of fat, especially saturated fat.

(4) We conducted a consultation on the intervention with 16 experts in Yoga, exercise, physical activity, diet, behavior change,

and/or diabetes from India and the UK. Like step number two, we used our multidisciplinary team's contact to approach these experts. The intervention was shared with them through email, and they further reviewed its structure and content, especially from the safety point of view. Their feedback (through email) was used to improve it.

(5) We pre-tested the intervention among eight Yoga practitioners (teachers) and six lay people (those at risk of T2DM and had not practiced Yoga before) at Swami Vivekananda Yoga Anusandhana Samsthana (S-VYASA), India. The objectives were to identify any difficulties they had in reading and understanding the intervention (i.e., comprehension of content/instructions) and to explore the acceptability of the intervention and ways to promote its uptake and adherence. In addition, Yoga practitioners were asked about the overall sequence and flow of the intervention and any difficulties they had in delivering the intervention, especially within the intended timeframe. They were purposively selected to ensure representation of diversity by age and sex. The intervention was shared with them prior to the following activities—to enable them to read and understand it in their free time:

(a) Yoga practitioners: A face-to-face meeting was held with them.

(b) Lay people: A Yoga session, based on the intervention, was delivered to them by two Yoga practitioners (one male and one female). This was followed by a face-to-face meeting with them.

With consent, the feedback was noted and digitally-recorded. Their feedback was used to finalize the intervention.

RESULTS

The results describe the outcome of each step of the intervention development process.

(1) A total of nine RCTs were included in our systematic review. **Supplementary Figure 1** shows the flowchart depicting the search and screening process of systematic reviews and RCTs.

(a) 501 systematic review records were identified until 7th May 2018. 468 records were excluded at the title and abstract screening stage. The full-texts of 33 systematic reviews were assessed for eligibility and 21 were excluded at this stage. The remaining 12 systematic reviews were included containing potential RCTs (19, 21, 22, 34–42). The full-texts of 67 potential RCTs were assessed for eligibility and 58 were excluded at this stage. The remaining eight RCTs (two similar articles from the same RCT were published in two different journals) were included in our systematic review (43–51).

(b) To supplement the above step, 384 RCT records were directly identified between 1st January 2015 and 7th May 2018. 374 records were excluded at the title and abstract screening stage. The full-texts of 10 RCTs were assessed for eligibility and nine were excluded at this stage. The remaining one RCT was included in our systematic review (52).

Supplementary Tables 2, 3 report the study characteristics and critical appraisal of the nine included RCTs, respectively. Briefly, all the RCTs were conducted in India. The sample size ranged from 30 to 337. Yoga was an adjuvant therapy

TABLE 1 | Intervention details of the included RCTs.

References	Intervention development information	Yoga sessions: frequency and duration	Yoga sessions: delivery (place and person)	Shithilikarana Vyayama	Surya Namaskar	Asana	Pranayama	Dhyana and relaxation practice	Extra features
Agrawal et al. (43)	NS	60 min/day X 5–7 days/week X 12 weeks	At the hospital, NS	Yes	Yes	Paschimottanasana, Ardhamatsyendrasana, Uttanapadasana, Sarvangasana, Matsyasana	Yes (NS)	Kayotsarga, Preksha meditation including Anupreksha	
Nagarathna et al. (44)	Developed by experts including Yoga, based on the knowledge culled out from Yoga scriptures (Patanjali Yoga Sutras, Bhagavad Gita, and Mandukya Karika)	60 min/day X 5 days/week X 12 weeks (and then till 9 months: 1 session (of 120 min)/week and 60 min/day X 7 days/week self-practice at home)	NS, by Yoga instructor	Yes	Yes	Parivrttatrikonasana, Vakrasana, Ardhamatsyendrasana, Ustrasana, Hamsasana, Mayurasana, Bhujangasana, Dhanurasana, Sarvangasana, Matsyasana, Padahastanasana, Ardhashakrasana, Trikonasana, Pavanamuktasana, Shavasana	Vibhagiya, Ujjayi, Nadishodhana, Sheetali, Shitkari, Bhramari, Kapalbhathi	Nadanusandhana (A Kara, U Kara, M Kara, and AUM chanting)	Self-reporting of Yoga practice at home (types and min/day), pre-recorded Yoga instruction audiotape for participants
Vaishali et al. (45, 46)	NS	45–60 min/day X 6 days/week X 12 weeks	At the hospital, by Yoga instructor			Vajrasana, Suptavajrasana, Tadasana, Padahastanasana, Trikonasana, Paravakonasana, Trikonasana, Vakrasana, Pavanamuktasana, Bhujangasana, Shalabhasana, Shavasana	Ujjayi, Anulom Vilom		Weekly talks by a motivated participant on perceived benefits and personal experiences of regular Yoga practice, followed by group discussions among participants for enhancing adherence
Yadav (47)	NS	? X 12 weeks	NS, NS			Poornabhujangasana, Dhanurasana, Baddhapadmasana, Kukkutasana, Halasana			
Kumar and Kalidasan (48)	NS	50 min/day X 6 days/week X 12 weeks (morning sessions)	At a Yoga center?, by Yoga instructor	Yes		Tadasana, Konasana, Padahastanasana, Piraianasana, Yoga Mudrasana (Padmasana, Vajrasana, Sukhasana), Janusirsasana, Vakrasana, Ustrasana, Makarasana, Pavanamuktasana, Uttanapadasana, Naukasana, Bhujangasana, Ardhashalabhasana, Poornashalabhasana, Dhanurasana, Shavasana			

(Continued)

TABLE 1 | Continued

References	Intervention development information	Yoga sessions: frequency and duration	Yoga sessions: delivery (place and person)	Shithilikarana Vyayama	Surya Namaskar	Asana	Pranayama	Dhyana and relaxation practice	Extra features
Kumpatla et al. (49)	Based on earlier reports	30 min/day X 7 days/week X 12 weeks (one training session in the morning and then self-practice at home)	At the hospital, by Yoga instructor			Vakrasana, Paschimottanasana, Mandukasana, Uttanapadasana, Naukasana, Bhujangasana, Trikonasana			Regular phone calls for encouraging self-practice at home, Yoga booklet for participants
Sharma et al. (50)	NS	45–60 min/day X 5 days/week X 12 weeks (morning sessions on empty stomach)	At the hospital, by Yoga instructor			Trikonasana, Tadasana, Sukhasana, Padmasana, Mandukasana, Paschimottanasana, Ardhamatsyendrasana, Pavanamuktasana, Bhujangasana, Vajrasana, Dhanurasana, Shavasana	Yes (NS)		
Singh et al. (51)	NS	? min/day X 7 days/week X 2 weeks (and then till 6 months: once/month supervision at the delivery center? and self-practice at home)	NS, by Yoga instructor	Yes	Yes	Tadasana, Trikonasana, Vajrasana, Padmasana, Ardhamatsyendrasana, Paschimottanasana, Bhujangasana, Dhanurasana, Halasana, Naukasana, Shavasana	Bhastrika, Kapalabhati, Anulom Vilom, Bhramari		Self-reporting of Yoga practice at home (types/day and lapse), requesting family/carer to accompany participant during sessions and to countersign once participant finishes self-practice at home, weekly phone call to participant and family/carer for monitoring adherence and knowing difficulties, Yoga booklet for participants
Keerthi et al. (52)	Formulated in accordance with guidelines of Morarji Desai National Institute of Yoga, India	45 min X 3 days/week X 12 weeks (and self-practice at home)	At the hospital, by Yoga instructor	Yes	Yes	Padahastanasana, Konasana, Vakrasana, Ardhamatsyendrasana, Paschimottanasana, Shalabhasana, Dhanurasana, Pavanamuktasana, Ardhalasana, Saralmatsyasana, Tadasana, Katichakrasana, Shavasana	Nadishodhana, Bhramari, Chandranadi	Nadanusandhana (A Kara, U Kara, M Kara, and AUM chanting), Yoga Nidra	Attendance documentation of Yoga sessions, regular phone calls for monitoring self-practice at home, Yoga booklet for participants

NS, Not specified; ?, Unclear.

TABLE 2 | Validation of the identified Yogic practices.

Yogic practices	CVR	Additional reason for exclusion	Included in the intervention?
Shithilikarana Vyayama	0.71		Yes
Surya Namaskar	0.80		Yes
Ardhachakrasana	0.61		Yes
Katichakrasana	0.90		Yes
Padahastasana	0.51	Part of Surya Namaskar	No
Piraisana	−0.56		No
Tadasana	0.37		Yes
Konasana	0.90		Yes
Paravakonasana	0.37		Yes
Trikonasana	0.56		Yes
Parivrttatrikonasana	0.27		No
Ardhamatsyendrasana	0.95		Yes
Janusirsasana	0.51		Yes
Kukkutasana	−0.95		No
Mandukasana	0.90		Yes
Padmasana	−0.02		No
Baddhapadmasana	−0.37		No
Paschimottanasana	0.66		Yes
Sukhasana	0.22		No
Ustrasana	0.66		Yes
Vajrasana	0.56		Yes
Vakrasana	1.00		Yes
Yoga Mudrasana 1 (Padmasana)	0.07		No
Yoga Mudrasana 2 (Vajrasana)	0.27		No
Yoga Mudrasana 3 (Sukhasana)	0.12		No
Bhujangasana	0.95	Part of Surya Namaskar	No
Poornabhujangasana	−0.71		No
Dhanurasana	0.80		Yes
Hamsasana	−0.51		No
Makarasana	0.66		Yes
Mayurasana	−0.51		No
Shalabhasana/Poornashalabhasana	0.32		Yes
Ardhashalabhasana	0.51		Yes
Halasana	0.12		No
Ardhahalasana	0.61		Yes
Matsyasana	0.17		No
Saralmatsyasana	0.37		Yes
Naukasana	0.66		Yes
Pavanamuktasana	0.95		Yes
Suptavajrasana	−0.22		No
Sarvangasana	0.07		No
Uttanapadasana	0.61		Yes
Shavasana	0.90	Similar to Yoga Nidra	No
Anulom Vilom Pranayama	0.80	Similar to Nadishodhana Pranayama	No
Nadishodhana Pranayama	0.85		Yes
Chandranadi Pranayama	−0.02		No
Bhastrika Pranayama	0.37		Yes
Kapalbhati Pranayama	0.56		Yes
Bhramari Pranayama	0.80		Yes
Sheetali Pranayama	−0.17		No
Shitkari Pranayama	−0.27		No
Ujjayi Pranayama	−0.17		No
Vibhagiya Pranayama	0.51		Yes
Nadanusandhana (A Kara, U Kara, M Kara, and AUM chanting)	0.76	AUM chanting removed on religious grounds	Partially
AUM chanting	0.46	On religious grounds	No
Kayotsarga	0.80	Part of Yoga Nidra	No
Preksha meditation including Anupreksha	0.32	Part of Yoga Nidra	No
Yoga Nidra	0.76		Yes

TABLE 3 | Structure of YOGA-DP.

Week	Group Yoga sessions delivered by YOGA-DP instructors	Self-practice of Yoga at home using YOGA-DP booklet and a video	Extra features
1–4 (month 1)	At least two sessions of 45 min per week. An attendance register is kept.	–	At the first session, the instructor is giving participants part one of our program booklet. This gives them information about being at high-risk of T2DM and how to prevent T2DM (i.e., by being more physically active, keeping a healthy weight, eating less fat (especially saturated fat), and eating more fiber).
5–12 (month 2–3)	At least two sessions of 75 min per week. An attendance register is kept.	–	At the last session, the instructor is giving participants part two of our program booklet and a video. These give them information on Yoga practice to prevent T2DM. Also, a Yoga diary and a non-slippery Yoga mat are provided for self-practice of Yoga at home.
13–24 (month 4–6)	At least one session of 75 min every 4 weeks. An attendance register is kept.	At least two sessions of 75 min per week. Participants are given the Yoga diary to record their Yoga practice (types and minutes).	The instructor is phoning participants every week to offer support and help and to troubleshoot any problems.
25+ (month 7+)	–	At least two sessions of 75 min per week. Participants are given the Yoga diary to record their Yoga practice (types and minutes).	–

in all the RCTs—all the RCTs were conducted among T2DM patients and one study also included people with prediabetes. The improvement in blood glucose levels was measured using FBG, PPBG, and/or HbA1c tests. One RCT mentioned that no adverse event occurred and four reported limited information on adverse events. The Jadad score of only four RCTs was high. Only four RCTs mentioned the allocation concealment (two provided only limited information). **Table 1** reports the intervention details of the included RCTs. More specifically, 58 Yogic practices that improve blood glucose levels among adults at high-risk of or with T2DM were identified.

(2) **Table 2** reports the validation of the identified Yogic practices. Out of the 58 identified Yogic practices, 31 were included in the intervention, namely, Shithilikarana Vyayama (loosening exercises), Surya Namaskar, 22 Asana (six standing poses, seven sitting poses, four lying poses-front/prone, and five lying poses-back/supine), five Pranayama, and two Dhyana and relaxation practices. There was one exception—Ardhastrasana, a simplified form of Ustrasana (a sitting pose included in the intervention), was additionally included in the intervention as recommended by the Yoga experts during the validation work.

(3–5) The intervention is for adults (18–74 years) who are at high-risk of T2DM and are currently safe to do physical activity, determined by the Physical Activity Readiness Questionnaire (PAR-Q)/clinician. The intervention is not suitable for pregnant women; people with chest pain, a heart condition, or any serious or uncontrolled medical condition; or people who have recently undergone surgery. People with high blood pressure are required to check first with their clinician that their blood pressure is well-controlled before taking part in the intervention.

Tables 3, 4 report the structure of YOGA-DP and structure and content of the Yoga sessions, respectively. The intervention is a structured lifestyle education and exercise program, provided

over a period of 24 weeks. The exercise part is based on Yoga and includes 32 Yogic practices, namely, Shithilikarana Vyayama, Surya Namaskar, 23 Asana (six standing poses, eight sitting poses, four lying poses-front/prone, and five lying poses-back/supine), five Pranayama, and two Dhyana and relaxation practices. Once participants complete the intervention, they are strongly encouraged to maintain a healthy lifestyle in the long-term, using the intervention booklet and video. It should be noted that, initially, we planned 52 supervised center-based group sessions (75 min/session X two sessions/week X 26 weeks). However, the intervention structure was modified after the consultation work to enhance intervention uptake and adherence i.e., based on the recommendations of experts in step number four. In the first instance, 75 min/session might appear a huge amount of time for the participants to commit to, and thus, we designed 45 min session in weeks 1–4 to avoid any physical or mental exhaustion and to gradually build their fitness. Second, to avoid the excessive burden of attending center-based sessions, weeks 13–24 comprise of one center-based session every 4 weeks and self-practice at home (using the intervention booklet and video) is recommended from week 13 onwards. Initial supervised center-based sessions are deemed to be appropriate for wider use in India due to the low levels of literacy. Similarly, initial group sessions are deemed to be appropriate for benefits from shared experiences and peer support. To improve intervention uptake and adherence, the group Yoga sessions are run locally (e.g., at Yoga centers and community centers) and at different time points of the day (with evening and weekend sessions), and participants can join as per their convenience. Some of their local travel costs for attending these sessions are reimbursed. A family member or someone close to the participant is invited to join them in these sessions. The intervention is delivered by YOGA-DP instructors—qualified and experienced Yoga teachers

TABLE 4 | Structure and content of the Yoga sessions.

Yogic practices	Week 1–4 Each session should last for 45 min with the time split as follows:	Week 5+ Each session should last for 75 min with the time split as follows:	Details
Shithilikarana Vyayama	Around 5 min	Around 5 min	(1) Neck rotation 30 s (2) Shoulder rotation 30 s (3) Elbow flexion and extension 30 s (4) Wrist rotation 30 s (5) Finger movement 30 s (6) Waist rotation 30 s (7) Knee flexion and extension 1 min (8) Ankle rotation 1 min (9) Toe movement 30 s
Surya Namaskar	–	Around 15 min	The below mentioned 12 steps constitute one set of Surya Namaskar. To complete one round of Surya Namaskar, participants need to repeat these 12 steps on the other side of their body (i.e., by extending their left leg behind in step number 4 and bringing their left leg forward in step number 9). Initially, they should practice Surya Namaskar at a slower pace. Only with practice over some time, they may try to do 12 rounds of it at a faster pace for around 15 min (i.e., a couple of seconds per step). (1) Pranamasana (prayer pose) (2) Hastauttanasana (raised arms pose) (3) Padahastanasana (hands to feet pose) (4) Ashwa Sanchalanasana (equestrian pose) (5) Dandasana (stick pose) (6) Ashtanga Namaskara Asana (salute with eight parts) (7) Bhujangasana (cobra pose) (8) Parvatasana (mountain pose) (9) Ashwa Sanchalanasana (equestrian pose) (10) Padahastanasana (hands to feet pose) (11) Hastauttanasana (raised arms pose) (12) Pranamasana (prayer pose)
Asana	Around 15 min	Around 30 min	Two-sided poses (right and left) are to be practiced for about 3 min (1.5 min on each side) and central-positioned poses are to be practiced for about 1.5 min. In each session, the Yogic poses are selected from the list below to prevent boredom from the similarity of routine. Advanced Yogic poses are introduced from week 5 onwards, for example, Konasana (angle pose), Trikonasana (triangle pose), Paravakonasana (lateral angle pose), Ardhastrasana (half camel pose), Ustrasana (camel pose), Dhanurasana (bow pose), and Naukasana (boat pose). (A) Standing poses (1) Tadasana (palm tree pose) 1.5 min (2) ArdhaChakrasana (half wheel pose) 1.5 min (3) Katichakrasana (waist wheel pose) 3 min (4) Konasana (angle pose) or Trikonasana (triangle pose) or Paravakonasana (lateral angle pose): alternatively 3 min (B) Sitting poses (1) Vajrasana (adamant pose) 1.5 min (2) Mandukasana (frog pose) 1.5 min (3) Ardhastrasana (half camel pose) or Ustrasana (camel pose): alternatively 1.5 min (4) Vakrasana (twisted pose) or Ardhamatsyendrasana (half spinal twist pose): alternatively 3 min (5) Paschimottanasana (seated forward bend pose) or Janusirsasana (head to knee pose): alternatively 1.5 or 3 min, respectively (C) Lying poses- front/prone (1) Ardhashalabhasana (half locust pose) or Poornashalabhasana (full locust pose): alternatively 3 or 1.5 min, respectively (2) Dhanurasana (bow pose) 1.5 min (3) Makarasana (crocodile pose) 1.5 min (D) Lying poses- back/supine (1) Uttanapadasana (raised legs pose) or ArdhaChakrasana (half plow pose): alternatively 1.5 min (2) Pavanamuktasana (wind relieving pose) 1.5 min (3) Naukasana (boat pose) 1.5 min (4) Saralmatsyasana (easy fish pose) 1.5 min

(Continued)

TABLE 4 | Continued

Yogic practices	Week 1–4 Each session should last for 45 min with the time split as follows:	Week 5+ Each session should last for 75 min with the time split as follows:	Details
Pranayama	Around 13 min	Around 13 min	(1) Vibhagiyā Pranayama (sectional breathing) 4 min (2) Nadishodhana Pranayama (alternate nostril breathing) 3 min (3) Kapalabhati Pranayama (skull shining breathing) or Bhastrika Pranayama (bellow breathing): alternatively 3 min (4) Bhramari Pranayama (bee breathing) 3 min
Dhyana and relaxation practices	Around 12 min	Around 12 min	In each session, the following Dhyana and relaxation practices are to be done in a darkened room. (1) A Kara chanting, U Kara chanting, and M Kara chanting 3 min (2) Yoga Nidra (Yogic sleep) 9 min

with formal training provided on the program, and they can speak the local languages. Female instructors are available for female participants.

DISCUSSION

We report the systematic development of a novel Yoga program for T2DM prevention (YOGA-DP) among high-risk people in India. The duration of our intervention (24 weeks) is longer than many other Yoga interventions (43, 45–50, 52). Even after formally completing the intervention, participants are strongly encouraged to maintain a healthy lifestyle in the long-term, using the intervention booklet and video. The long-term maintenance of a healthy lifestyle is required, not just for preventing T2DM but also for overall health (3). However, lifestyle interventions' poor uptake and adherence (especially over the long-term) are well-recognized and can negatively affect the effectiveness of these interventions (53). This is the reason we incorporated multiple strategies to enhance uptake and adherence to our intervention. Some of these have already been used in previous successful studies (44–46, 49, 51, 52) and some came up during the intervention development process (e.g., female YOGA-DP instructors for female participants). In fact, as mentioned in the results section, the structure of our intervention evolved during the development process to enhance its uptake and adherence. Similar to many other Yoga interventions, our intervention includes Shithilikarana Vyayama, Asana (standing, sitting, and lying poses), Pranayama, and Dhyana and relaxation practices (43, 44, 52). Surya Namaskar is something additional in our intervention which is not always found in Yoga interventions. It can help in the prevention of T2DM, as it is considered a moderate-intensity activity and burns about 3.8–6.7 kcal/min (16, 17). Second, based on the suggestion of Yoga experts, AUM chanting (under Dhyana and relaxation practices) was not retained on religious grounds. Thus, the acceptance of the intervention could be high among people irrespective of their religious beliefs.

Yoga is a complex intervention, and the MRC guidance on developing and evaluating complex interventions provided the overall framework to develop the intervention (9). In fact, intervention development is the first step, and there are

other steps as well, such as feasibility/piloting, evaluation, and implementation. There are questions throughout this guidance which helped us to design the study and to follow a systematic iterative process. It is not a “one size fits all” guidance but a generic one, and thus, not all the questions were relevant in our context. A major challenge was to systematically integrate traditional and western medical systems for T2DM prevention. Any traditional advice which is based on anecdotal (or contradictory) evidence was not included in the intervention. A similar systematic approach could be used to develop other local and cross-cultural health interventions.

The study has several strengths and weaknesses. This is one of the few studies to report the systematic development of a Yoga intervention. Another example is a Yoga-based cardiac rehabilitation (Yoga-CaRe) program which has been developed for secondary prevention of myocardial infarction in India (54). The interventions, study participants, and outcomes are different in the two studies. We followed a systematic process and reviewed the scientific literature as part of the process. In other words, we summarized the heterogeneous contents of successful and relevant Yoga interventions. The process also helped us to reach consensus on this complex intervention. A range of stakeholders (including healthcare, medical, and Yoga experts and practitioners and the public) were involved to explore issues like safety and acceptability of the intervention. The systematic review included only those studies that showed evidence of effectiveness in one of the prespecified outcomes. It should be noted that this was not a typical effectiveness systematic review, and the ultimate aim was to develop an intervention based on previous successful interventions. We also excluded studies if they did not report the Sanskrit name of the Yogic practice. Without the Sanskrit name, the English translation could mean more than one Yogic practice (and sometimes even modified or patented Yoga), and it is difficult to replicate such interventions for multiple reasons. There is a chance of missing a relevant Yogic practice. However, Yoga experts were involved in the next step, and they confirmed the inclusion of all the essential Yogic practices. Second, the Jadad score was calculated as part of the methodological quality assessment of the included RCTs. Apart from its many advantages, as mentioned before, it has disadvantages as well. For example, it is over-simplistic and does

not take into account many essential methodological issues, such as the concealment of treatment allocation (55). Therefore, in addition to the Jadad score calculation, we assessed the allocation concealment. Third, due to the accessibility issues in India, we had to compress the video, which affected its quality. However, we have archived the original high-quality video for future use.

A multi-center feasibility RCT is currently in progress in India to determine the feasibility of undertaking the main RCT (56). If the feasibility is acceptable, we will design and conduct the main RCT. If the intervention is found to be effective, it will be a low-cost, acceptable, and local solution for preventing T2DM among high-risk people in India and for improving their overall health. It will also prevent the future clinical, personal, and economic burden of T2DM on patients, their families, the health system, and the economy. The advantages of preventing T2DM may extend to the prevention of T2DM related complications. More evidence-based choices will be available to people for preventing T2DM. The intervention will simultaneously empower people to manage their health. Given that T2DM and its related costs are global concerns and Yoga is popular or is becoming popular globally, there will be worldwide interest in this low-cost Yoga-based T2DM prevention program, particularly in other South Asian countries and in countries with South Asian ethnic minorities (57, 58). The intervention could be adapted, evaluated, and implemented to prevent T2DM in other settings or populations.

In conclusion, we systematically developed a novel Yoga program for T2DM prevention (YOGA-DP) among high-risk people in India. A multi-center feasibility RCT is in progress in India.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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ETHICS STATEMENT

The study was approved by four research ethics committees, namely, Faculty of Medicine and Health Sciences, University of Nottingham (UK); Centre for Chronic Disease Control (CCDC, India); Swami Vivekananda Yoga Anusandhana Samsthana (S-VYASA, India); and Bapu Nature Cure Hospital and Yogashram (BNCHY, India). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KC conceptualized, designed, and conducted the study with the help of other authors, wrote the first draft of the manuscript, and other authors contributed significantly to the revision of the manuscript. All authors read and approved the final manuscript.

FUNDING

This study was funded by the UK's DFID/MRC/NIHR/Wellcome Trust Joint Global Health Trials (MR/R018278/1). The funding agencies had no role in developing the intervention or writing the manuscript.

ACKNOWLEDGMENTS

We thank all the people who have contributed to the development of YOGA-DP, Leicester Diabetes Centre, and Diabetes UK.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpubh.2020.548674/full#supplementary-material>

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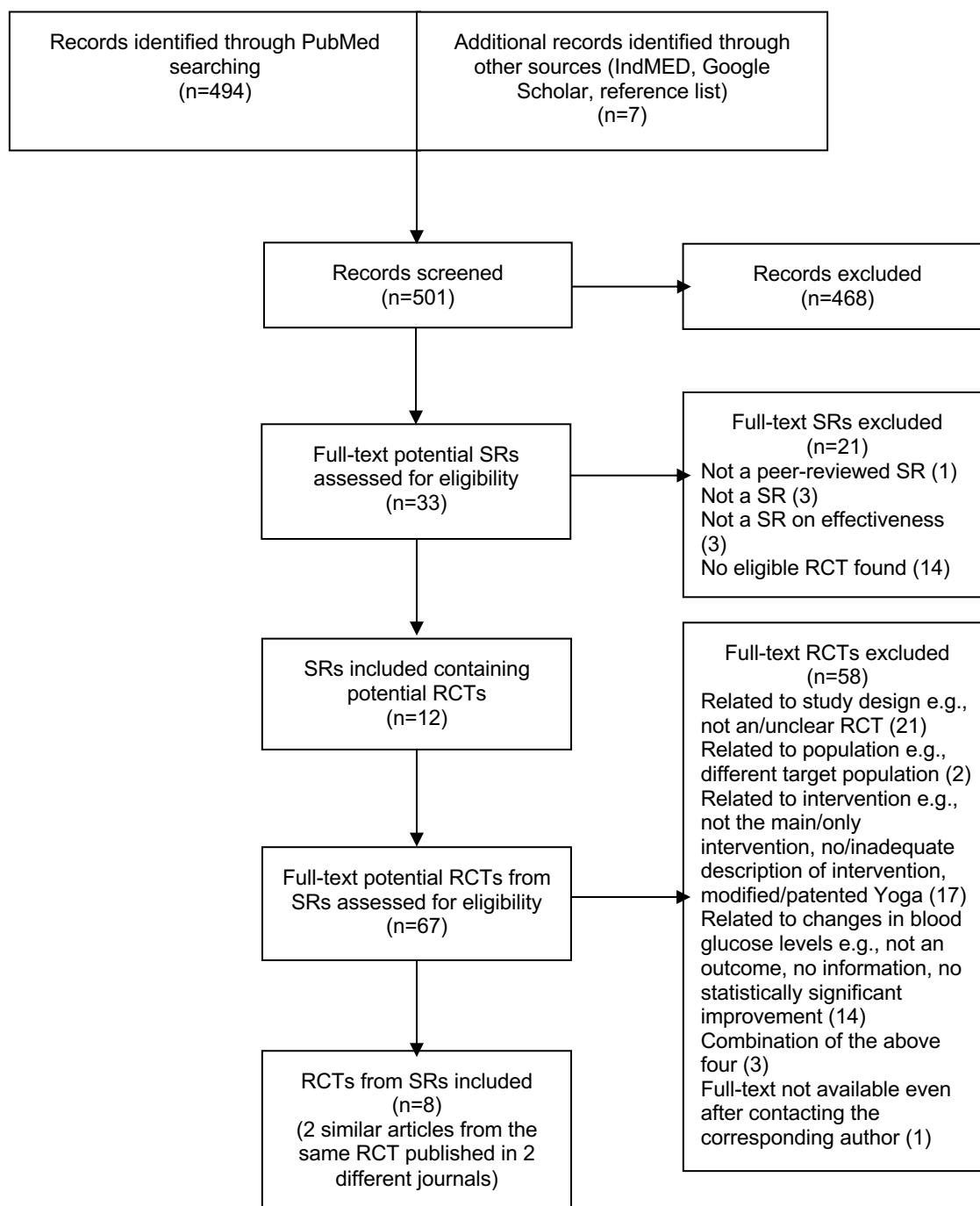
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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figure S1: Flowchart depicting the search and screening process of systematic reviews (SRs) and randomized controlled trials (RCTs)
(a) SR



(b) RCT

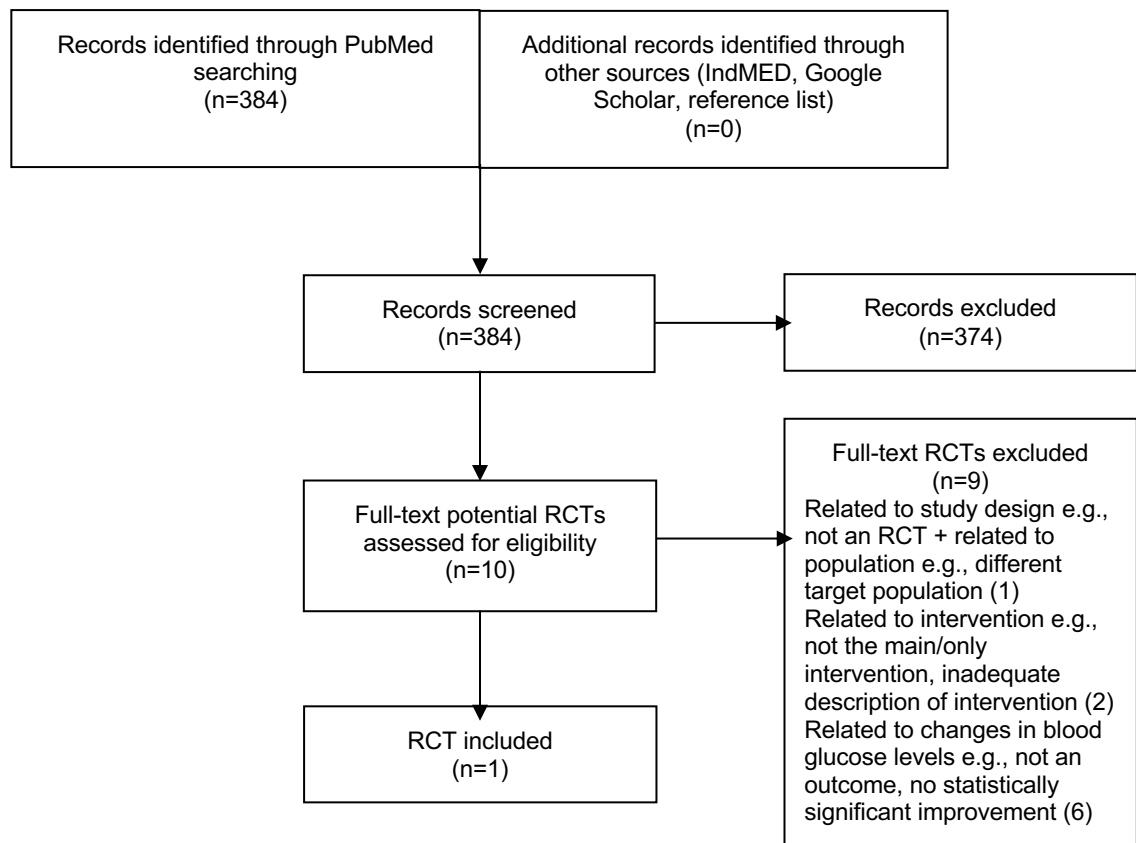


Table S1: Excluded studies (systematic reviews (SRs) and randomized controlled trials (RCTs)) with reasons for exclusion

(a) SR Full-text SRs excluded (n=21) Not a peer-reviewed SR (1) Cosman J. Yoga and diabetes: a systematic review of recent literature concerning the impact of yoga practice on diabetic symptoms. USA: University of Texas Health Science Center. 2014. https://digitalcommons.library.tmc.edu/dissertations/AAI1599374 [dissertation]. Not a SR (3) Pandey A, Tripathi P, Pandey R, et al. Alternative therapies useful in the management of diabetes: a systematic review. J Pharm Bioallied Sci. 2011;3(4):504-12. Apor P. Preventive and curative value of yoga in cardiometabolic diseases. Orv Hetil. 2016;157(9):323-7. Prajapati S, Vyas G, Vyas G. Yoga practice for the prevention and management of diabetes mellitus: a systematic review. Research and Reviews: Journal of Microbiology and Virology. 2017;7(1):31-5. Not a SR on effectiveness (3) Cramer H, Lauche R, Dobos G. Characteristics of randomized controlled trials of yoga: a bibliometric analysis. BMC Complement Altern Med. 2014;14:328. McCall MC. In search of yoga: research trends in a western medical database. Int J Yoga. 2014;7(1):4-8. Jeter PE, Slutsky J, Singh N, et al. Yoga as a therapeutic intervention: a bibliometric analysis of published research studies from 1967 to 2013. J Altern Complement Med. 2015;21(10):586-92. No eligible RCT found (14) Jayasinghe SR. Yoga in cardiac health (a review). Eur J Cardiovasc Prev Rehabil. 2004;11(5):369-75. Innes KE, Bourguignon C, Taylor AG. Risk indices associated with the insulin resistance syndrome, cardiovascular disease, and possible protection with yoga: a systematic review. J Am Board Fam Pract. 2005;18(6):491-519. Innes KE, Vincent HK. The influence of yoga-based programs on risk profiles in adults with type 2 diabetes mellitus: a systematic review. Evid Based Complement Alternat Med. 2007;4(4):469-86. Pilkington K, Stenhouse E, Kirkwood G, et al. Diabetes and complementary therapies: mapping the evidence. Practical Diabetes International. 2007;24(7):371-6. Yang K. A review of yoga programs for four leading risk factors of chronic diseases. Evid Based Complement Alternat Med. 2007;4(4):487-91. Anderson JG, Taylor AG. The metabolic syndrome and mind-body therapies: a systematic review. J Nutr Metab. 2011;2011:276419. Sharma M, Knowlden AP. Role of yoga in preventing and controlling type 2 diabetes mellitus. J Evid Based Complementary Altern Med. 2012;17(2):88-95. Rioux JG, Ritenbaugh C. Narrative review of yoga intervention clinical trials including weight-related outcomes. Altern Ther Health Med. 2013;19(3):32-46. Thent ZC, Das S, Henry LJ. Role of exercise in the management of diabetes mellitus: the global scenario. PLoS One. 2013;8(11):e80436. Hartley L, Dyakova M, Holmes J, et al. Yoga for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2014;(5):CD010072. Barrows JL, Fleury J. Systematic review of yoga interventions to promote cardiovascular health in older adults. West J Nurs Res. 2016;38(6):753-81. Cramer H, Langhorst J, Dobos G, et al. Yoga for metabolic syndrome: a systematic review and meta-analysis. Eur J Prev Cardiol. 2016;23(18):1982-93. Cai H, Li G, Zhang P, et al. Effect of exercise on the quality of life in type 2 diabetes mellitus: a systematic review. Qual Life Res. 2017;26(3):515-30. Haider T, Sharma M, Branscum P. Yoga as an alternative and complimentary therapy for cardiovascular disease: a systematic review. J Evid Based Complementary Altern Med. 2017;22(2):310-6. Full-text RCTs excluded (n=58) Related to study design e.g., not an/unclear RCT (21) Jain SC, Uppal A, Bhatnagar SO, et al. A study of response pattern of non-insulin dependent diabetics to yoga therapy. Diabetes Res Clin Pract. 1993;19(1):69-74. Jain SC, Talukdar B. Role of yoga in control of hyperglycemia in middle aged patients of non-insulin dependent diabetes mellitus. Indian J Clin Biochem. 1995;10(2):62-5. Malhotra V, Singh S, Singh KP, et al. Study of yoga asanas in assessment of pulmonary function in NIDDM patients. Indian J Physiol Pharmacol. 2002;46(3):313-20. Malhotra V, Singh S, Tandon OP, et al. Effect of yoga asanas on nerve conduction in type 2 diabetes. Indian J Physiol Pharmacol. 2002;46(3):298-306. Singh S, Malhotra V, Singh KP, et al. Role of yoga in modifying certain cardiovascular functions in type 2 diabetic patients. J Assoc Physicians India. 2004;52:203-6. Malhotra V, Singh S, Tandon OP, et al. The beneficial effect of yoga in diabetes. Nepal Med Coll J. 2005;7(2):145-7.

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Madanmohan, Bhavanani AB, Dayanidy G, et al. Effect of yoga therapy on reaction time, biochemical parameters and wellness score of peri and post-menopausal diabetic patients. *Int J Yoga*. 2012;5(1):10-5.

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Popli U, Subbe CP, Sunil K. The role of yoga as a lifestyle modification in treatment of diabetes mellitus: results of a pilot study. *Altern Ther Health Med*. 2014;20(6):24-6.

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Related to population e.g., different target population (2)

Lee JA, Kim JW, Kim DY. Effects of yoga exercise on serum adiponectin and metabolic syndrome factors in obese postmenopausal women. *Menopause*. 2012;19(3):296-301.

Seo DY, Lee S, Figueroa A, et al. Yoga training improves metabolic parameters in obese boys. *Korean J Physiol Pharmacol*. 2012;16(3):175-80.

Related to intervention e.g., not the main/only intervention, no/inadequate description of intervention, modified/patented Yoga (17)

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Balaji PV, Thirumaran M. Effects of 10 weeks yoga training on blood glucose and lipid profile in type II diabetic patients. *Sch J App Med Sci.* 2015;3(5):1876-9.

Related to changes in blood glucose levels e.g., not an outcome, no information, no statistically significant improvement (14)

Cohen BE, Chang AA, Grady D, et al. Restorative yoga in adults with metabolic syndrome: a randomized, controlled pilot trial. *Metab Syndr Relat Disord.* 2008;6(3):223-9.

Amita S, Prabhakar S, Manoj I, et al. Effect of yoga-nidra on blood glucose level in diabetic patients. *Indian J Physiol Pharmacol.* 2009;53(1):97-101.

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Combination of the above four (3)

Kerr D, Gillam E, Ryder J, et al. An eastern art form for a western disease: randomised controlled trial of yoga in patients with poorly controlled insulin-treated diabetes. *Practical Diabetes International.* 2002;19(6):164-6.

Agte VV, Tarwadi K. Sudarshan kriya yoga for treating type 2 diabetes: a preliminary study. *Altern Complement Ther.* 2004;10(4):220-2.

Skoro-Kondza L, Tai SS, Gadelrab R, et al. Community based yoga classes for type 2 diabetes: an exploratory randomised controlled trial. *BMC Health Serv Res.* 2009;9(1):1-8.

Full-text not available even after contacting the corresponding author (1)

Anitha S, Moses CRA, Judie A. Yoga therapy on quality of life, selected physiological and bio-chemical parameters of patients with type 2 diabetes mellitus. *The Journal of Nursing Trendz.* 2013;4(2):3-8.

(b) RCT

Full-text RCTs excluded (n=9)

Related to study design e.g., not an RCT + related to population e.g., different target population (1)

Wolff M, Memon AA, Chalmers JP, et al. Yoga's effect on inflammatory biomarkers and metabolic risk factors in a high risk population: a controlled trial in primary care. *BMC Cardiovasc Disord.* 2015;15:91.

Related to intervention e.g., not the main/only intervention, inadequate description of intervention (2)

Mullur RS, Ames D. Impact of a 10 minute seated yoga practice in the management of diabetes. *J Yoga Phys Ther.* 2016;6(1):1000224.

Nagasukeerthi P, Mooventhana A, Manjunath NK. Short-term effect of add on bell pepper (*Capsicum annuum* var. *grossum*) juice with integrated approach of yoga therapy on blood glucose levels and cardiovascular functions in patients with type 2 diabetes mellitus: a randomized controlled study. *Complement Ther Med.* 2017;34:42-5. {Nagasukeerthi P, Mooventhana A, Manjunath NK. Corrigendum to "Short-term effect of add on bell pepper (*Capsicum annuum* var. *grossum*) juice with integrated approach of yoga therapy on blood

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Related to changes in blood glucose levels e.g., not an outcome, no statistically significant improvement (6)

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Table S2: Study characteristics of the included nine RCTs

Author and year	In systematic review and year	Location	Population	Sample size	Intervention	Comparator	Improvement in blood glucose levels in the Yoga group (from baseline to follow-up [^])	Adverse events
Agrawal 2003	Aljasir 2010, Cramer 2014, Innes 2016, Vizcaino 2016, Eun 2017, Kumar 2016, Thind 2017	Bikaner, India	T2DM, both sexes	200 (I=100?, C=100?)	Standard medical management?+Yoga	Standard medical management+exercise?	FBG (from 183.9±39.3 to 150.7±34.2 mg/dl), HbA1c (from 9.4±1.0 to 8.6±1.0 %)	Yes*
Nagarathna 2012	Cramer 2014, Innes 2016, Vizcaino 2016, Cui 2017, Kumar 2016, Thind 2017, Jayawardena 2018	Bangalore, India	T2DM, both sexes, above 25 years?	277 (I=141, C=136)	Standard medical management?+Yoga	Standard medical management?+exercise and walking	HbA1c (from 8.5±1.7 to 7.3±3.0 %)	Yes*
Vaishali 2011, 2012	Cramer 2014, Bhurji 2016, Chu 2016, Innes 2016, Pai 2016, Vizcaino 2016, Cui 2017, Kumar 2016, Thind 2017, Jayawardena 2018	Mangalore, India	T2DM with cardiometabolic risk factors, both sexes, above 60 years	60 (I=30, C=30)	Standard medical management+Yoga	Standard medical management	FBG (from 163.5±14.8 to 115.6±13.7 mg/dl), HbA1c (from 10.3±0.9 to 9.1±0.6 %)	Yes*
Yadav 2013	Kumar 2016	Gwalior, India	T2DM, male, 30-55 years	30 (I=15, C=15)	Yoga	NS	FBG (from 234.5±46.9 to 127.7±15.2 mg/dl?)	NS

Kumar 2014	Thind 2017, Vizcaino 2016	Salem, India	T2DM, male, 35-60 years	30 (I=15, C=15)	Standard medical management+Yoga	Standard medical management	FBG (from 309.5±19.3 to 287.9±19.9 mg/dl)	NS
Kumpatla 2015	Thind 2017	Chennai, India	T2DM, both sexes, 25-60 years	303 (I=154, C=149)	Standard medical management+Yoga	Standard medical management	HbA1c (from 10.6±2.5 to 7.2±1.4 %)	None
Sharma 2015	Thind 2017, Vizcaino 2016	Jaipur, India	T2DM, both sexes, 35-55 years	80 (I=40, C=40)	Standard medical management+Yoga	Standard medical management	FBG (from 139.2±16.6 to 99.8±15.9 mg/dl), PPBG (from 174.1±7.9 to 141.7±8.4 mg/dl), HbA1c (from 9.3±1.0 to 7.1±0.7 %)	NS
Singh 2015	Vizcaino 2016	Gangtok?, India	T2DM, both sexes, above 20 years	337 (I-Yoga=112, I-music therapy=110, C=115)	Standard medical management+Yoga, Standard medical management+music therapy	Standard medical management	FBG (from 166.9±6.1 to 140.0±3.2 mg/dl), PPBG (from 214.1±7.6 to 173.3±5.9 mg/dl), HbA1c (from 8.6±0.6 to 7.6±0.6 %)	Yes*
Keerthi 2017		Puducherry, India	Prediabetes and T2DM with normal BP, both sexes, 18-45 years	310 (Healthy with normal BP: C=62; Prediabetes with normal BP: I=62, C=62; T2DM with normal BP: I=62, C=62)	Prediabetes and T2DM with normal BP: standard medical management+Yoga	Healthy with normal BP: no change in lifestyle; Prediabetes and T2DM with normal BP: standard medical management+walking	Prediabetes with normal BP- FBG (from 112.2±7.6 to 83.4±12.9 mg/dl); Diabetes with normal BP- FBG (from 195.4±49.9 to 152.3±31.3 mg/dl)	NS

NS=Not specified

*Limited information

^Mean±standard deviation

?Unclear

Table S3: Critical appraisal of the included nine RCTs

Author and year	Randomization method	Allocation concealment	Blinding of outcome assessors	Withdrawals and dropouts	Jadad score
Agrawal 2003	NS	NS	NS	Yes	Low
Nagarathna 2012	Yes	Yes	Yes	Yes	High
Vaishali 2011, 2012	Yes*	Yes*	NS	Yes	High
Yadav 2013	NS	NS	NS	NS	Low
Kumar 2014	NS	NS	NS	NS	Low
Kumpatla 2015	Yes±	NS	NS	Yes*	Low±
Sharma 2015	NS	NS	Yes	NS	Low
Singh 2015	Yes	Yes	NS^	Yes	High
Keerthi 2017	Yes*	Yes*	Yes	Yes*	High

NS=Not specified

*Limited information

±Not true randomization

^Data analyst was blind

Chattopadhyay K, Mishra P, Singh K, Singh K, Harris T, Hamer M, Greenfield SM, Manjunath NK, Nair R, Mukherjee S, Tandon N, Lewis SA, Kinra S, Prabhakaran D. Yoga programme for type 2 diabetes prevention (YOGA-DP) among high-risk people in India: a multicenter feasibility randomized controlled trial. *Diabetes Ther.* 2023.

In this second empirical chapter, which follows the first empirical chapter on intervention (YOGA-DP) development, a multicentre, two-arm, parallel-group, feasibility RCT was conducted in India. In other words, the feasibility of undertaking a definitive RCT was explored that will evaluate YOGA-DP's effectiveness in preventing T2DM among high-risk individuals in India. In this study, adults at high risk for T2DM (i.e., fasting blood glucose 100 to 125 mg/dL) were eligible for recruitment. In the intervention group, participants received YOGA-DP. In the control group, participants received enhanced standard care. Central randomisation was used for allocation concealment. The outcome assessors and data analysts were blinded to intervention status.



ORIGINAL RESEARCH

Yoga Programme for Type 2 Diabetes Prevention (YOGA-DP) Among High-Risk People in India: A Multicenter Feasibility Randomized Controlled Trial

Kaushik Chattopadhyay · Pallavi Mishra · Kavita Singh ·
Kalpana Singh · Tess Harris · Mark Hamer · Sheila Margaret Greenfield ·
Nandi Krishnamurthy Manjunath · Rukamani Nair · Somnath Mukherjee ·
Nikhil Tandon · Sarah Anne Lewis · Sanjay Kinra · Dorairaj Prabhakaran

Received: February 19, 2023 / Accepted: March 8, 2023
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ABSTRACT

Introduction: Many Indians are at high risk of type 2 diabetes mellitus (T2DM). The blood glucose level can be improved through a healthy lifestyle (such as physical activity and a healthy diet). Yoga can help in T2DM prevention, being a culturally appropriate approach to improving lifestyle. We developed the Yoga Programme for T2DM Prevention (YOGA-DP), a 24-week structured lifestyle education and exercise (Yoga) program that included 27 group Yoga sessions and self-practice of Yoga at home.

In this study, the feasibility of undertaking a definitive randomized controlled trial (RCT) was explored that will evaluate the intervention's effectiveness among high-risk individuals in India.

Methods: A multicenter, two-arm, parallel-group, feasibility RCT was conducted in India. The outcome assessors and data analysts were blinded. Adults with a fasting blood glucose level of 100–125 mg/dL (i.e., at high risk of T2DM) were eligible. Participants were randomized centrally using a computer-generated randomization schedule. In the intervention

K. Chattopadhyay (✉) · S. A. Lewis
Lifespan and Population Health Academic Unit,
University of Nottingham, Nottingham, UK
e-mail: kaushik.chattopadhyay@nottingham.ac.uk

P. Mishra · K. Singh · K. Singh · D. Prabhakaran
Centre for Chronic Disease Control, New Delhi,
India

T. Harris
Population Health Research Institute, St. George's
University of London, London, UK

M. Hamer
Division of Surgery and Interventional Science,
Institute of Sport, Exercise and Health, University
College London, London, UK

S. M. Greenfield
Institute of Applied Health Research, University of
Birmingham, Birmingham, UK

N. K. Manjunath
Swami Vivekananda Yoga Anusandhana Samsthana,
Bengaluru, India

R. Nair · S. Mukherjee
Bapu Nature Cure Hospital and Yogashram, New
Delhi, India

N. Tandon
Department of Endocrinology, Metabolism and
Diabetes, All India Institute of Medical Sciences,
New Delhi, India

S. Kinra
Department of Non-communicable Disease
Epidemiology, London School of Hygiene and
Tropical Medicine, London, UK

group, participants received YOGA-DP. In the control group, participants received enhanced standard care.

Results: In this feasibility trial, the recruitment of participants took 4 months (from May to September 2019). We screened 711 people and assessed 160 for eligibility. Sixty-five participants (33 in the intervention group and 32 in the control group) were randomized, and 57 (88%) participants were followed up for 6 months (32 in the intervention group and 25 in the control group). In the intervention group, the group Yoga sessions were continuously attended by 32 (97%) participants (median (interquartile range, IQR) number of sessions attended = 27 (3)). In the intervention group, Yoga was self-practiced at home by 30 (91%) participants (median (IQR) number of days per week and minutes per day self-practiced = 2 (2) and 35 (15), respectively). In the control group, one (3%) participant attended external Yoga sessions (on Pranayama) for 1 week during the feasibility trial period. There was no serious adverse event.

Conclusions: The participant recruitment and follow-up and adherence to the intervention were promising in this feasibility study. In the control group, the potential contamination was low. Therefore, it should be feasible to undertake a definitive RCT in the future that will evaluate YOGA-DP's effectiveness among high-risk people in India.

Feasibility Trial Registration: Clinical Trials Registry—India (CTRI) CTRI/2019/05/018893; registered on May 1, 2019.

Keywords: Blood glucose; Prediabetes; Prevention; Yoga; Lifestyle; Physical activity; Diet; Feasibility study; Randomized controlled trial

Key Summary Points

Many Indians are at high risk for type 2 diabetes mellitus. The blood glucose level can be improved through a healthy lifestyle (such as physical activity and a healthy diet). Yoga can help in type 2 diabetes mellitus prevention, being a culturally appropriate approach to improving lifestyle.

A multicenter, two-arm, parallel-group, feasibility randomized controlled trial was conducted in India. The outcome assessors and data analysts were blinded. Adults at high risk for type 2 diabetes mellitus were eligible. In the intervention group, participants received a Yoga program to prevent type 2 diabetes mellitus. In the control group, participants received enhanced standard care.

The participant recruitment and follow-up and adherence to the intervention were promising in this feasibility study. In the control group, the potential contamination was low. Therefore, it should be feasible to undertake a definitive randomized controlled trial in the future that will evaluate the effectiveness of the intervention among high-risk individuals in India.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder with significant health and socioeconomic consequences, and India has the

second-largest T2DM population in the world [1]. An individual at high risk of T2DM has a higher blood glucose level than normal but lower than the level for T2DM, and more than 77 million people in India are at high risk of T2DM [2]. The chances of developing T2DM and its complications are higher among these people compared to individuals with a normal blood glucose level [3]. Indians rapidly develop T2DM from the high-risk state and have one of the highest rates across many ethnicities [4]. The major risk factors for T2DM are physical inactivity and an unhealthy diet, i.e., an unhealthy lifestyle [3]. A cost-effective and sustainable strategy is to screen individuals at high risk of T2DM and provide a lifestyle intervention that is effective [3, 5, 6]. Effective lifestyle interventions can improve their blood glucose level and can have other health benefits [7–9]. However, Indians usually have a low physical activity level, and they usually consume an unhealthy diet [10–12].

Yoga, an ancient mind–body discipline, originated in the Indian subcontinent and incorporates physical activity and a healthy diet [13]. Various styles of Yoga are practiced, but one style is not necessarily superior or more authentic than another, and all focus on the same important topic, i.e., a healthy lifestyle [14]. In general, Yoga's acceptability is high in India as it fits people's health beliefs and culture [15, 16]. A gentle approach is used in Yoga, and it is safe and easy to learn, requires minimal guidance and maintenance costs, and can be practiced indoors as well as outdoors [15]. People who are old or with comorbidities can practice it [14, 15]. Yoga includes low-intensity and moderate-intensity practices (< 3.5 kcal/min and 3.5–7.0 kcal/min, respectively) [14, 17–19]. In addition, it is an activity that strengthens the muscles [14]. Therefore, Yoga can contribute to the goal of routine lifestyle advice which is given to individuals at high risk of T2DM to prevent it.

Yoga's mechanism of action in T2DM and related conditions has been reported before [20]. Briefly, its benefits on T2DM-related risk profiles seem to occur predominantly through the following pathways: (1) by decreasing the activation and reactivity of the

sympathoadrenal system and the hypothalamic–pituitary–adrenal axis, and by fostering feelings of well-being, it may lessen the effects of stress and promote multiple beneficial downstream effects on the neuroendocrine status, metabolic function, and related systemic inflammatory responses; (2) by directly stimulating the vagus nerve, it may improve the parasympathetic activity and lead to beneficial changes in the cardiovagal function, energy state, mood, and related neuroendocrine, metabolic, and inflammatory responses. Furthermore, Yoga may reduce body mass index (BMI), and the reduction in BMI lowers the risk of T2DM [3].

Effectiveness systematic reviews suggest the benefits and safety of Yoga in T2DM and related conditions [21–24]. However, the duration of most of the primary studies was short (≤ 3 months), and these studies often had significant methodological limitations. In addition, the intervention development process was not always reported, and some did not describe the intervention in detail. Even if they did, the interventions were heterogeneous. Therefore, robustly designed studies are needed to evaluate the utility of Yoga for preventing T2DM among high-risk individuals. We systematically developed the Yoga Programme for T2DM Prevention (YOGA-DP) [25]. Our aim is to conduct a definitive randomized controlled trial (RCT) in the future that will evaluate YOGA-DP's effectiveness among high-risk individuals in India compared to enhanced standard care. The chances of successful completion of the definitive RCT will improve if the feasibility of its key elements is tested before commencement [26, 27]. Therefore, the feasibility of undertaking the definitive RCT was explored in this study.

METHODS

The feasibility study protocol is published elsewhere [28].

Study Design

A multicenter, two-arm, parallel-group, feasibility RCT was conducted. The outcome assessors and data analysts were blinded.

Study Setting

We conducted this feasibility study at two Yoga centers in India, namely Bapu Nature Cure Hospital and Yogashram (BNCHY, New Delhi) in north India and Swami Vivekananda Yoga Anusandhana Samsthana (S-VYASA, Bengaluru) in south India. These centers are accessed by individuals from a range of socioeconomic backgrounds. We used three languages (English, Hindi, and Kannada) in conducting this feasibility study.

Sample Size

In a feasibility trial, a formal sample size estimation is not usually needed [29]. It is recommended to recruit at least 50 participants in a feasibility trial [30]. Thus, we recruited a total of 65 participants in this feasibility trial, after taking into consideration the loss to follow-up.

Screening and Recruitment Strategies

The following strategies were used to inform people about this feasibility study: posters were placed and pamphlets were distributed at several locations (such as in these Yoga centers, health clinics, communities, parks, and religious places) and door-to-door visits were conducted in several communities at different times of the day. Screening camps were organized at several places (such as in these Yoga centers, communities, and religious places) for identifying potential participants. After giving the participant information sheet to potential participants, describing this feasibility study to them, and answering their questions, we requested that those interested in this feasibility trial provide written informed consent. The screening was conducted after receiving written informed consent, i.e., the fasting blood glucose

level was assessed using a glucometer (by finger-prick; using either HemoCue Glucose 201⁺ System or Accu-Chek Active) [31, 32]. People with a fasting blood glucose level of 100–125 mg/dL (i.e., potentially at high risk of T2DM) [33] were requested to visit the Yoga center for eligibility assessment, including a confirmatory venous blood test using the standardized glucose oxidase–peroxidase method. This eligibility assessment was conducted after receiving further written informed consent. Blood samples collected were sent immediately to the accredited laboratories for analysis within an hour. If this was not possible for any reason, the serum was immediately separated by centrifugation and stored in a -80°C freezer for analysis on the next day.

Eligibility Criteria

People aged 18–74 years, with a fasting blood glucose level of 100–125 mg/dL (i.e., at high risk of T2DM) [33], and who were safe to do physical activities (checked using the Physical Activity Readiness Questionnaire (PAR-Q)/clinician) [34], willing and able to attend the intervention/control sessions on their own, and able to provide written informed consent were included in this feasibility study. The following people were excluded: pregnant women, those with glycated hemoglobin (HbA1c) $\geq 6.5\%$ (i.e., with T2DM [33]; venous blood test using the high-performance liquid chromatography method) or a serious or uncontrolled medical condition (e.g., cancer), or those who regularly practiced Yoga (i.e., ≥ 150 min/week) or were receiving (or had plans to receive during the feasibility trial period) any related non-pharmaceutical/pharmaceutical intervention (e.g., glucose-lowering medication).

Randomization

A computer-generated randomization schedule was used to randomize eligible participants to the intervention or control group (1:1, block randomization, stratified by sex and site). Sequential random sampling (140/group) was used, with 35 equal blocks generated using

STATA V.15. The block size was four and fixed. This central randomization was performed by an independent statistician, based at the Centre for Chronic Disease Control (CCDC), New Delhi, India, and the allocation was accessed by the recruiting site staff by telephone call. There was an exception to this rule to avoid contamination, i.e., people recruited from the same household or who were close relatives or friends were randomized to the same group. Baseline data were collected after randomization. Participants and intervention/control providers were not blinded to group allocation, but the outcome assessors and data analysts were blinded to the feasibility trial assignment.

Interventions

Intervention (YOGA-DP)

Intervention details are published elsewhere [25]. Briefly, YOGA-DP was a 24-week structured lifestyle education and exercise (Yoga) program and included 27 group Yoga sessions and self-practice of Yoga at home using the program booklet and a video. The intervention was delivered by YOGA-DP instructors, qualified and experienced Yoga teachers with formal training received on the program. The program included Shithilikarana Vyayama (loosening exercises), Surya Namaskar (sun salutation exercises), Asana (Yogic poses), Pranayama (breathing practices), and Dhyana (meditation) and relaxation practices. Female instructors were available for women. Group sessions were delivered locally (e.g., at these Yoga centers and community centers). Participants were able to join at their convenience as these sessions were run at different time points of the day (including evening and weekend sessions). We reimbursed participants' local travel costs to attend these sessions. We also invited a family member or someone close to the participant to join him/her in these sessions. After completing the program, participants were strongly encouraged to use the intervention materials and maintain a healthy lifestyle in the long term.

We ensured intervention fidelity, and YOGA-DP instructors were regularly trained on the basis of an instructor manual. In addition, we

regularly observed and evaluated these sessions using a checklist to ensure delivery according to the manual. Structured and instructive feedback was provided to them to improve their performance.

Control (Enhanced Standard Care)

No formal T2DM prevention program is available in India, although some healthcare professionals offer rudimentary advice. Therefore, in the control group, participants received the routine lifestyle advice to prevent T2DM among them in the form of a leaflet, provided by another team member (i.e., different from the YOGA-DP instructor) to avoid contamination.

Study Parameters and Data Collection

We estimated the essential parameters needed for designing the definitive RCT, e.g., participant recruitment and follow-up (for 6 months), adherence to the intervention, potential contamination in the control group, and standard deviations (SDs) of the outcomes. Details are provided in the feasibility study protocol [28]. Briefly, the following outcomes were assessed: biochemical parameters (fasting blood glucose, HbA1c, total cholesterol, high-density lipoprotein, low-density lipoprotein, very low-density lipoprotein, and triglyceride), physiological parameters (systolic blood pressure, diastolic blood pressure, and heart rate), anthropometric parameters (weight, BMI, and waist circumference), lifestyle (diet, physical activity (the International Physical Activity Questionnaire (IPAQ)-Short was used and categorized into low and moderate/high and vigorous, moderate, walking, and sitting) [35], tobacco usage, and alcohol consumption), health-related quality-of-life (the EuroQol-5D (EQ-5D) dimensions were categorized into no (level 1; no problems) and yes (level 2 to 5; problems)) [36], depression, anxiety, and stress (the Depression, Anxiety and Stress Scale (DASS) dimensions were categorized into normal and mild/moderate/severe/extremely severe) [37], and self-efficacy (for assessing confidence in participant's ability to practice Yoga) [38].

Data Analyses and Reporting

For categorical data, numbers and percentages were calculated. For continuous data, summary measures of mean or median and spread were calculated. In terms of the percentage of loss to follow-up and withdrawal, the two groups were compared using the chi-squared test. Being a feasibility trial, it was not powered to find a difference in trial outcomes at 6 months between the two trial arms. However, unadjusted mean difference (MD) or odds ratio (OR) with a 95% confidence interval (CI) were reported to indicate initial estimates of effects. Subsequently, we conducted the analysis of covariance (ANCOVA) for four critical outcomes (fasting blood glucose, HbA1c, BMI, and waist circumference), and regression coefficient and 95% CI were reported. In model 1, the respective baseline value was adjusted for; in model 2, the respective baseline value and age were adjusted for. The analysis was based on the intention-to-treat principle. There was no plan to conduct an interim analysis. STATA V.15 was used to analyze the data. The extension of the Consolidated Standards of Reporting Trials (CONSORT) statement for randomized pilot and feasibility trials was used to report the results [39].

Ethics and Related Issues

The study was conducted in accordance with the Declaration of Helsinki. The research ethics committees of the following institutes gave ethics approval: Faculty of Medicine and Health Sciences, University of Nottingham (UK), CCDC (India), BNCHY (India), and S-VYASA (India). This feasibility study was performed in accordance with relevant guidelines and regulations. We obtained written informed consent from participants. This feasibility trial was registered with the Clinical Trials Registry—India (CTRI) (CTRI/2019/05/018893; registered on May 1, 2019). India's Health Ministry's Screening Committee (HMSC) also approved this feasibility study. The independent Trial Steering Committee (TSC) monitored and supervised this feasibility study.

Serious Adverse Events

We planned to collect information on serious adverse events (including hospitalization for at least 24 h and mortality) occurring in the feasibility trial participants that might be attributed to the interventions. An independent clinician was to adjudicate the association of any such event to the interventions on the basis of medical and scientific judgment.

Participant Withdrawal

We planned to withdraw participants from the feasibility trial on the basis of their request or at the discretion of the site investigator, e.g., in case the participant was no longer safe to do physical activities (determined by PAR-Q/clinician) [34] or was diagnosed with diabetes (and would receive the standard treatment).

RESULTS

Recruitment and Follow-up

In this feasibility trial, participants were recruited from 18 May 2019 to 19 September 2019 (i.e., when the first person was approached to participate and the last participant was randomized, respectively). It took 4 months and 2 days to recruit participants. We approached 727 people to participate. Of these, 711 were screened before eligibility assessment and 160 were assessed for eligibility. Sixty-five participants (33 in the intervention group and 32 in the control group) were randomized, and this excludes deregistered participants who did not meet the inclusion criteria but were recruited or who were recruited late. Five participants were randomized to the same group as the first participant (as either they were from the same household or were close relatives or friends). Fifty-seven (88%) participants were followed up for 6 months (32 in the intervention group and 25 in the control group). There was one (3%) loss to follow-up in the intervention group and six (19%) loss to follow-up in the control group, and the difference was statistically significant

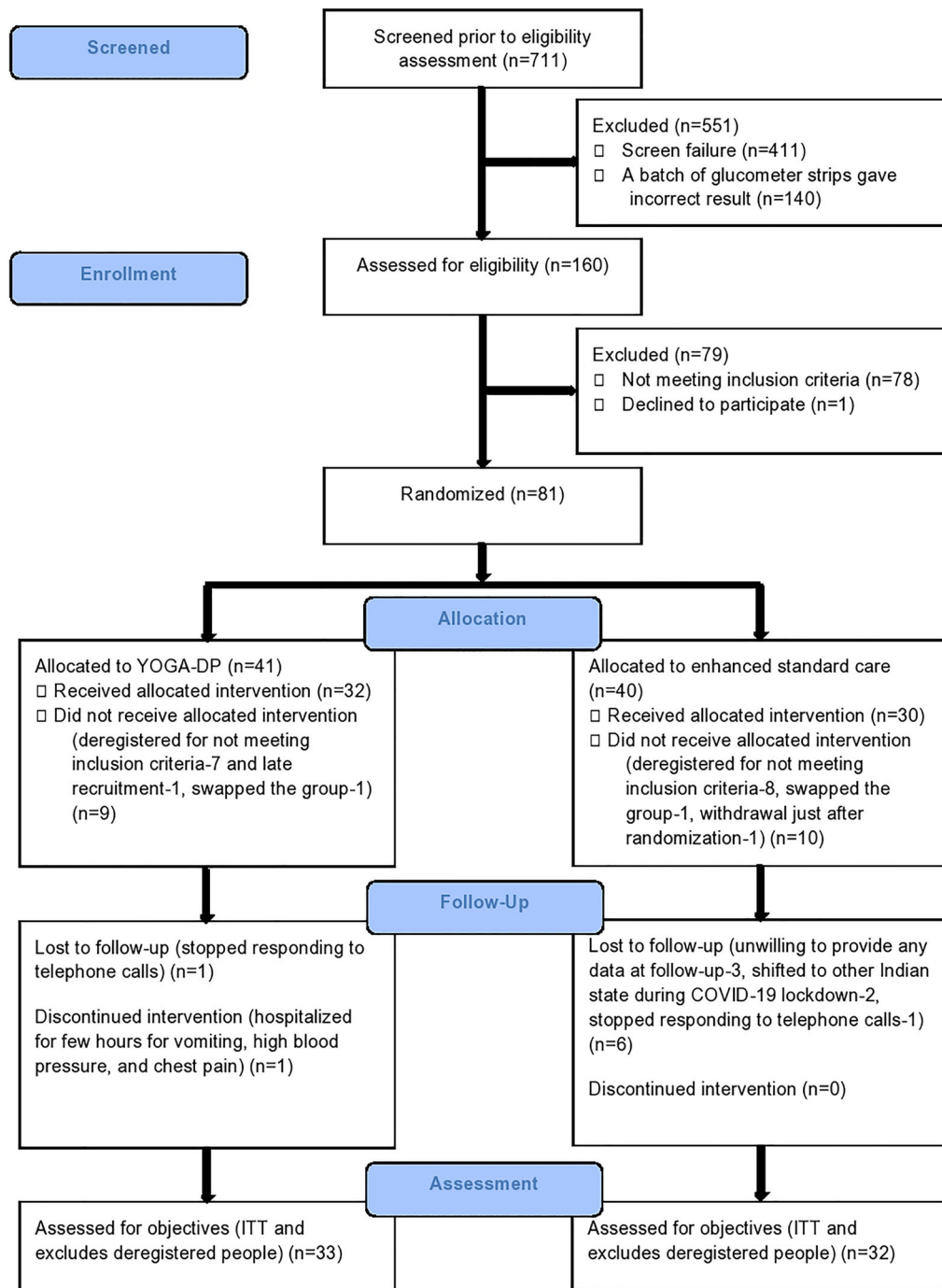


Fig. 1 CONSORT flowchart

($p = 0.04$). There was no withdrawal in the intervention group and one (3%) withdrawal in the control group, but the difference was statistically insignificant ($p = 0.31$) (see Fig. 1 CONSORT flowchart for details). As a result of

the COVID-19 lockdown in India, the follow-up of one intervention group participant was delayed and limited information was collected over the telephone from two intervention

group participants and one control group participant.

Intervention Adherence

In this feasibility study, the group Yoga sessions were continuously attended by 32 (97%) participants, and one participant discontinued because of hospitalization for a few hours for vomiting, high blood pressure, and chest pain (this was not counted as a serious adverse event). The median (interquartile range, IQR) number of group Yoga sessions attended was 27 (3). Yoga was self-practiced at home by 30 (91%) participants, and the median (IQR) number of days per week and minutes per day self-practiced was 2 (2) and 35 (15), respectively.

Potential Contamination in the Control Group

One (3%) participant attended external Yoga sessions (on Pranayama) for 1 week during the feasibility trial period (self-reported). Yoga classes were available outside, but YOGA-DP was not available externally.

Outcomes

Table 1 reports the baseline characteristics of the feasibility trial participants. The mean ($\pm$ SD) age of participants was 42.1 (7.7) years, and 25 (38%) were female. The mean ($\pm$ SD) fasting blood glucose was 110.3 (8.3) mg/dL, HbA1c was 5.9 (0.3) %, BMI was 27.6 (5) kg/m², and waist circumference was 93 (13.2) cm. At baseline, the two groups were mostly similar except for a few variables, which could be due to the small sample size.

Table 2 reports the unadjusted outcomes at 6 months.

Biochemical, physiological, and anthropometric parameters—The fasting blood glucose, HbA1c, weight, BMI, and waist circumference were lower in the intervention group compared to the control, but the differences were statistically insignificant. The high-density lipoprotein was higher in the intervention group compared

to the control, but the difference was statistically insignificant.

Lifestyle—The percentage of participants reporting no/occasional intake of high-fat/deep-fried food was higher in the intervention group compared to the control. The moderate physical activity time was higher in the intervention group compared to the control, but the difference was statistically insignificant. Sitting time was lower in the intervention group compared to the control, but the difference was statistically insignificant. The percentage of participants reporting no tobacco usage was higher in the intervention group compared to the control. In addition, the odds of tobacco usage were lower in the intervention group compared to the control, but the difference was statistically insignificant.

Health-related quality-of-life—The percentage of participants reporting no problems in all five dimensions of EQ-5D was higher in the intervention group compared to the control. In addition, the odds of problems in the three dimensions (mobility problems, problems in taking self-care, and problems in doing usual activities) were lower in the intervention group compared to the control, but the differences were statistically insignificant. The visual analog scale score was higher in the intervention group compared to the control, but the difference was statistically insignificant.

Depression, anxiety, and stress—The percentage of participants reporting no problems in all three dimensions of DASS was higher in the intervention group compared to the control.

Self-efficacy in Yoga practice—The self-efficacy was higher in the intervention group compared to the control, but the difference was statistically insignificant.

Table 3 reports the adjusted four critical outcomes at 6 months.

Fasting blood glucose, HbA1c, BMI, and waist circumference—After adjustment for the respective baseline value (model 1) and baseline value and age (model 2), BMI was found to be lower in the intervention group compared to the control, and the difference was statistically significant (regression coefficient -0.56 ; 95% CI -1.00 to -0.11 and regression

Table 1 Baseline characteristics of the feasibility trial participants

	YOGA-DP, N = 33	Enhanced standard care, N = 32
Age (years)	41.3 (7.4)	42.8 (8.0)
Sex		
Male	20/33 (61%)	20/32 (62%)
Female	13/33 (39%)	12/32 (38%)
Mother tongue (language)		
Indo-Aryan	23/33 (70%)	22/32 (69%)
Dravidian	10/33 (30%)	9/32 (28%)
Sino-Tibetan	0/33 (0%)	1/32 (3%)
Married	33/33 (100%)	32/32 (100%)
Formal education of > 10 years	25/33 (76%)	20/32 (62%)
Employed	16/33 (48%)	11/31 (35%)
Gross monthly household income (₹)	26,896.8 (32,303.9)	47,322.6 (50,708.6)
Obesity	6/33 (18%)	4/30 (13%)
Hypertension	2/33 (6%)	1/32 (3%)
Dyslipidemia	0/32 (0%)	1/30 (3%)
Coronary heart disease	0/33 (0%)	0/32 (0%)
Stroke	0/33 (0%)	0/32 (0%)
Peripheral arterial disease	0/33 (0%)	0/32 (0%)
Family history of diabetes	14/31 (45%)	14/32 (44%)
Fasting blood glucose (mg/dL)	110.3 (8.0)	110.4 (8.7)
HbA1c (%)	5.9 (0.3)	5.9 (0.4)
Total cholesterol (mg/dL)	200.7 (43.7)	206.3 (41.0)
High-density lipoprotein (mg/dL)	45.0 (11.9)	45.7 (13.7)
Low-density lipoprotein (mg/dL)	118.9 (29.1)	120.5 (27.2)
Very low-density lipoprotein (mg/dL)	29.5 (18.4)	30.5 (16.5)
Triglyceride (mg/dL)	148.5 (92.2)	140.9 (66.3)
Systolic blood pressure (mmHg)	115.2 (9.8)	117.1 (12.7)
Diastolic blood pressure (mmHg)	74.7 (8.4)	74.2 (8.7)
Heart rate (beats/min)	79.0 (11.8)	81.7 (13.0)
Weight (kg)	69.0 (14.7)	69.8 (11.6)
Height (cm)	160.3 (11.2)	157.4 (8.8)
BMI (kg/m ²)	26.9 (5.6)	28.2 (4.4)

Table 1 continued

	YOGA-DP, N = 33	Enhanced standard care, N = 32
Waist circumference (cm)	91.1 (15.1)	94.9 (10.8)
Diet		
High-fat/deep-fried food		
No	3/33 (9%)	4/32 (13%)
Occasionally	10/33 (30%)	15/32 (47%)
Regularly (at least 3–4 times/week)	20/33 (61%)	13/32 (40%)
Fruit and vegetables		
< 5 portions/day	27/33 (82%)	27/32 (84%)
≥ 5 portions/day	6/33 (18%)	5/32 (16%)
Physical activity (IPAQ-Short)		
Low	7/26 (27%)	6/22 (27%)
Moderate	19/26 (73%)	16/22 (73%)
High	0/26 (0%)	0/22 (0%)
Vigorous (mins/week)	210.0 (160.6)	210.0 (110.6)
Vigorous (mins/week) ^a	195.0 (75.0–345.0)	255.0 (90.0–300.0)
Moderate (mins/week)	152.0 (205.9)	10.0 (*)
Moderate (mins/week) ^a	52.5 (20.0–300.0)	10.0 (10.0–10.0)
Walking (mins/week)	40.2 (18.9)	40.4 (30.3)
Walking (mins/week) ^a	30.0 (30.0–60.0)	30.0 (20.0–45.0)
Sitting (mins/day)	333.9 (174.3)	339.0 (186.0)
Sitting (mins/day) ^a	360.0 (180.0–480.0)	360.0 (180.0–450.0)
Current tobacco usage	1/33 (3%)	4/32 (12%)
Current alcohol consumption	2/33 (6%)	1/32 (3%)
Health-related quality-of-life (EQ-5D)		
Mobility problems	6/33 (18%)	6/32 (19%)
Problems in taking self-care	2/33 (6%)	2/32 (6%)
Problems in doing usual activities	4/33 (12%)	2/32 (6%)
Pain/discomfort	13/33 (39%)	11/32 (34%)
Anxiety/depression	9/33 (27%)	7/31 (23%)
Visual analog scale score (0 to 100)	69.8 (19.1)	69.0 (16.5)
Depression, anxiety, and stress (DASS)		
Depression ^b	2/33 (6%)	3/32 (9%)

Table 1 continued

	YOGA-DP, <i>N</i> = 33	Enhanced standard care, <i>N</i> = 32
Anxiety ^b	2/33 (6%)	4/32 (12%)
Stress ^b	2/33 (6%)	2/32 (6%)
Self-efficacy in Yoga practice (0 to 100)	71.5 (22.8)	70.3 (20.2)

Values are mean ($\pm$ SD) or *n/N* (%) unless otherwise indicated

*Not enough data to calculate

^aValues are median (IQR)

^bMild/moderate/severe/extremely severe

coefficient -0.56 ; 95% CI -1.02 to -0.11 , respectively). In addition, fasting blood glucose, HbA1c, and waist circumference were lower, but the differences were statistically insignificant.

Serious Adverse Events

There was no serious adverse event.

DISCUSSION

We conducted a multicenter feasibility RCT in India to assess the feasibility of undertaking the definitive RCT in the future that will evaluate YOGA-DP's effectiveness among high-risk individuals in India. The participant recruitment and follow-up and adherence to the intervention were promising in this feasibility study. There was low potential contamination in the control group. Compared to other T2DM prevention RCTs in India and globally [27, 40], the recruitment in this feasibility trial was without any major hurdles. In this feasibility study, the dropout rate was 12% which is consistent with the findings of a systematic review (less than 15–20% in most RCTs on Yoga interventions) [41]. The only follow-up-related challenge we faced was towards the end of this feasibility trial, and this was due to the COVID-19 lockdown in India. Therefore, it should be feasible to undertake a definitive RCT. This feasibility study provided estimates of important parameters needed for designing the definitive RCT.

In the definitive RCT, the first co-primary outcome will be the incidence of T2DM,

indicated by either a fasting blood glucose level of at least 126 mg/dL or an HbA1c level of at least 6.5% at 1-year follow-up [3]. Repeat testing will be conducted in asymptomatic participants to confirm the diagnosis [3], and they will only be included as achieving the co-primary outcome if repeat testing of either fasting blood glucose or HbA1c is above the cutoff. The second co-primary outcome will be BMI at 1-year follow-up [42]. The reduction in BMI lowers the risk of T2DM [3]. It should be noted that compared to other ethnicities, South Asians are at higher risk of T2DM at equivalent BMI levels [43]. We expect that the cumulative incidence of T2DM over 1 year will be 18% in the control group [44, 45]. In the intervention group, we will be interested in a 50% reduction in the cumulative incidence of T2DM [46, 47]. Therefore, in the definitive RCT, we will need to recruit at least 356 participants per group (a total of 712), with 90% power and assuming significance (alpha; two-tailed) of 2.5% to conservatively allow for co-primary outcomes. This sample size will be sufficient for the other primary outcome, considering the mean ($\pm$ SD) BMI at the baseline was 27.6 (5) kg/m² in this feasibility trial and our interest in at least a 5% reduction in BMI at 1 year in the intervention group [42, 48].

Initial estimates (as this feasibility trial was not powered for effectiveness) show some beneficial effects of the intervention on many critical outcomes, including fasting blood glucose, HbA1c, BMI, and waist circumference. In the adjusted models, BMI was lower in the intervention group compared to the control and the

Table 2 Unadjusted outcomes at 6 months

	YOGA-DP, N = 33	Enhanced standard care, N = 32	Unadjusted MD/OR (95% CI)
Fasting blood glucose (mg/dL)	104.5 (12.0)	107.6 (11.8)	− 3.19 (− 9.60, 3.23)
HbA1c (%)	5.6 (0.4)	5.6 (0.5)	− 0.07 (− 0.32, 0.18)
Total cholesterol (mg/dL)	219.9 (66.7)	207.6 (62.7)	12.32 (− 22.68, 47.33)
High-density lipoprotein (mg/dL)	52.6 (15.4)	49.4 (16.4)	3.27 (− 5.35, 11.89)
Low-density lipoprotein (mg/dL)	139.6 (46.9)	126.0 (40.0)	13.57 (− 10.27, 37.41)
Very low-density lipoprotein (mg/dL)	28.5 (18.3)	27.5 (15.2)	1.00 (− 8.23, 10.23)
Triglyceride (mg/dL)	153.8 (106.0)	139.2 (76.9)	14.58 (− 36.16, 65.32)
Systolic blood pressure (mmHg)	121.4 (11.2)	119.8 (13.4)	1.67 (− 4.82, 8.15)
Diastolic blood pressure (mmHg)	78.2 (7.3)	76.3 (8.6)	1.92 (− 2.25, 6.10)
Heart rate (beats/min)	77.8 (7.1)	79.0 (9.3)	− 1.15 (− 5.47, 3.17)
Weight (kg)	69.1 (14.3)	68.9 (11.2)	− 0.27 (− 6.61, 7.14)
BMI (kg/m ²)	26.5 (5.0)	28.3 (4.1)	− 1.74 (− 4.19, 0.72)
Waist circumference (cm)	89.6 (15.2)	93.8 (9.7)	− 4.19 (− 11.07, 2.68)
Diet			
High-fat/deep-fried food			
No/occasionally	20/32 (62%)	16/26 (61%)	Ref
Regularly (at least 3–4 times/week)	12/32 (38%)	10/26 (39%)	1.07 (0.36, 3.16)
Fruit and vegetables			
< 5 portions/day	28/32 (88%)	20/26 (77%)	Ref
≥ 5 portions/day	4/32 (12%)	6/26 (23%)	0.45 (0.11, 1.82)
Physical activity (IPAQ-Short)			
Low	5/28 (18%)	0/21 (0%)	
Moderate/high	23/28 (82%)	21/21 (100%)	*
Vigorous (mins/week)	155.0 (204.8)	270.0 (52.0)	− 115 (− 453.6, 223.6)
Vigorous (mins/week) ^a	60.0 (15.0–390.0)	300.0 (210.0–300.0)	–
Moderate (mins/week)	72.5 (112.7)	23.6 (18.4)	48.9 (− 43.6, 141.5)
Moderate (mins/week) ^a	37.5 (30.0–60.0)	15.0 (10.0–30.0)	–
Walking (mins/week)	37.5 (15.8)	48.3 (29.7)	− 10.8 (− 24.5, 3.0)
Walking (mins/week) ^a	30.0 (30.0–60.0)	42.5 (30.0–60.0)	–
Sitting (mins/day)	160.3 (144.4)	242.0 (224.9)	− 81.6 (− 184.9, 21.7)
Sitting (mins/day) ^a	120.0 (30.0–240.0)	120.0 (30.0–420.0)	–

Table 2 continued

	YOGA-DP, <i>N</i> = 33	Enhanced standard care, <i>N</i> = 32	Unadjusted MD/OR (95% CI)
Tobacco usage			
Never/past	32/33 (97%)	28/32 (88%)	Ref
Current	1/33 (3%)	4/32 (12%)	0.22 (0.02, 2.07)
Alcohol consumption			
Never/past	31/33 (94%)	31/32 (97%)	Ref
Current	2/33 (6%)	1/32 (3%)	2.00 (0.17, 23.21)
Health-related quality-of-life (EQ-5D)			
Mobility problems			
No	29/32 (91%)	20/26 (77%)	Ref
Yes	3/32 (9%)	6/26 (23%)	0.41 (0.09, 1.93)
Problems in taking self-care			
No	31/32 (97%)	20/26 (77%)	Ref
Yes	1/32 (3%)	6/26 (23%)	0.13 (0.01, 1.19)
Problems in doing usual activities			
No	27/32 (84%)	20/26 (77%)	Ref
Yes	5/32 (16%)	6/26 (23%)	0.21 (0.04, 1.16)
Pain/discomfort			
No	32/32 (100%)	18/26 (69%)	
Yes	0/32 (0%)	8/26 (31%)	*
Anxiety/depression			
No	32/32 (100%)	21/26 (81%)	
Yes	0/32 (0%)	5/26 (19%)	*
Visual analog scale score (0 to 100)	76.6 (13.1)	71.2 (12.0)	5.43 (− 1.33, 10.18)
Depression, anxiety, and stress (DASS)			
Depression			
Normal	32/32 (100%)	24/26 (92%)	
Mild/moderate/severe/extremely severe	0/32 (0%)	2/26 (8%)	*
Anxiety			
Normal	32/32 (100%)	22/26 (85%)	
Mild/moderate/severe/extremely severe	0/32 (0%)	4/26 (15%)	*

Table 2 continued

	YOGA-DP, <i>N</i> = 33	Enhanced standard care, <i>N</i> = 32	Unadjusted MD/OR (95% CI)
Stress			
Normal	32/32 (100%)	25/26 (96%)	
Mild/moderate/severe/extremely severe	0/32 (0%)	1/26 (4%)	*
Self-efficacy in Yoga practice (0 to 100)	74.1 (15.0)	68.5 (20.7)	4.86 (− 4.64, 14.37)

Values are mean ($\pm$ SD) or *n/N* (%) unless otherwise indicated

^aValues are median (IQR)

*Not enough data to calculate

Table 3 Adjusted four critical outcomes at 6 months

	YOGA-DP, <i>N</i> = 33	Enhanced standard care, <i>N</i> = 32	Model 1* Regression coefficient (95% CI)	Model 2** Regression coefficient (95% CI)
Fasting blood glucose (mg/dL)	104.5 (12.0)	107.6 (11.8)	− 3.96 (− 9.81, 1.89)	− 3.79 (− 9.72, 2.13)
HbA1c (%)	5.6 (0.4)	5.6 (0.5)	− 0.07 (− 0.29, 0.16)	− 0.05 (− 0.28, 0.18)
BMI (kg/m ²)	26.5 (5.0)	28.3 (4.1)	− 0.56 (− 1.00, − 0.11)	− 0.56 (− 1.02, − 0.11)
Waist circumference (cm)	89.6 (15.2)	93.8 (9.7)	− 1.92 (− 4.91, 1.06)	− 1.89 (− 4.90, 1.12)

Values are mean ($\pm$ SD) unless otherwise indicated

*ANCOVA analysis adjusted for the respective baseline value

**ANCOVA analysis adjusted for the respective baseline value and age

difference was statistically significant. No serious adverse events occurred. Similar beneficial effects and safety of Yoga on T2DM-related outcomes have been synthesized in several effectiveness systematic reviews [21–24]. In the future, the adequately powered definitive RCT will be able to provide a clear answer.

In the definitive RCT, if YOGA-DP is found to be effective, it will be a need-sensitive and evidence-based intervention for preventing T2DM among high-risk individuals, not only in India but also globally. Yoga's popularity is not

restricted to India and other South Asian countries, and it is increasingly becoming popular in other nations [49, 50]. T2DM and its associated costs are global concerns, and a low-cost intervention to prevent T2DM will be of worldwide interest. More evidence-based choices will be available to people for preventing T2DM. The future burden of T2DM (such as clinical, personal, and economic) on patients, families, health systems, and economies will be prevented. The prevention of T2DM may extend to the prevention of its complications.

Individuals will become healthier overall, and the intervention may empower people at the same time for managing their health. The intervention has become even more relevant during the COVID-19 pandemic, as it can be delivered online or in-person (outdoors or indoors by following the social distancing rules), and Yoga can be self-practiced at home.

Semi-structured qualitative interviews (as part of the qualitative process evaluation) were conducted with feasibility trial non-participants, participants, YOGA-DP instructors, and staff to explore trial- and intervention-related barriers and facilitators [28, 51, 52]. The findings will inform decisions on modifying the definitive RCT and intervention to further improve participation and adherence. For example, the intervention duration was 6 months in this feasibility trial, and we intend to deliver a year-long intervention in the definitive RCT. The relatively short-term follow-up was another limitation in this feasibility trial, and we intend to do long-term follow-ups (at least for a year) in the definitive RCT. In terms of glycemic control, this feasibility trial gave some hints about the effectiveness of the intervention, and we intend to assess the cumulative incidence of T2DM in the definitive RCT as a co-primary outcome. We reimbursed participants' local travel costs for attending the Yoga sessions at BNCHY, and at SVYASA, Yoga sessions were run locally and close to their residence. The reimbursement could have boosted participant recruitment and follow-up in this feasibility trial and adherence to the intervention; however, this would not be available in real-world settings.

CONCLUSIONS

The participant recruitment and follow-up and adherence to the intervention were promising in this feasibility study. In the control group, the potential contamination was low. Therefore, it should be feasible to undertake a definitive RCT in the future that will evaluate YOGA-DP's effectiveness among high-risk individuals in India.

ACKNOWLEDGMENT

The authors would like to thank the funding agencies, participants, and TSC members, namely Prof. Nitin Kapoor (chair), Prof. Mohammed K Ali, Dr. Ajay Vamadevan, and Dr. Dimple Kondal.

Funding. The study was funded by the UK's FCDO/MRC/NIHR/Wellcome Trust Joint Global Health Trials (MR/R018278/1). The funding agencies had no role in designing the study or in writing the manuscript. The publication fee was covered through the UKRI block grant.

Author Contributions. KC wrote the first draft of the manuscript. PM, KavS, KalS, TH, MH, SMG, NKM, RN, SM, NT, SAL, SK, and DP contributed significantly to the revision of the manuscript. All the authors read and approved the final manuscript.

List of Investigators. KC (Principal Investigator) conceptualized and designed the study with the help of Co-Investigators (TH, MH, SMG, NKM, NT, SAL, SK, and DP).

Prior Presentation. The study abstract was selected for presentation at the International Diabetes Federation (IDF) Congress 2021 (held virtually from 6 to 11 December 2021 due to the COVID-19 pandemic) and published in the event material. <https://doi.org/10.26226/morressier.617c37317c09fc044a9751b2>.

Disclosures. KC, PM, KavS, KalS, TH, MH, SMG, NKM, RN, SM, NT, SAL, SK, and DP have nothing to disclose.

Compliance with Ethics Guidelines. The study was conducted in accordance with the Declaration of Helsinki. The research ethics committees of the following institutes gave ethics approval: Faculty of Medicine and Health Sciences, University of Nottingham, UK (14-1805); CCDC, India (CCDC_IEC_09_2018); BNCHY, India (BNCHY/IEC/2/2019); and S-VYASA, India (RES/IEC-SVYASA/138/2018). We obtained written informed consent from participants.

Data Availability. The data set generated during the current study is available from the corresponding author on reasonable request.

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Chattopadhyay K, Wang H, Kaur J, Nalbant G, Almaqhawi A, Kundakci B, Panniyammakal J, Heinrich M, Lewis SA, Greenfield SM, Tandon N, Biswas TK, Kinra S, Leonardi-Bee J. Effectiveness and safety of Ayurvedic medicines in type 2 diabetes mellitus management: a systematic review and meta-analysis. *Front Pharmacol.* 2022;13:821810.

In this third empirical chapter, a comprehensive systematic review and meta-analysis was conducted to synthesise evidence on the effectiveness and safety of Ayurvedic medicines for managing T2DM. The JBI systematic review methodology was followed. Published and unpublished RCTs assessing the effectiveness and safety of Ayurvedic medicines for managing T2DM in adults were included. A comprehensive search of sources (including 18 electronic databases) was performed from inception to 16 January 2021. No language restrictions were applied. Data synthesis was conducted using narrative synthesis and random effects meta-analyses.



Effectiveness and Safety of Ayurvedic Medicines in Type 2 Diabetes Mellitus Management: A Systematic Review and Meta-Analysis

Kaushik Chattopadhyay^{1,2*}, Haiquan Wang¹, Jaspreet Kaur¹, Gamze Nalbant¹, Abdullah Almaqhawi³, Burak Kundakci¹, Jeemon Panniyammakal⁴, Michael Heinrich⁵, Sarah Anne Lewis¹, Sheila Margaret Greenfield⁶, Nikhil Tandon⁷, Tuhin Kanti Biswas⁸, Sanjay Kinra⁹ and Jo Leonardi-Bee^{1,2}

OPEN ACCESS

Edited by:

Alexander N. Shikov,
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Malaysia

*Correspondence:

Kaushik Chattopadhyay
kaushik.chattopadhyay@
nottingham.ac.uk

Specialty section:

This article was submitted to
Ethnopharmacology,
a section of the journal
Frontiers in Pharmacology

Received: 24 November 2021

Accepted: 07 April 2022

Published: 08 June 2022

Citation:

Chattopadhyay K, Wang H, Kaur J,
Nalbant G, Almaqhawi A, Kundakci B,
Panniyammakal J, Heinrich M,
Lewis SA, Greenfield SM, Tandon N,
Biswas TK, Kinra S and
Leonardi-Bee J (2022) Effectiveness
and Safety of Ayurvedic Medicines in
Type 2 Diabetes Mellitus Management:
A Systematic Review and Meta-
Analysis.
Front. Pharmacol. 13:821810.
doi: 10.3389/fphar.2022.821810

¹Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, United Kingdom, ²The Nottingham Centre for Evidence-Based Healthcare: A JBI Centre of Excellence, Nottingham, United Kingdom, ³Department of Family and Community Medicine, College of Medicine, King Faisal University, Alahsa, Saudi Arabia, ⁴Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, India, ⁵Centre for Pharmacognosy and Phytotherapy, School of Pharmacy, University College London, London, United Kingdom, ⁶Institute of Applied Health Research, University of Birmingham, Birmingham, United Kingdom, ⁷Department of Endocrinology, Metabolism and Diabetes, All India Institute of Medical Sciences, New Delhi, India, ⁸Department of Kayachikitsa, J B Roy State Ayurvedic Medical College and Hospital, Kolkata, India, ⁹Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom

Introduction: Many Ayurvedic medicines have the potential for managing type 2 diabetes mellitus (T2DM), with previous systematic reviews demonstrating effectiveness and safety for specific Ayurvedic medicines. However, many of the reviews need updating and none provide a comprehensive summary of all the Ayurvedic medicines evaluated for managing T2DM.

Objective: The objective of this systematic review was to evaluate and synthesize evidence on the effectiveness and safety of Ayurvedic medicines for managing T2DM.

Inclusion criteria: Published and unpublished RCTs assessing the effectiveness and safety of Ayurvedic medicines for managing T2DM in adults.

Methods: The JBI systematic review methodology was followed. A comprehensive search of sources (including 18 electronic databases) from inception to 16 January 2021 was made. No language restrictions were applied. Data synthesis was conducted using narrative synthesis and random effects meta-analyses, where appropriate. Pooled results are reported as mean differences (MD) with 95% confidence intervals (CI).

Results: Out of 32,519 records identified from the searches, 219 articles were included in the systematic review representing 199 RCTs (21,191 participants) of 98 Ayurvedic medicines. Overall, in the studies reviewed the methodology was not adequately reported, resulting in poorer methodological quality scoring. Glycated hemoglobin (HbA1c) was reduced using *Aegle marmelos* (L.) Corrêa (MD -1.6%; 95% CI -3 to -0.3), *Boswellia serrata* Roxb. (-0.5; -0.7 to -0.4), *Gynostemma pentaphyllum* (Thunb.)

Makino (−1; −1.5 to −0.6), *Momordica charantia* L. (−0.3; −0.4 to −0.1), *Nigella sativa* L. (−0.4; −0.6 to −0.1), *Plantago ovata* Forssk. (−0.9; −1.4 to −0.3), *Tinospora cordifolia* (Willd.) Hook.f. and Thomson (−0.5; −0.6 to −0.5), *Trigonella foenum-graecum* L. (−0.6; −0.9 to −0.4), and *Urtica dioica* L. (−1.3; −2.4 to −0.2) compared to control. Similarly, fasting blood glucose (FBG) was reduced by 4–56 mg/dl for a range of Ayurvedic medicines. Very few studies assessed health-related quality of life (HRQoL). Adverse events were not reported in many studies, and if reported, these were mostly none to mild and predominately related to the gastrointestinal tract.

Conclusion: The current evidence suggests the benefit of a range of Ayurvedic medicines in improving glycemic control in T2DM patients. Given the limitations of the available evidence and to strengthen the evidence base, high-quality RCTs should be conducted and reported.

Keywords: ayurveda, effectiveness, meta-analysis, safety, systematic review, type 2 diabetes mellitus

1 INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex disorder that has major health, social, and economic consequences. (European Medicines Agency, 2018; International Diabetes Federation, 2019) Chronic hyperglycemia is associated with macro- and micro-vascular complications and even death. (European Medicines Agency, 2018; International Diabetes Federation, 2019) Ayurveda is a dominant traditional medical system that has been used for thousands of years in many South Asian countries. (Sharma et al., 2007) In Ayurveda, the corresponding term for diabetes mellitus is madhumeha (madhu means “sweetness” and meha means “excessive urination”). (Ministry of Ayush, 2016; Central Council for Research in Ayurvedic Sciences, 2017) Classical Ayurvedic texts, written in Sanskrit, have described this condition and its management in detail. (Ministry of Ayush, 2016; Central Council for Research in Ayurvedic Sciences, 2017) Briefly, a multi-pronged and individualized approach is used to manage the condition such as through lifestyle modification (including diet), Ayurvedic detoxifying and purifying therapies (e.g., Panchakarma), and Ayurvedic medicines (containing plant-, animal- or mineral-origin ingredients—single or in combination). It is hypothesized that many of these medicines work through pancreatic as well as extrapancreatic effects. (Ministry of Ayush, 2016; Central Council for Research in Ayurvedic Sciences, 2017) T2DM is one of the main diseases for which patients consult Ayurvedic practitioners and use Ayurvedic medicines, often continuously from the point of diagnosis. (Mehrotra et al., 2004; Kumar et al., 2006; Priya and Shweta, 2010; Chandra, 2011; Bhalerao et al., 2013; Chandra, 2013) Ayurveda is commonly used by patients as it fits with their health beliefs and culture; thus, its acceptability, satisfaction, and perceived relief are usually high, especially among rural, poor, older, and indigenous/minority populations. (Chacko, 2003; Bhalerao et al., 2013) Many T2DM patients prefer not to use Western medicines due to the associated side effects, cost, and mode of administration (e.g., injections). (Chandra, 2011; Bhalerao et al., 2013; Chandra, 2013)

Previous systematic reviews of clinical trials suggest beneficial effects of several Ayurvedic medicines on T2DM-related

outcomes, including improvement in blood glucose, with no major safety issues. (Hardy et al., 2001; Shekelle et al., 2005; Sridharan et al., 2011) However, they are now outdated, and one was limited in scope in terms of the Ayurvedic medicines considered. The evidence base over the past 10 years has grown substantially, thereby highlighting the need to refocus and update the reviews to provide contemporary estimates of effect and safety for all the Ayurvedic medicines for the management of T2DM. Additionally, the review findings will be used to guide the development of a clinical guideline for managing T2DM using Ayurvedic medicines.

2 REVIEW QUESTIONS

- i) Are Ayurvedic medicines effective in controlling blood glucose levels in T2DM patients?
- ii) Are Ayurvedic medicines effective in improving health-related quality of life (HRQoL) for T2DM patients?
- iii) Are Ayurvedic medicines safe for use by T2DM patients?

3 MATERIALS AND METHODS

The systematic review process adhered to the JBI Systematic Reviews of Effectiveness guidance and was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (Moher et al., 2009; Tufanaru et al., 2017) This review was conducted according to a *a priori* published protocol, (Chattopadhyay et al., 2020a) and registered with PROSPERO (CRD42018118285).

3.1 Inclusion Criteria

3.1.1 Participants

The systematic review included studies conducted among adults (≥18 years) with T2DM, irrespective of associated comorbidities (e.g., obesity, hypertension, dyslipidemia) or T2DM complications (such as macro- or micro-vascular). Both newly

diagnosed T2DM/treatment naïve, as well as existing cases/on treatment, were eligible. Studies with mixed populations, e.g., adults and children, were included if the mean age of the participants was ≥ 18 years or the study findings were reported separately for adults. Studies that included participants with type 1 diabetes were excluded unless it was possible to extract the data on T2DM participants.

3.1.2 Interventions

Studies were included if they assessed any classical or proprietary Ayurvedic medicine (such as containing plant- or mineral-origin ingredients—single or in combination) in any form (e.g., tablets, capsules, powder, decoction) and administered for at least 8 weeks. Cross-checking of the eligibility of Ayurvedic medicine (to distinguish it from traditional Chinese and Western medicines) was performed by Ayurveda experts in the team *via* searching the Indian Medicinal Plants Database (<http://medicinalplants.in>), Encyclopedia on Indian Medicinal Plants (<http://envs.frlht.org/implad>), Traditional Knowledge Digital Library (<http://www.tkdlib.res.in>), Ayurvedic Pharmacopoeia of India, and Ayurvedic Formulary of India. Studies on multi-modal interventions that included Ayurvedic medicine were included if it was possible to extract data relating to Ayurvedic medicine. To distinguish between Ayurvedic medicines and dietary ingredients, studies were excluded where medicines were used as dietary ingredients or foods. In addition, Ayurvedic detoxifying and purifying therapies (e.g., Panchakarma) were beyond the scope of this review.

3.1.3 Comparators

Studies comparing Ayurvedic medicines with no intervention, placebo (as defined by the study authors), non-pharmaceutical intervention (e.g., yoga), or pharmaceutical intervention (i.e., Western oral antidiabetic drug [OAD] or head-to-head comparison with another Ayurvedic medicine) were eligible for inclusion in the review. Co-intervention was allowed if all the eligible study arms received the same co-intervention. If a study had multiple treatment arms (multi-arms), the authors only included the arms that met the review inclusion criteria. Studies comparing two or more drug manufacturing processes, forms or timings of administration, doses, or Anupans (Ayurvedic medicines are usually taken with an Anupan, a carrier substance such as a liquid drink) of the same Ayurvedic medicine without any other comparator were excluded.

3.1.4 Outcomes

The following outcomes were included:

- Primary outcomes: blood glucose (i.e., glycated hemoglobin [HbA1c], fasting blood glucose [FBG]), HRQoL, and adverse events.
- Secondary outcomes: postprandial blood glucose (PPBG), fasting and stimulated insulin, fasting and stimulated C-peptide, insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR]), body weight, body mass index (BMI), waist circumference, systolic blood pressure (SBP), diastolic blood pressure

(DBP), heart rate, and serum lipid (i.e., total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], triglycerides [TG]).

The timing of outcome measurement had to be at least 8 weeks from randomization since this is the recommended minimum time for T2DM management studies. (Sridharan et al., 2011; European Medicines Agency, 2018) The management of complications of T2DM was beyond the scope of this review.

3.1.5 Types of Studies

The review included RCTs, of any design. Only the first phase of cross-over trials was included to avoid any carry-over of treatment effect.

3.2 Search Strategy

The authors searched for both published and unpublished studies via the following electronic databases and gray literature sources: MEDLINE (Ovid; from 1946), Embase (Ovid; from 1974), CINAHL (EBSCOhost; from 1937), PsycINFO (Ovid; from 1806), Web of Science (from 1900), Cochrane Central Register of Controlled Trials (CENTRAL; from 1996), Allied and Complementary Medicine Database (AMED; Ovid; from 1985), International Pharmaceutical Abstracts (Ovid; from 1970), Turning Research Into Practice (TRIP; from 1997), AYUSH Research Portal (a database of Ayurveda and other research articles; <http://ayushportal.nic.in>), Digital Helpline for Ayurveda Research Articles (DHARA; <http://dharaonline.org>), A Bibliography of Indian Medicine (ABIM; <http://indianmedicine.eldoc.ub.rug.nl>), CAM-QUEST (a database of complementary and alternative medicine research articles; <https://www.camquest.org/en>), Directory of Open Access Journals, EthOS, OpenGrey, and ProQuest Dissertations and Theses. The databases were searched on 16th January 2021. The search strategies are detailed in **Supplementary Appendix S1**, which were developed based on the previous systematic reviews and clinical guidelines on this topic (Hardy et al., 2001; Shekelle et al., 2005; Central Council for Research in Ayurvedic Sciences, 2011; Sridharan et al., 2011; National Institute for Health and Care Excellence, 2015; Ministry of Ayush, 2016; Ministry of Health and Family Welfare, 2016; Central Council for Research in Ayurvedic Sciences, 2017; Central Council for Research in Ayurvedic Sciences and Directorate General of Health Services, 2018) and in consultation with an experienced information specialist. A combination of search terms and index terms was used. No language restrictions were applied, and an external company was hired for professional translations. Similarly, no date restrictions were applied. Furthermore, Researches in Ayurveda and Ayurvedic Research Database (ARD; databases of Ayurveda-related dissertations and theses; seventh edition; 2001–2008; <https://ayurvedahealthcare.info>) was searched for additional studies. The reference list of relevant previous systematic reviews and included studies and the tables of content of 48 Ayurveda journals were screened till 16th January 2021 for additional studies. Relevant experts in the field were contacted (at least twice through email), including

the Central Council for Research in Ayurvedic Sciences (Ministry of Ayush, India) and authors of the included studies (and manufacturers of the included Ayurvedic medicines), to locate additional studies.

3.3 Study Selection

Following the searches, the identified citations were collated and uploaded into EndNote v8.2 (Clarivate, Philadelphia, United States), and duplicate citations were removed. The remaining citations were uploaded into Rayyan [Qatar Computing Research Institute (Data Analytics), Doha, Qatar], and titles and abstracts were screened for eligibility by two independent reviewers. Studies identified as potentially eligible or those without an abstract had their full text retrieved. In case the full text of an article was not available even through the interlibrary loan service/British Library, the author and journal editor were approached (at least twice through email). Potentially eligible ongoing RCTs were contacted (at least twice through email) by the authors to access the study results. Full texts of the studies were assessed for eligibility by two independent reviewers. Any disagreements that arose between the two reviewers were resolved through discussion and in consultation with a third reviewer. Full texts of the studies that did not meet the inclusion criteria were excluded, and reasons for exclusion were recorded. In the case of multiple publications of the same study, the article having the most complete data was included. If partial data were provided in each article, then all such articles were included.

3.4 Assessment of Methodological Quality

Included studies were critically assessed using the standardized JBI critical appraisal checklist for RCTs independently by two reviews, assigning a score as met (yes), not met (no), or unclear. (Tufanaru et al., 2017) A third reviewer compared their work and highlighted the disagreements between the two reviewers. Any such disagreements were resolved through discussion between the three reviewers. All studies, regardless of their methodological quality, were included in the review.

3.5 Data Extraction

Two reviewers independently extracted data from the included studies, using a pre-developed and pre-tested data extraction tool. A third reviewer compared their work and highlighted the disagreements between the two reviewers. Any such disagreements were resolved through discussion between the three reviewers. Data extraction included details about the population, intervention, comparator, and outcomes. For biochemical, anthropometric, and physiological parameters and HRQoL data, the authors extracted the 8-week time point data. Where this time point was not reported or multiple time points were reported, data from the time point closest to 8 weeks were extracted. For adverse events, the authors extracted the end of study data. Intention-to-treat (ITT) data were preferred compared to per-protocol data. Post-intervention data were extracted in preference to change from baseline data (i.e., post-intervention score–baseline score). Percentage change from baseline was not extracted due to the sensitivity to changes in variance and failure to protect from baseline imbalances, thus leading to non-normally distributed outcome data.

(Vickers, 2001) For each outcome, the data were converted into one standard unit of measurement. In multi-arm studies, where two or more drug manufacturing processes, forms or timings of administration, doses, or Anupans of the same Ayurvedic medicine were compared with another comparator, the two or more study arms were combined together before pooling with other studies. (Hedges and Olkin, 1985; Cohen, 1988) This was also performed for multi-arm studies when the interventions and comparators were provided with co-interventions (e.g., Ayurvedic medicine arm pooled with Ayurvedic medicine and exercise arm versus placebo arm pooled with placebo and exercise arm).

Multiple strategies were used to obtain the relevant missing data. The corresponding author of the included study was contacted by email (at least two times per author) to obtain the missing data. If the standard deviation (SD) was missing (in a small number of studies), SD was imputed from a similar study (in terms of intervention, comparator, sample size, and numerical outcome data). If only a median and interquartile range (IQR) was reported (in a small number of studies), the mean was assumed to be equal to the median and the SD was calculated using a standard formula ($=IQR/1.35$). (Higgins et al., 2019)

3.6 Data Synthesis

Initially, narrative syntheses were conducted to describe the studies. For each outcome, where at least two studies on an Ayurvedic medicine were included, random-effects meta-analyses were conducted to provide a weighted measure of treatment effect. For continuous outcomes, mean differences (MD) with 95% confidence intervals (CI) were reported where the same scale was used across studies. Where different scales were used across studies, standardized mean differences (SMD) with 95% CIs were reported. Where necessary, post-intervention data were pooled with change from baseline data and only for MDs but not SMDs. For the purpose of analysis, the following comparators were combined together: no medicine, no additional medicine, and placebo. For studies with more than one comparator group (e.g., mentioned above, OAD), the comparisons were included in separate meta-analysis models to avoid the issue of double-counting of the comparator group. Statistical heterogeneity was quantified using the I^2 statistic. Analyses were conducted using STATA v16 for Windows (STATA Corp, College Station, Texas, United States). The findings are interpreted from the clinical point of view.

3.7 Assessment of Publication Bias

Funnel plots were used to assess publication bias, where there were at least 10 studies included in the meta-analysis.

3.8 Sensitivity Analyses

Where a significant pooled association was found between the intervention and primary outcome, sensitivity analysis was performed to assess the robustness of the result by excluding studies that were not journal publications (i.e., not peer-reviewed). After excluding these studies, at least two eligible studies were needed for the sensitivity analysis.

3.9 Subgroup Analyses

Where a significant pooled association was found between the intervention and primary outcome, subgroup analysis was performed to explore the influence of the following factors on the result:

- Country: South Asia (i.e., Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, or Sri Lanka) versus others.
- Comparator: no medicine or no additional medicine versus placebo.

For this purpose, at least two eligible studies per subgroup were needed.

4 ASSESSING CERTAINTY IN THE FINDINGS

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method was used to assess the certainty of the findings (i.e., the primary outcomes). (Schünemann et al., 2013) Only those Ayurvedic medicines were included where the meta-analysis (at least two studies were needed) was possible on at least one primary outcome. Two reviewers were involved in the process, and the findings were initially ranked as high and were downgraded to moderate, low, or very low if there was evidence of the following: risk of bias, inconsistency of results, indirectness of evidence, imprecision, and/or publication bias. More specifically, in the risk of bias domain, the following were considered for downgrading: no allocation concealment (no to Q2 in the JBI critical appraisal checklist for RCTs), lack of blinding (no to Q4,5,6), attrition bias (no to Q9), and selective outcome reporting. If an issue out of these four was present in the majority of studies (i.e., >50%), then it was downgraded by one level. If more than one issue was present, then it was downgraded by two levels. In the inconsistency of results domain, if the statistical heterogeneity (i.e., I^2 statistic) was 75%–89%, then it was downgraded by one level. If the I^2 statistic was $\geq 90\%$, then it was downgraded by two levels. In the imprecision domain, if the total sample size was 100 to <400, then it was downgraded by one level. If the total sample size was <100, then it was downgraded by two levels. If the total sample size was ≥ 400 with wide CI and not earlier downgraded for inconsistency, then it was downgraded by one level. If publication bias was detected, then it was downgraded by one level. (See Summary of Findings table [Supplementary Material]).

5 RESULTS

5.1 Inclusion of Studies

The literature search identified 32,519 records. After removing duplicate records, 27,635 titles and abstracts were screened. Full texts of 309 records were sought, and their eligibility for inclusion was assessed. 219 records were included in this systematic review

representing 199 RCTs and including 21,191 participants (in the eligible study arms) (Figure 1). Data from 144 RCTs (160 records) were included in the meta-analyses. A further 28 ongoing RCTs were included, which are reported in Supplementary Appendix S2. The reasons for the exclusion of 90 records excluded at the full text screening stage are reported in Supplementary Appendix S3.

5.2 Characteristics of Included Studies

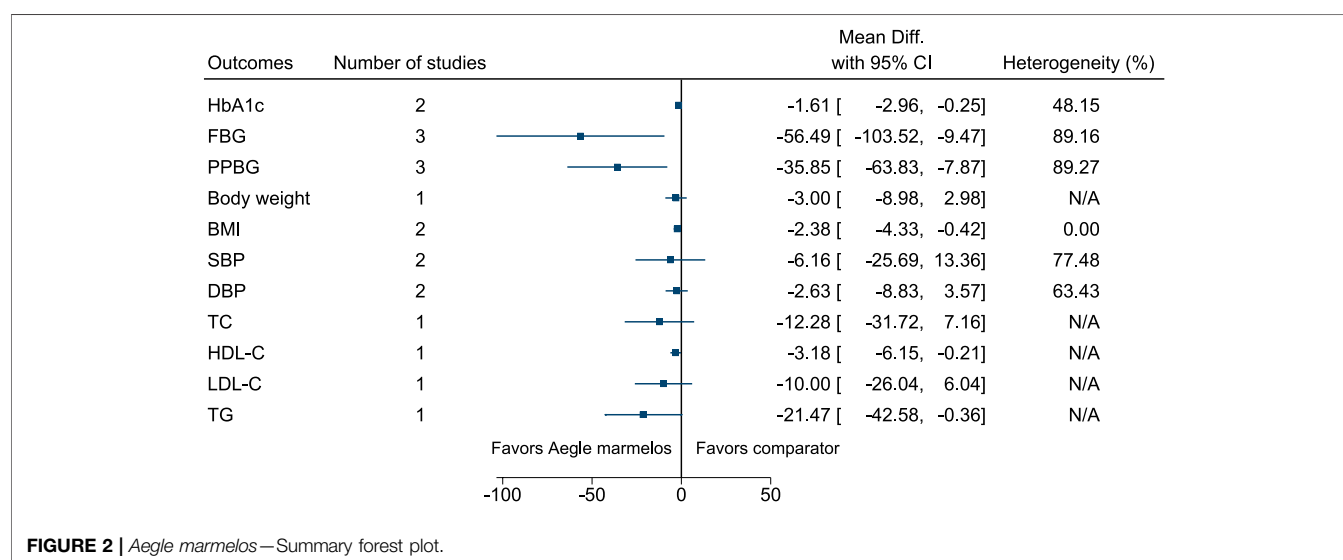
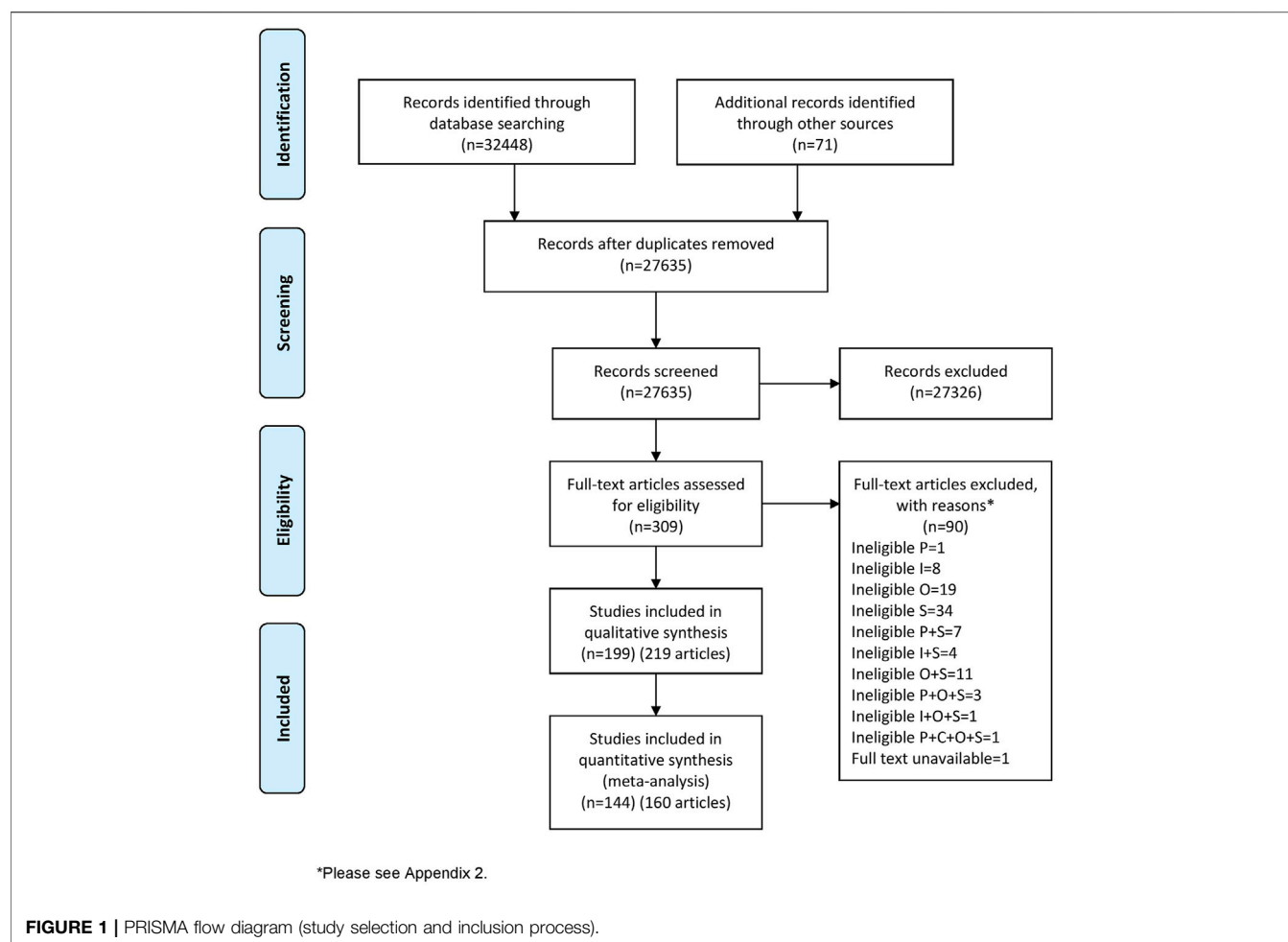
Characteristics of 199 included studies are reported in Supplementary Appendix S4. 82 studies (41%) were conducted in South Asia (one in Bangladesh, 72 in India, eight in Pakistan, and one in Sri Lanka), and 72 studies (36%) in Iran. 26 RCTs (13%) recruited newly diagnosed/treatment naïve T2DM patients, 146 (73%) recruited existing cases/on OAD, and 22 (11%) recruited both; it was unclear in the remaining five RCTs. The mean duration of T2DM in existing cases ranged from 2.5 to 12.8 years. 28 RCTs recruited participants with physical or mental health comorbidities or complications of T2DM. The sample size of the studies ranged from 12 to 6,114 (only eligible study arms were considered). The mean age of participants ranged from 37.5 to 65.4 years. The percentage of female participants ranged from 0% to 100%. At baseline, the mean HbA1c and FBG ranged from 6.4 to 11.8% and 118–360 mg/dl, respectively. 42 RCTs (21%) received commercial funding or other support; however, it was unclear in 86 RCTs (43%).

5.3 Interventions

98 Ayurvedic medicines were included in the systematic review. The details of the interventions are provided in Supplementary Appendix S5. 56 Ayurvedic medicines were of single plant-origin (i.e., single herbs), two were of single mineral-origin (namely, Swarnamakshika Bhasma [ash obtained through incineration] and Yashad Bhasma), and Shilajit (a blackish-brown powder or an exudate from high mountain rocks). 31 Ayurvedic medicines contained ≥ 2 plant-origin ingredients, and one contained ≥ 2 mineral-origin ingredients (namely, Trivanga Bhasma). Seven Ayurvedic medicines were herbo-mineral formulations (namely, Hyponidd, Inolter, Madhumeha Nashini Gutika, Naga Bhasma and Nishamalaki combination, Nishamalaki and Shilajit combination, Salasaradi Kashaya, and Tejashiladi Vati). An oral route of administration was used for all of the Ayurvedic medicines, using a range of administration forms (including tablets, capsules, and powder) and timings of administration (ranging from one to four times daily). The daily doses of Ayurvedic medicines varied, depending on their type and form and timing of administration. Similarly, a range of Anupan of Ayurvedic medicines were reported. The treatment duration (and trial follow-up) ranged from 8 (i.e., based on the systematic review inclusion criteria) to 78 weeks (six RCTs reported 26 weeks, and one each reported 36, 39, 52, and 78 weeks).

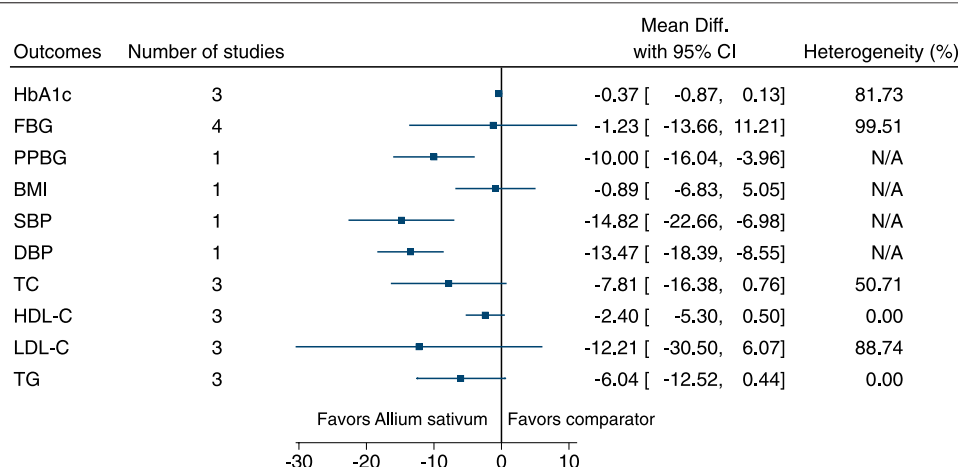
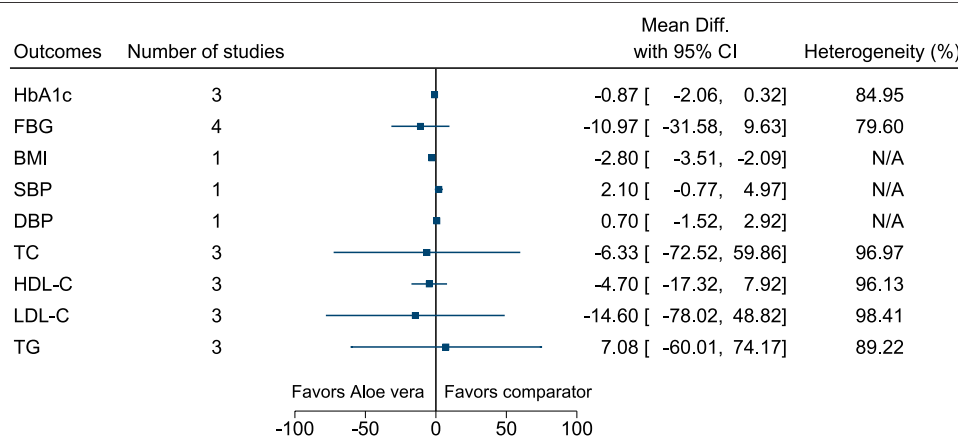
5.4 Methodological Quality

Overall, in the studies reviewed the methodology was not adequately reported, resulting in poorer methodological quality scoring (Supplementary Appendix S6). The major issues in these studies were: 1) inadequately reporting the randomization process that was used to assign participants to study arms; 2)



inadequately reporting the allocation concealment process; 3) inadequately reporting who was blinded to intervention assignment and how blinding was performed; 4) inadequate reporting of the

placebo and on further interrogation some placebos were actually Ayurvedic medicines, and it was unclear if placebos were identical especially when other forms of administration like powder or liquid

FIGURE 3 | *Allium sativum*—Summary forest plot.FIGURE 4 | *Aloe vera*—Summary forest plot.

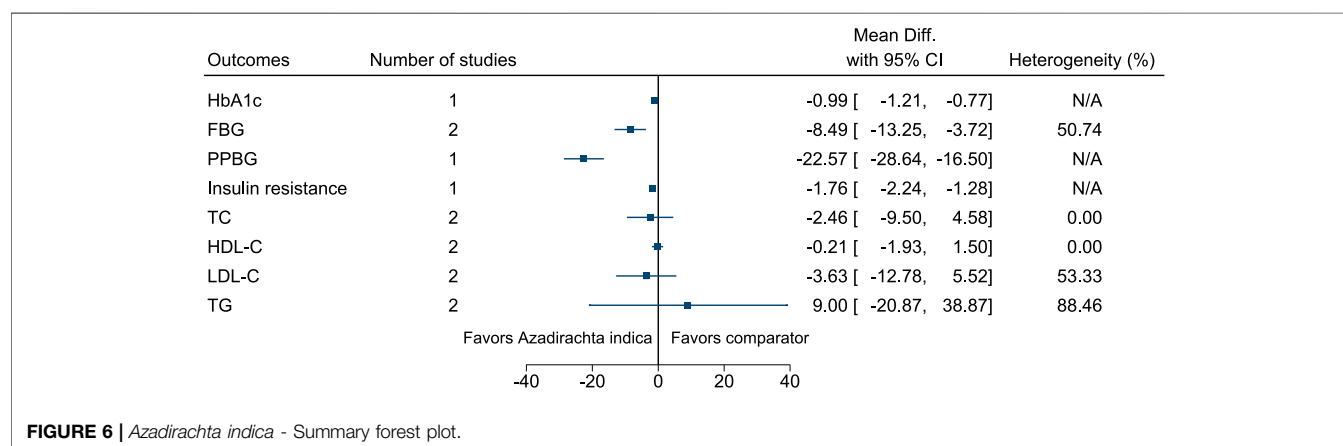
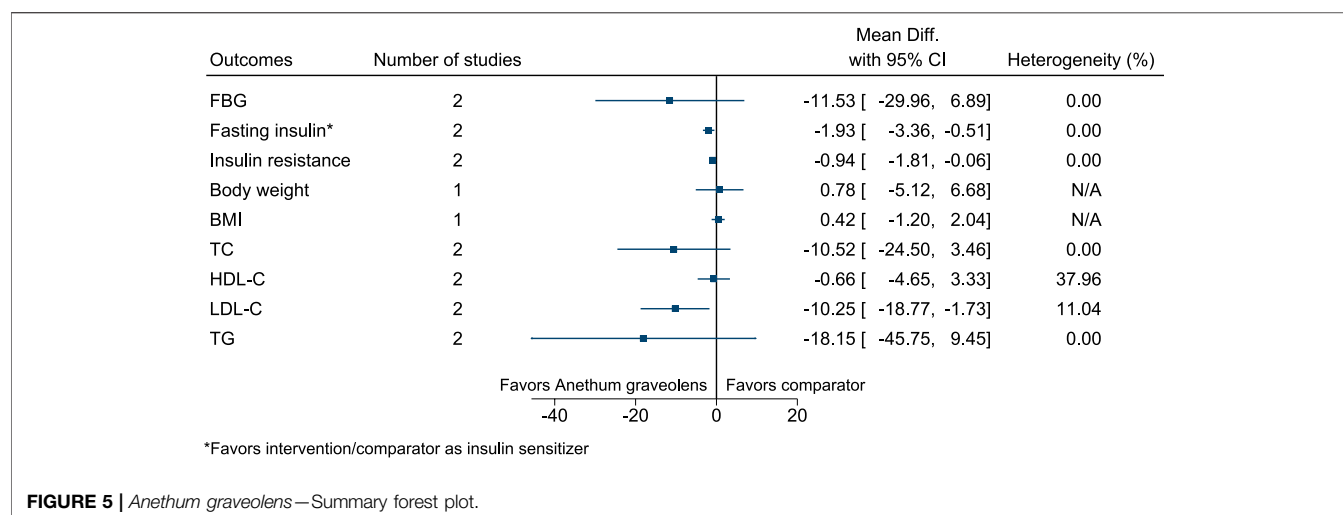
were used which are easy to differentiate taste and/or smell wise; 5) inadequately reporting whether the study arms were treated identically other than the intervention of interest and particularly, in existing cases/on OAD, it was not always clear whether OAD was continued for the rest of the trial; 6) inadequately reporting the ascertainment of outcomes (including adverse events); 7) errors/issues in the sample size calculation and reporting (e.g., not using the primary outcome or using an inappropriate outcome as primary for the sample size calculation, unclear *minimum* clinically important difference or using an inappropriate *minimum* clinically important difference for the sample size calculation; 8) errors/issues in data analysis and reporting (e.g., not performing ITT analysis or doing pre-post analysis of outcomes within study arms but no comparative analysis between study arms); and 9) in terms of the follow-up, not analyzing the differences between study arms, such as no analysis of the patterns of loss to follow-up and the impact of the loss to follow-up on results.

5.5 Effects of Interventions

Meta-analyses were conducted on 33 Ayurvedic medicines (32 single herbs and Shilajit). The majority of the Ayurvedic medicines were compared to no medicine or no additional medicine or placebo; however, two were compared to both no medicine or no additional medicine or placebo and OAD (*Momordica charantia* L. and *Trigonella foenum-graecum* L.) and two were compared to OAD (*Enicostemma axillare* (Lam.) Raynal and *Pterocarpus marsupium* Roxb.). (See ZIP file for forest and funnel plots [Supplementary Material]).

5.5.1 *Aegle marmelos* (L.) Corrêa

Aegle marmelos significantly reduced HbA1c (MD -1.6%; 95% CI -3 to -0.3), FBG (-56 mg/dl; -104 to -9), PPBG (-36 mg/dl; -64 to -8), and BMI (-2.4 kg/m²; -4.3 to -0.4) (see Figure 2). (Sankhla et al., 2009; Yaheya and Ismail, 2009; Sharma and Sharma, 2013; Nigam and Nambiar, 2019).



5.5.2 *Allium sativum* L.

Allium sativum significantly reduced PPBG (−10 mg/dl; −16 to −4), SBP (−15 mmHg; −23 to −7), and DBP (−13 mmHg; −18 to −9) (see **Figure 3**). (Ashraf et al., 2005; Balasubramaniam et al., 2010; Ashraf et al., 2011a; Ashraf et al., 2011b; Kumar et al., 2013; Mansouri et al., 2018).

5.5.3 *Aloe vera* L.

Aloe vera significantly reduced BMI (−2.8 kg/m²; −3.5 to −2.1) (see **Figure 4**). (Arora et al., 2009; Huseini et al., 2012a; Huseini et al., 2012b; Zarrintan et al., 2015; Maurya et al., 2017).

5.5.4 *Anethum graveolens* L.

Anethum graveolens significantly reduced fasting insulin (as insulin sensitizer; −2 mIU/L; −3 to −1), insulin resistance (−0.9; −1.8 to −0.1), and LDL-C (−10 mg/dl; −19 to −2) (see **Figure 5**). (Mobasseri et al., 2014; Haidari et al., 2020).

5.5.5 *Azadirachta indica* A.Juss.

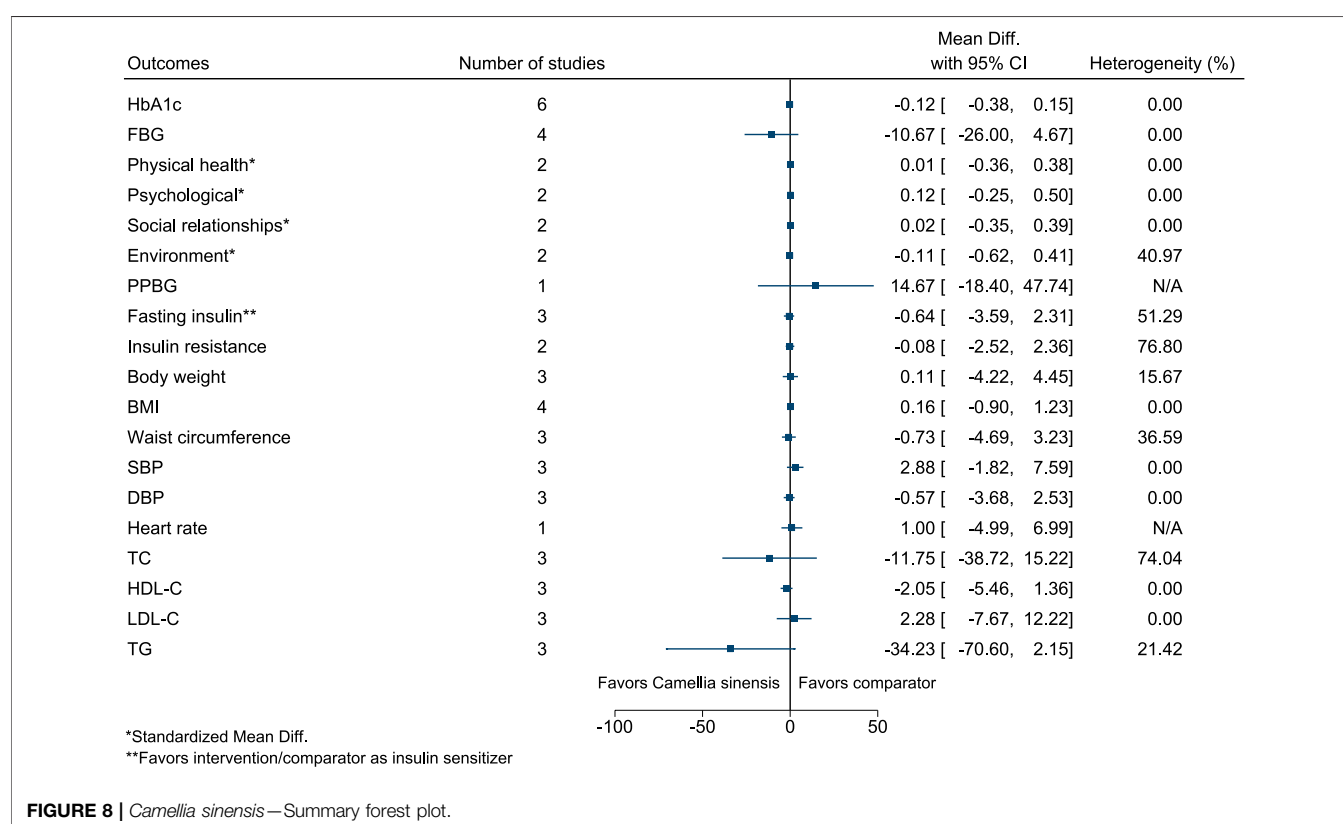
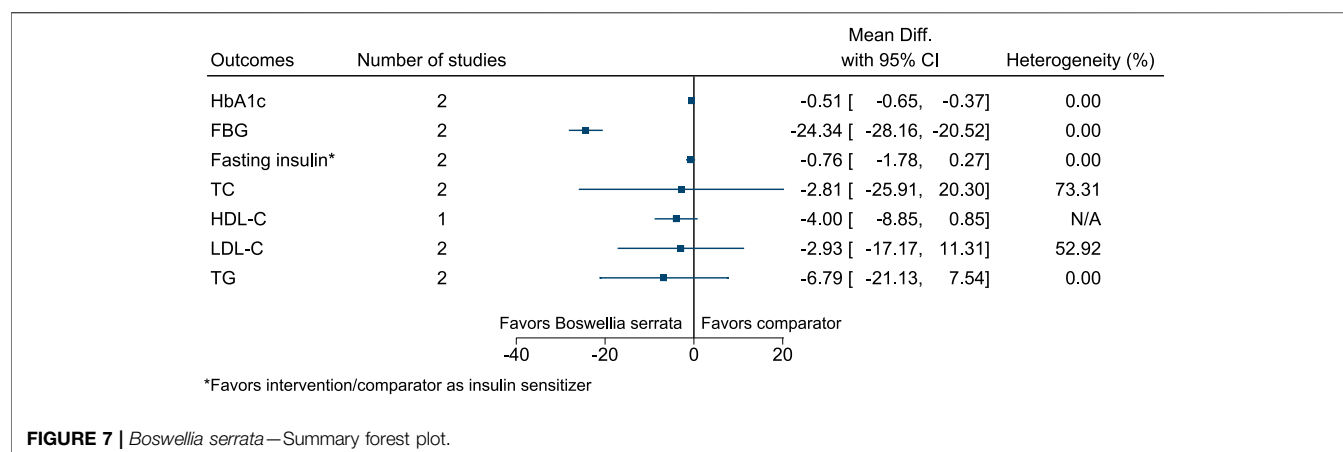
Azadirachta indica significantly reduced HbA1c (−1%; −1.2 to −0.8), FBG (−8 mg/dl; −13 to −4), PPBG (−23 mg/dl; −29 to −17), and insulin resistance (−1.8; −2.2 to −1.3) (see **Figure 6**). (Balasubramaniam et al., 2010; Pingali et al., 2020).

5.5.6 *Boswellia serrata* Roxb.

Boswellia serrata significantly reduced HbA1c (−0.5%; −0.7 to −0.4) and FBG (−24 mg/dl; −28 to −21) (see **Figure 7**). (Azadmehr et al., 2014; Mehrzadi et al., 2018).

5.5.7 *Camellia sinensis* (L.) Kuntze

Figure 8 shows the summary forest plot for *Camellia sinensis*. (MacKenzie et al., 2007; Mirzaei et al., 2009; Hsu et al., 2011; Lasaite et al., 2014; Liu et al., 2014; Quezada-Fernández et al., 2019).



5.5.8 *Cinnamomum aromaticum* Nees

Cinnamomum aromaticum significantly increased HDL-C (2 mg/dl; 1–2) (see **Figure 9**). (Mang et al., 2006; Suppakitporn et al., 2006; Blevins et al., 2007; Crawford, 2009; Akilen et al., 2010; Wainstein et al., 2011; Lu et al., 2012; Sharma et al., 2012; Hasanade et al., 2013; Tangvarasittichai et al., 2015; Sengsuk et al., 2016).

5.5.9 *Cinnamomum verum* J.Presl

Cinnamomum verum significantly reduced FBG (–11 mg/dl; –19 to –3), insulin resistance (–1; –1.2 to –0.8), body weight (–2.1 kg; –2.7 to –1.5), and SBP (–4 mmHg; –5 to –2) (see **Figure 10**). (Vafa et al.,

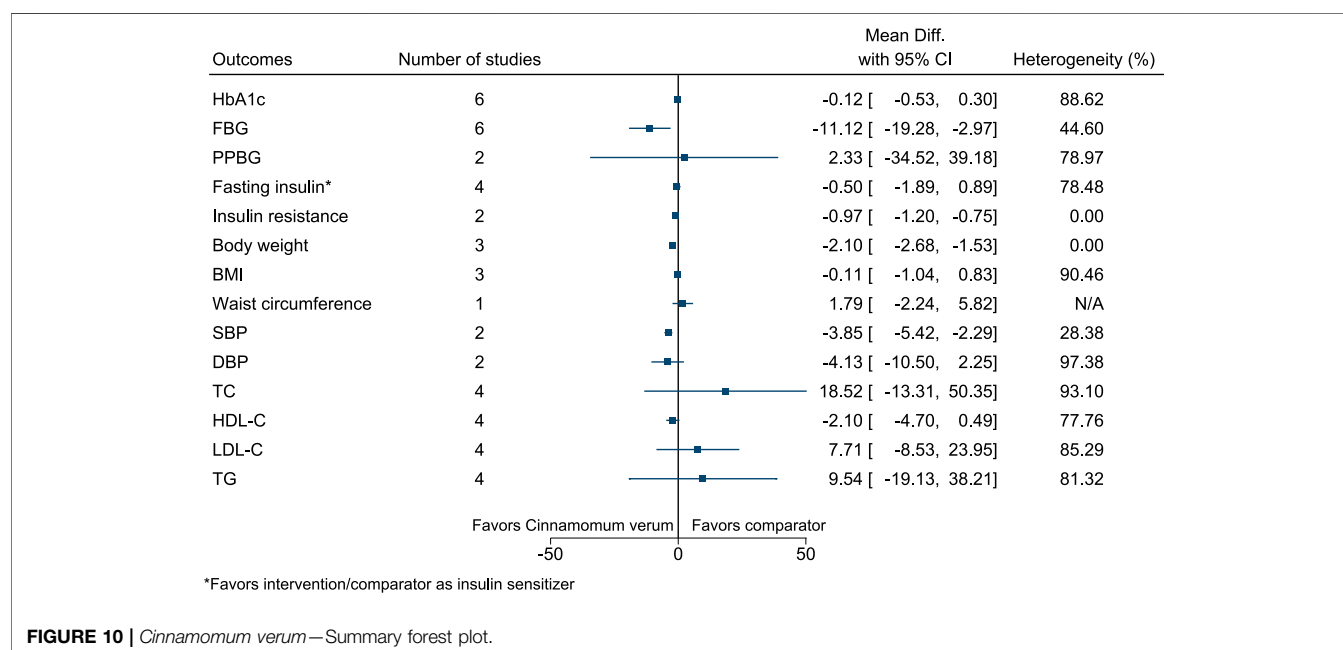
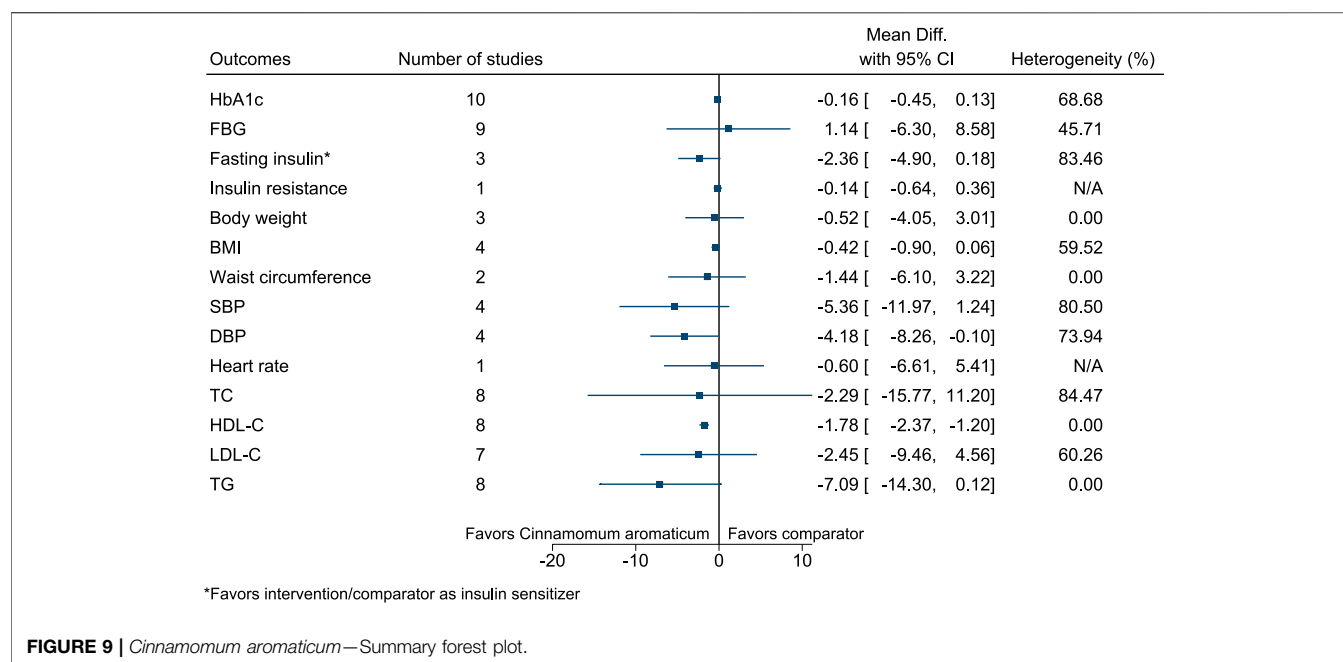
2012; Zahmatkesh et al., 2012; Azimi et al., 2014; Azimi et al., 2016; Talaei et al., 2017a; Zare et al., 2019; Mirmiranpour et al., 2020).

5.5.10 *Citrullus colocynthis* (L.) Schrad.

Citrullus colocynthis significantly reduced TG (–45 mg/dl; –86 to –4) (see **Figure 11**). (Huseini et al., 2009; Barghamdi et al., 2016).

5.5.11 *Coccinia grandis* (L.) Voigt

Coccinia grandis significantly reduced FBG (–22 mg/dl; –25 to –19), insulin resistance (–1.2; –2.3 to –0.2), and TG (–23 mg/dl;



-35 to -11) (see **Figure 12**). (Kuriyan et al., 2008; Kurpad and Raj, 2008; Wasana et al., 2021).

5.5.12 *Crocus sativus* L.

Figure 13 shows the summary forest plot for *Crocus sativus*. (Azimi et al., 2014; Azimi et al., 2016; Milajerdi et al., 2018; Ebrahimi et al., 2019; Moravej Aleali et al., 2019; Mobasseri et al., 2020).

5.5.13 *Cuminum cyminum* L.

Cuminum cyminum significantly reduced insulin resistance (-1; -1.6 to -0.4), SBP (-17 mmHg; -24 to -10), and DBP (-11 mmHg; -16 to -6) (see **Figure 14**). (Jafari et al., 2017; Mansouri et al., 2018; Hendre et al., 2020).

5.5.14 *Curcuma longa* L.

Curcuma longa significantly reduced FBG (-10 mg/dl; -15 to -5), fasting insulin (as insulin sensitizer; -2 mIU/L; -3 to -1), TC

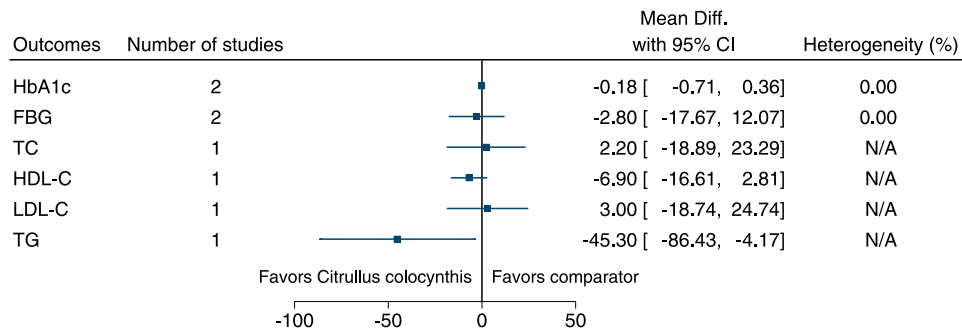
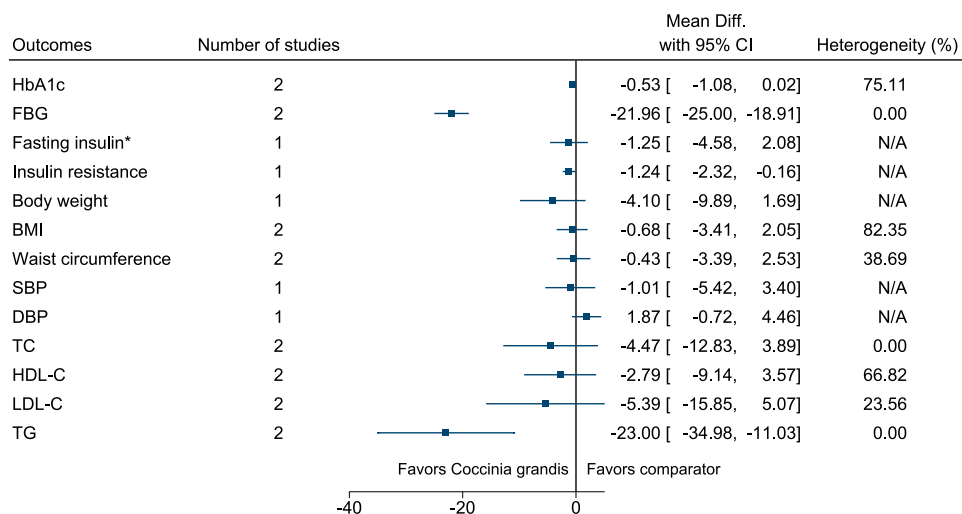
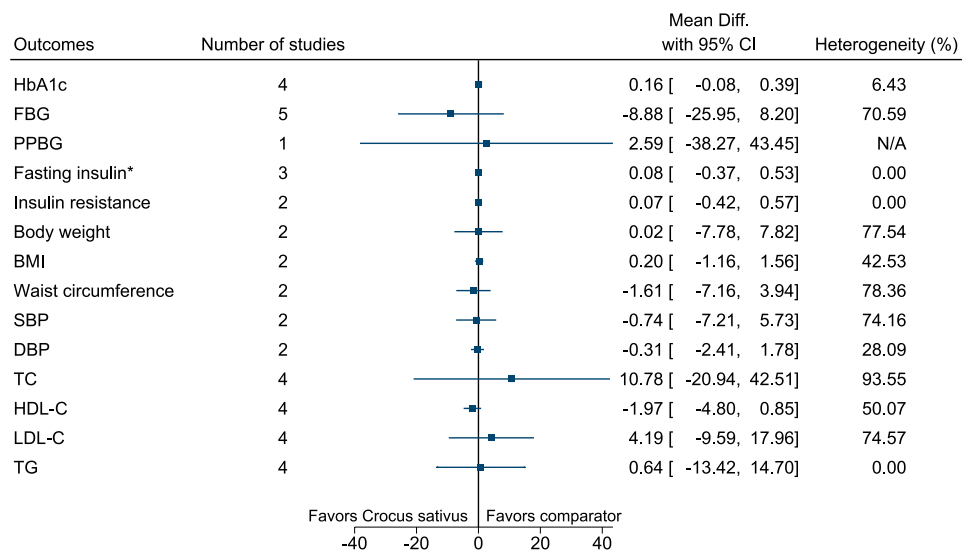


FIGURE 11 | *Citrullus colocynthis* - Summary forest plot.



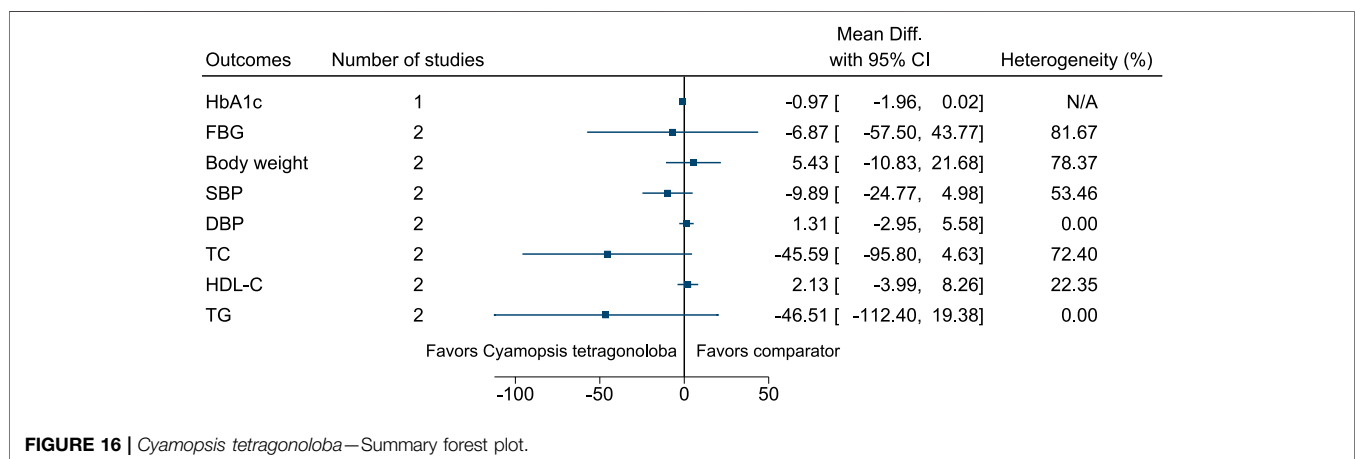
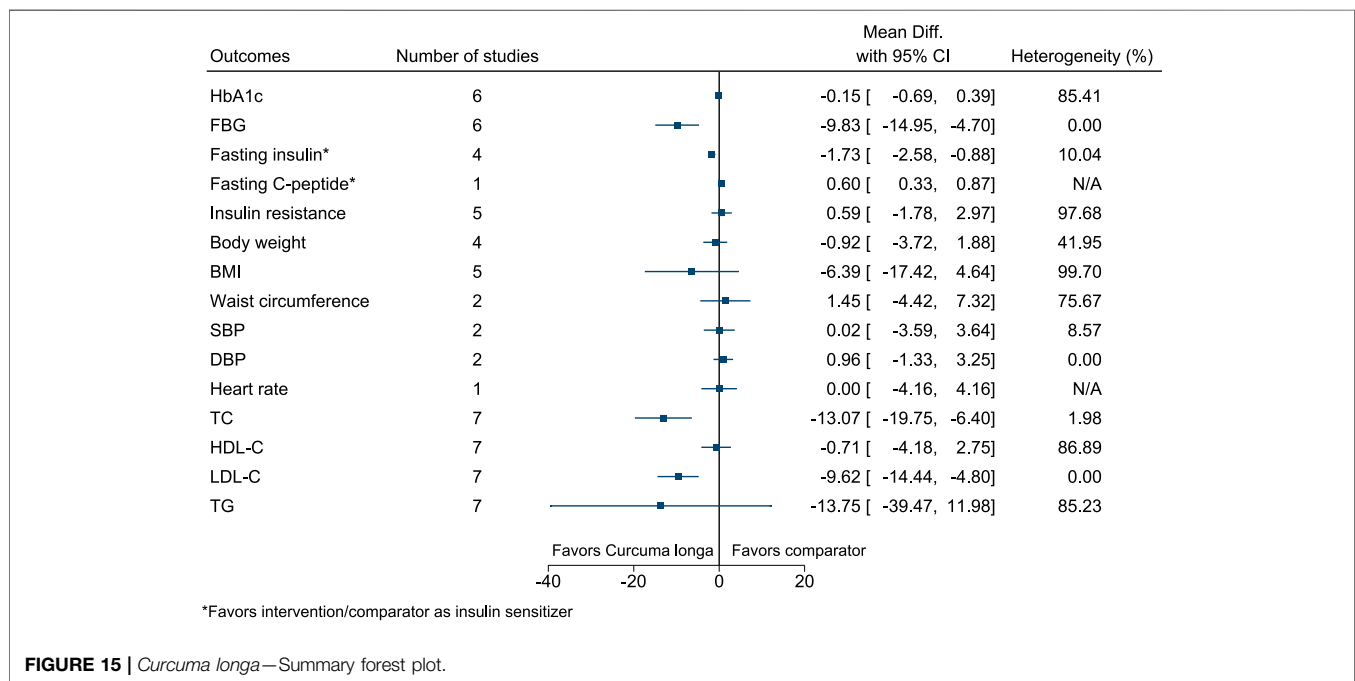
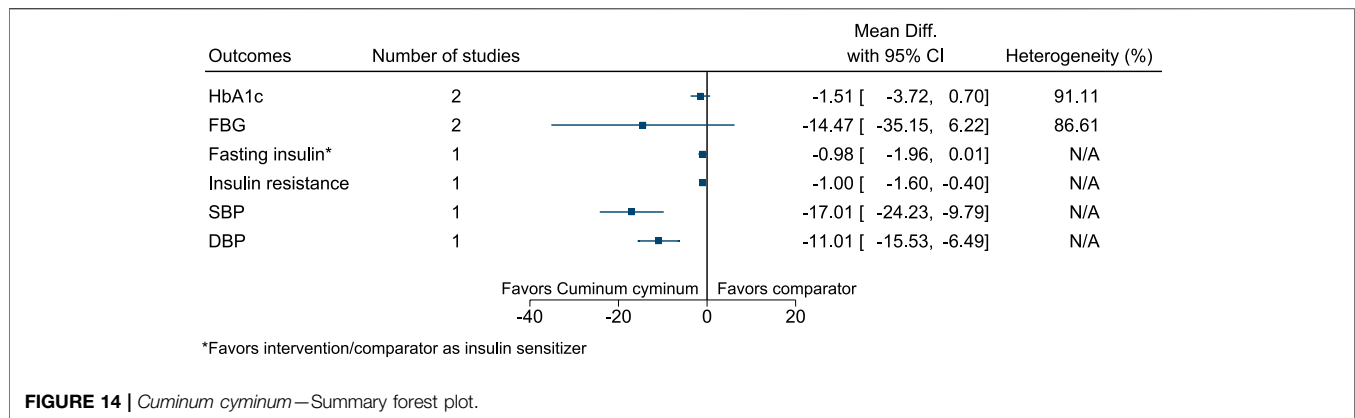
*Favors intervention/comparator as insulin sensitizer

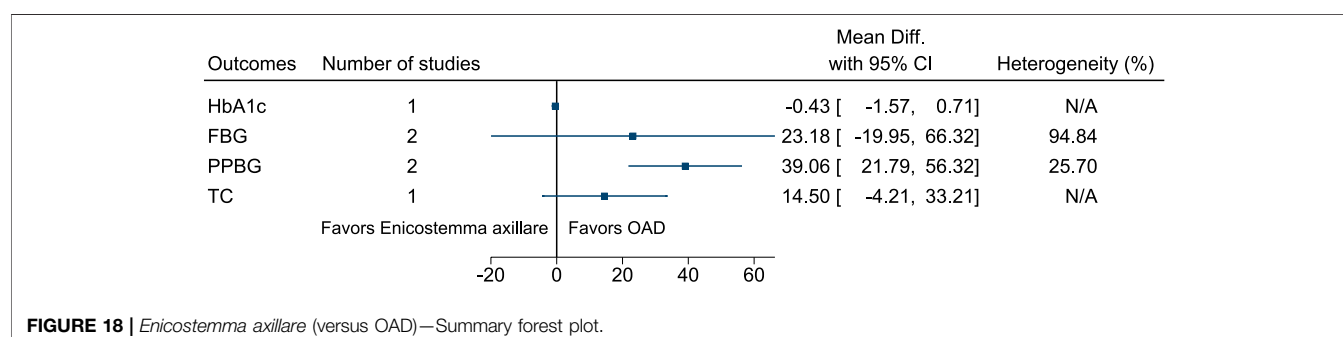
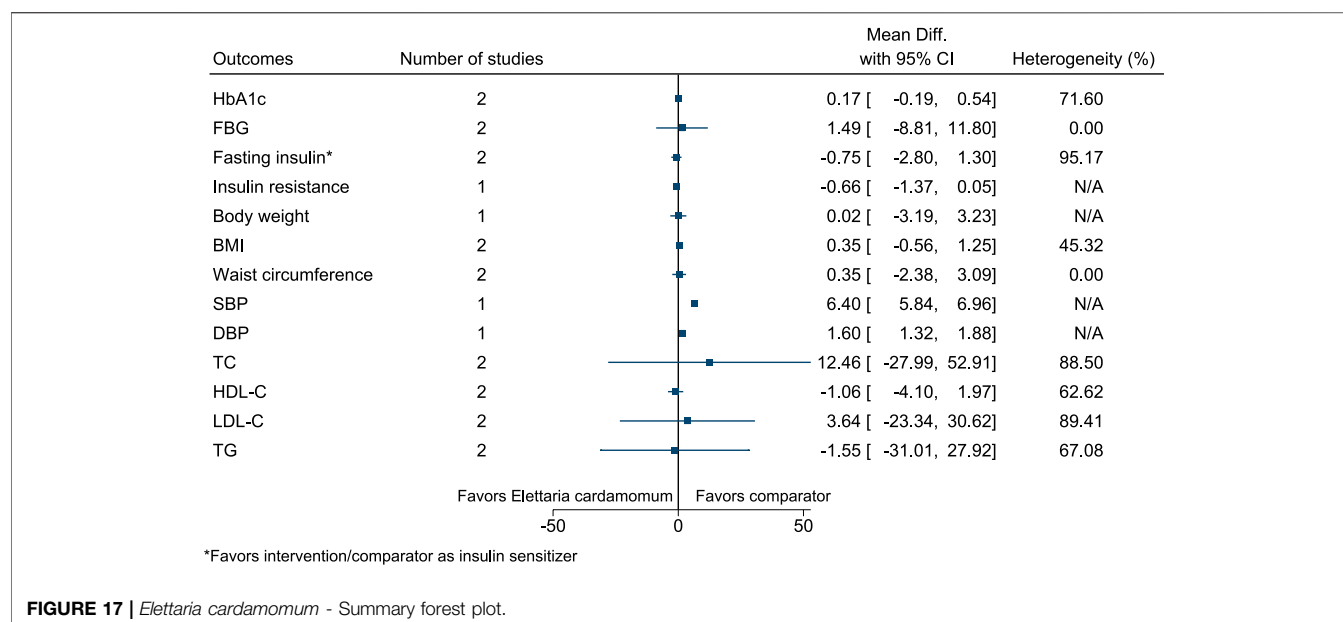
FIGURE 12 | *Coccinia grandis*—Summary forest plot.



*Favors intervention/comparator as insulin sensitizer

FIGURE 13 | *Crocus sativus*—Summary forest plot.





(−13 mg/dl; −20 to −6), and LDL-C (−10 mg/dl; −14 to −5), and increased fasting C-peptide (as insulin sensitizer; 0.6 ng/ml; 0.33–0.87) (see **Figure 15**). (Usharani et al., 2008; Na et al., 2013; Chuengsamarn et al., 2014; Panahi et al., 2017; Panahi et al., 2018; Adab et al., 2019; Adibian et al., 2019; Srinivasan et al., 2019; de Sousa et al., 2020).

5.5.15 *Cyamopsis tetragonoloba* (L.) Taub.

Figure 16 shows the summary forest plot for *Cyamopsis tetragonoloba*. (Uusitupa et al., 1984; Uusitupa et al., 1989).

5.5.16 *Eleteria cardamomum* (L.) Maton

Eleteria cardamomum significantly increased SBP (6 mmHg; 6–7) and DBP (2 mmHg; 1–2) (see **Figure 17**). (Azimi et al., 2014; Azimi et al., 2016; Aghasi et al., 2019).

5.5.17 *Enicostemma axillare* (Lam.) Raynal (versus OAD)

Compared to *Enicostemma axillare*, OAD significantly reduced PPBG (−39 mg/dl; −56 to −22) (see **Figure 18**). (Kumar et al., 2014; Shankarrao et al., 2017).

5.5.18 *Gynostemma pentaphyllum* (Thunb.) Makino

Gynostemma pentaphyllum significantly reduced HbA1c (−1%; −1.5 to −0.6), FBG (−29 mg/dl; −43 to −15), and PPBG (−80 mg/dl; −134 to −25), and increased LDL-C (23 mg/dl; 5–41) (see **Figure 19**). (Huyen et al., 2010; Huyen et al., 2012).

5.5.19 *Ipomoea batatas* (L.) Lam.

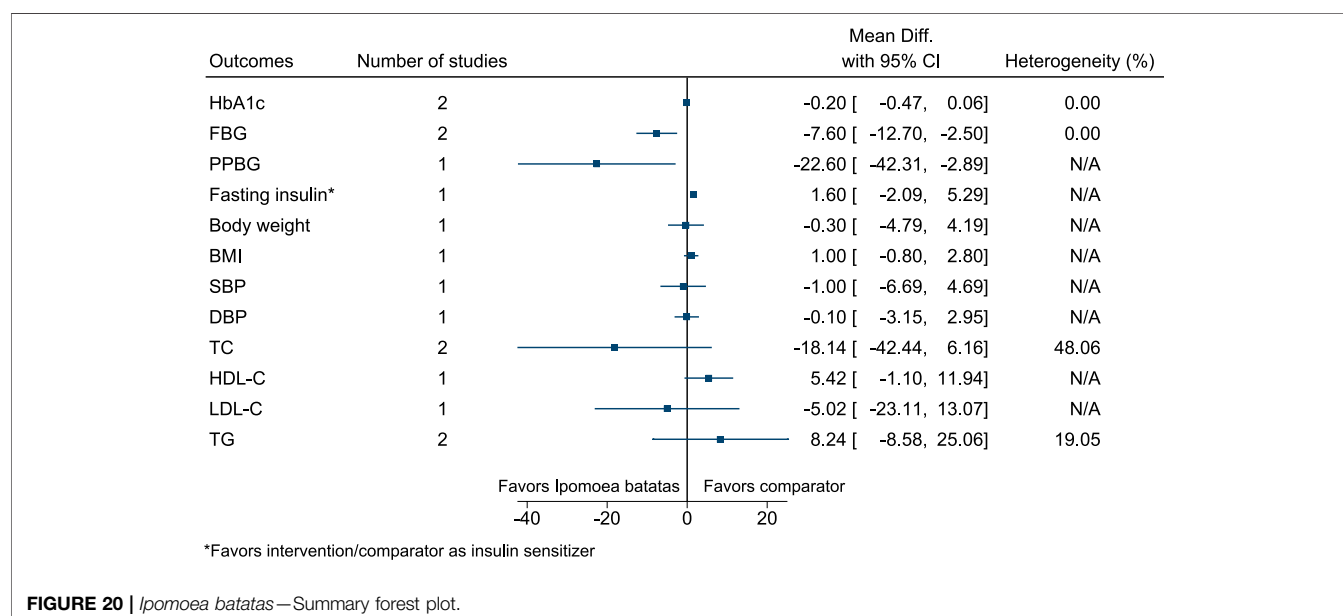
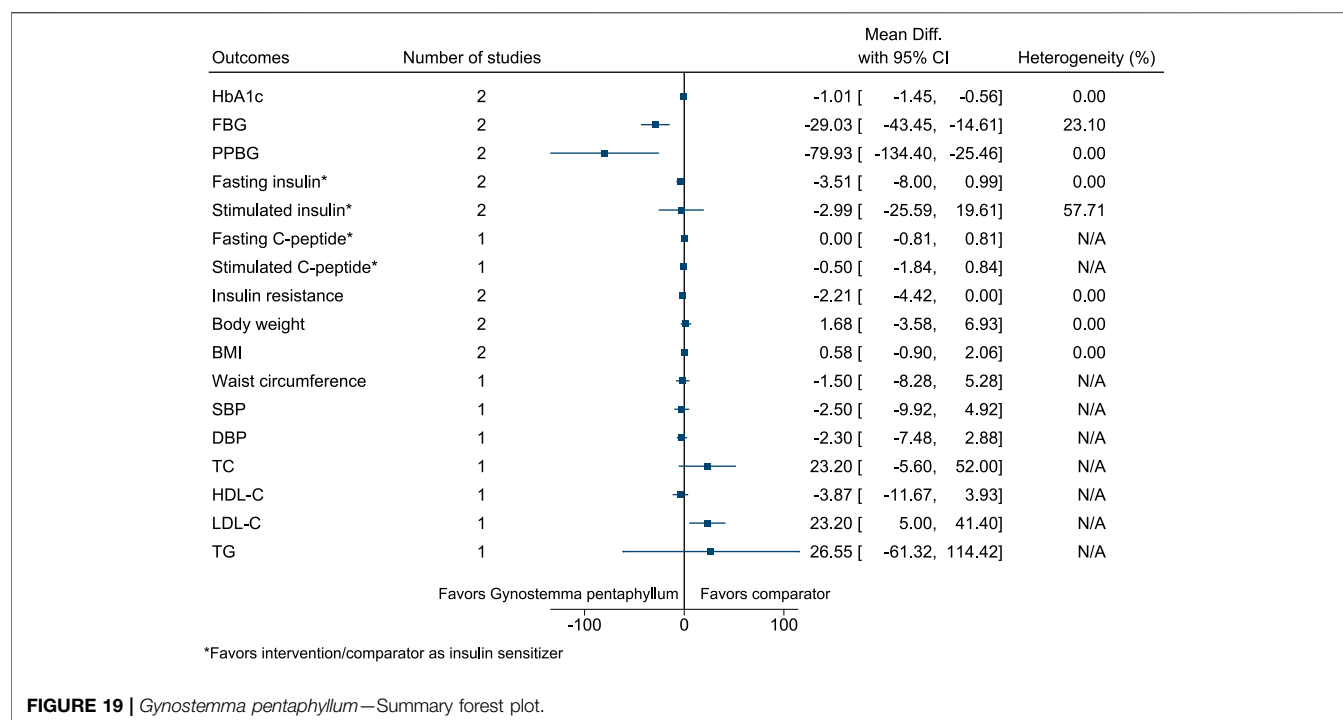
Ipomoea batatas significantly reduced FBG (−8 mg/dl; −13 to −3) and PPBG (−23 mg/dl; −42 to −3) (see **Figure 20**). (Ludvik et al., 2004; Ludvik et al., 2008).

5.5.20 *Juglans regia* L.

Juglans regia significantly reduced FBG (−14 mg/dl; −24 to −4) (see **Figure 21**). (Hosseini et al., 2014a; Hosseini et al., 2014b; Zibaenezhad et al., 2016; Abdoli et al., 2017; Zibaenezhad et al., 2017; Rabiei et al., 2018).

5.5.21 *Momordica charantia* L.

Momordica charantia significantly reduced HbA1c (−0.3%; −0.4 to −0.1), FBG (−14 mg/dl; −23 to −4), PPBG (−26 mg/dl; −47 to



-4), and fasting insulin (as insulin sensitizer; -13 mIU/L; -16 to -10) (see **Figure 22**). (Dans et al., 2007; Zänker et al., 2012; Trakoon-osot et al., 2013; Suthar et al., 2016a; Cortez-Navarrete et al., 2018; Kumari et al., 2018; Amini et al., 2020; Kim et al., 2020) In the country subgroup analysis for HbA1c and FBG, no statistically significant difference was found between subgroups ($p = 0.25$ and $p = 0.14$, respectively).

5.5.22 *Momordica charantia* L. (versus OAD)

Compared to *Momordica charantia*, OAD significantly reduced HbA1c (-0.4%; -0.7 to -0.2) and FBG (-14 mg/dl; -19 to -9). Compared to OAD, *Momordica charantia* significantly increased HDL-C (6 mg/dl; 4–7) and reduced TG (-16 mg/dl; -23 to -9) (see **Figure 23**). (Inayat U Rahman et al., 2015; Suthar et al., 2016b).

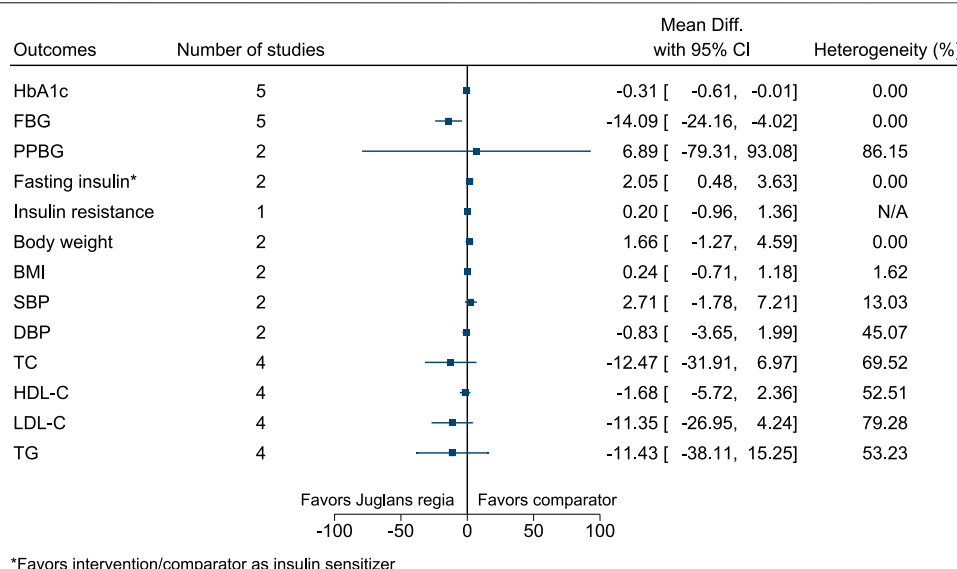


FIGURE 21 | *Juglans regia*—Summary forest plot.

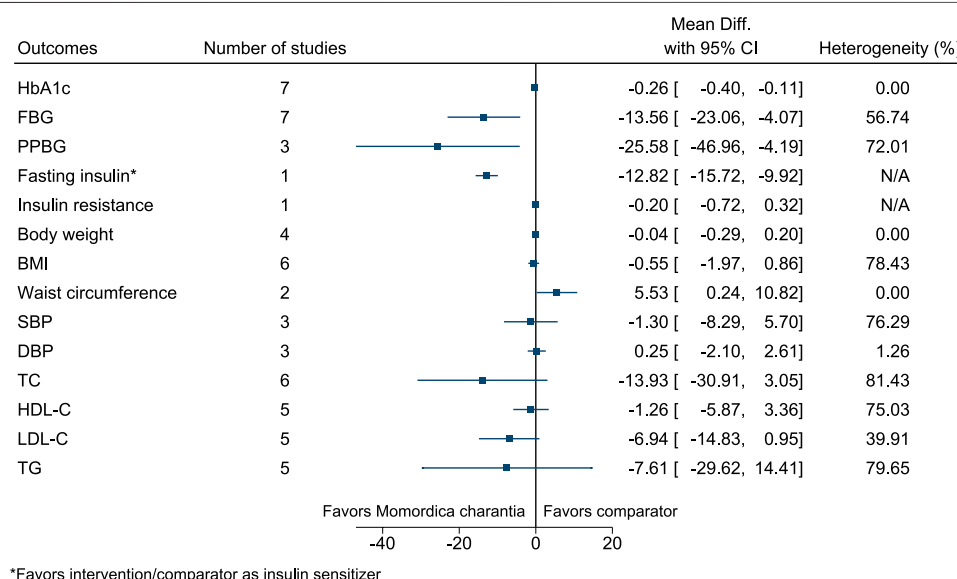


FIGURE 22 | *Momordica charantia*—Summary forest plot.

5.5.23 *Nigella sativa* L.

Nigella sativa significantly reduced HbA1c (−0.4%; −0.6 to −0.1), body weight (−4.2 kg; −7.2 to −1.2), TC (−17 mg/dl; −31 to −3), LDL-C (−11 mg/dl; −17 to −6), and TG (−12 mg/dl; −21 to −3) (see **Figure 24**). (Najmi et al., 2012; Hosseini et al., 2013; Hadi et al., 2015; Heshmati et al., 2015; Kaatabi et al., 2015; Kooshki et al., 2020; Jangjo-Borazjani et al., 2021).

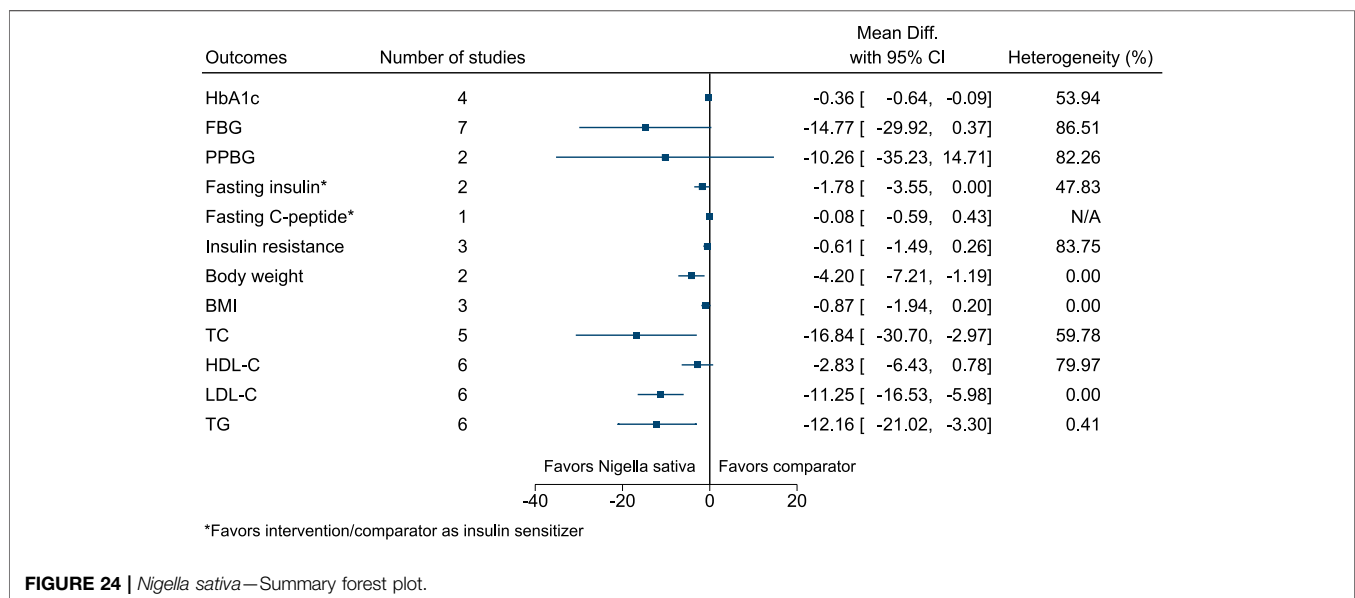
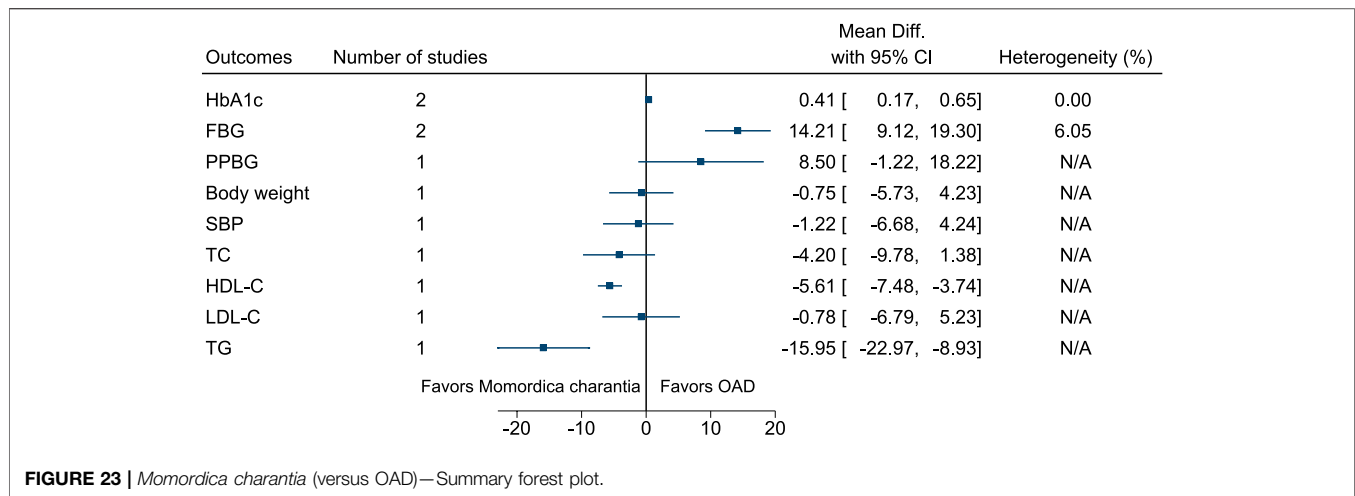
5.5.24 *Plantago ovata* Forssk.

Plantago ovata significantly reduced HbA1c (−0.9%; −1.4 to −0.3), FBG (−32 mg/dl; −40 to −23), fasting C-peptide (as

insulin sensitizer; −2.5 ng/ml; −3.22 to −1.78), and insulin resistance (−3.5; −4.6 to −2.4), and increased HDL-C (7 mg/dl; 1–13) (see **Figure 25**). (Ziai et al., 2005; Feinglos et al., 2013; Abutair et al., 2016).

5.5.25 *Portulaca oleracea* L.

Portulaca oleracea significantly reduced TC (−19 mg/dl; −32 to −6) and LDL-C (−12 mg/dl; −17 to −6), and increased DBP (6 mmHg; 2–10) (see **Figure 26**). (Farzanegi, 2014; Dehghan et al., 2016; Wainstein et al., 2016).



5.5.26 *Pterocarpus marsupium* Roxb. (versus OAD)

Figure 27 shows the summary forest plot for *Pterocarpus marsupium* (versus OAD). (Hariharan et al., 2005; Maurya et al., 2017).

5.5.27 *Punica granatum* L.

Punica granatum significantly reduced SBP (−12 mmHg; −21 to −2) (see Figure 28). (Babaeian et al., 2013; Sohrab et al., 2014; Sohrab et al., 2015; Faghihimani et al., 2016; Khajebishak et al., 2019a; Khajebishak et al., 2019b; Grabež et al., 2020; Hashemi et al., 2020).

5.5.28 *Sesamum indicum* L.

Figure 29 shows the summary forest plot for *Sesamum indicum*. (Mohammad Shahi et al., 2017; Aslam et al., 2018).

5.5.29 Shilajit

Shilajit significantly reduced body weight (−1.5 kg; −1.9 to −1.2), BMI (−0.7 kg/m²; −1 to −0.4), TC (−19 mg/dl; −28 to −10), LDL-C

(−15 mg/dl; −23 to −7), and TG (−20 mg/dl; −33 to −7) (see Figure 30). (Narasimha Raju and Sharma, 2016; Niranjan et al., 2016).

5.5.30 *Syzygium cumini* (L.) Skeels

Syzygium cumini significantly reduced TG (−27 mg/dl; −42 to −12) (see Figure 31). (Sahana et al., 2010; Sidana et al., 2016; Sidana et al., 2017).

5.5.31 *Tinospora cordifolia* (Willd.) Hook.f. & Thomson

Tinospora cordifolia significantly reduced HbA1c (−0.5%; −0.6 to −0.5), FBG (−4 mg/dl; −6 to −3), and PPBG (−8 mg/dl; −10 to −6) (see Figure 32). (Balasubramaniam et al., 2010; Mishra et al., 2015; Roy et al., 2015).

5.5.32 *Trigonella foenum-graecum* L.

Trigonella foenum-graecum significantly reduced HbA1c (−0.6%; −0.9 to −0.4), FBG (−14 mg/dl; −22 to −5), PPBG (−21 mg/dl; −34

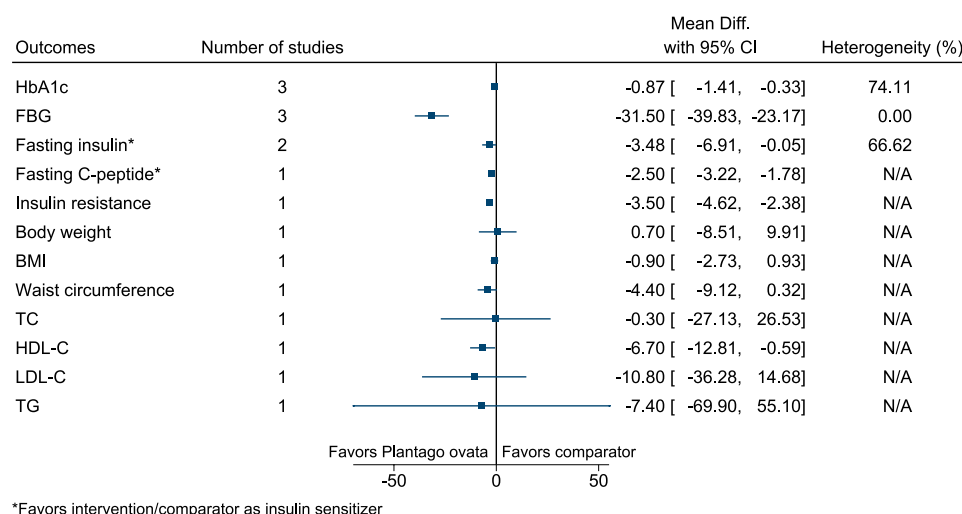


FIGURE 25 | *Plantago ovata*—Summary forest plot.

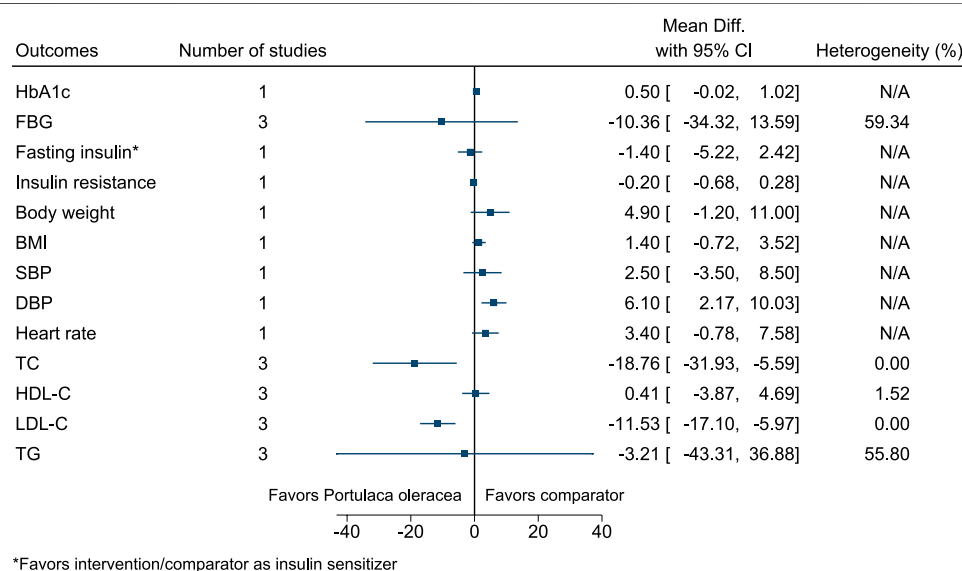


FIGURE 26 | *Portulaca oleracea*—Summary forest plot.

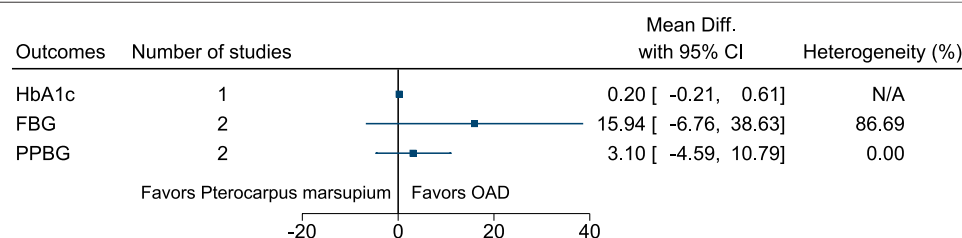


FIGURE 27 | *Pterocarpus marsupium* (versus OAD)—Summary forest plot.

to -7), stimulated insulin (as insulin sensitizer; -21 mIU/L; -36 to -5), fasting C-peptide (as insulin sensitizer; -0.41 ng/ml; -0.67 to -0.16), BMI (-0.6 kg/m²; -1.1 to -0.1), waist circumference

(-4 cm; -7 to -1), and TG (-23 mg/dl; -46 to -1), and increased stimulated C-peptide (as insulin sensitizer; 0.93 ng/ml; 0.09–1.77) (see **Figure 33**). (Gupta et al., 2001; Lu et al., 2008; Yaheya and

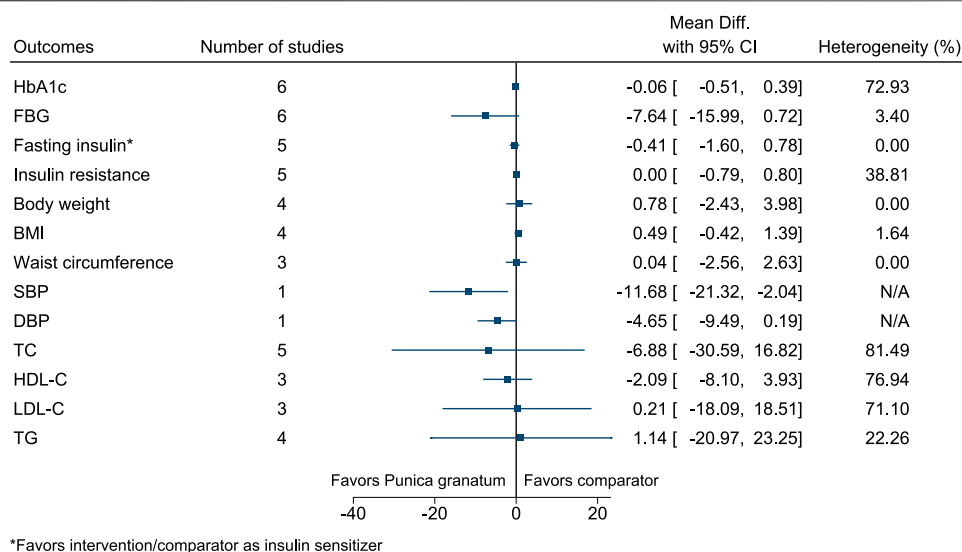


FIGURE 28 | *Punica granatum*—Summary forest plot.

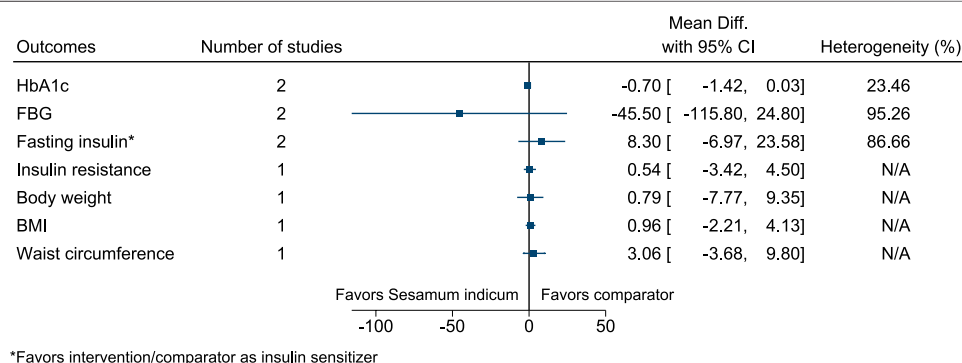


FIGURE 29 | *Sesamum indicum*—Summary forest plot.

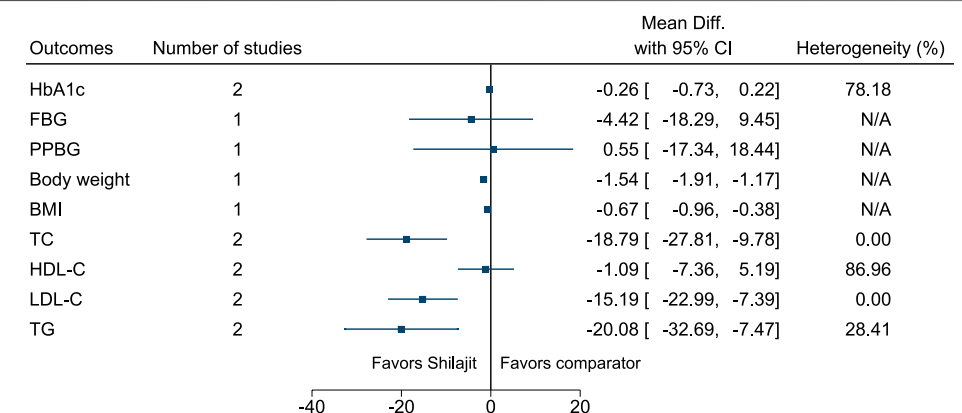


FIGURE 30 | *Shilajit*—Summary forest plot.

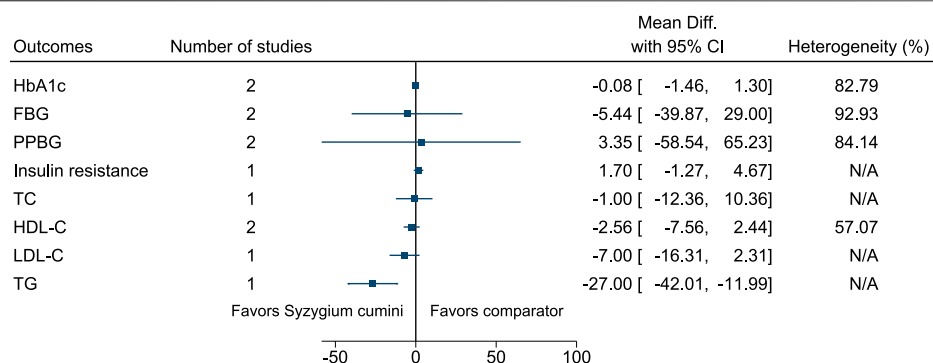


FIGURE 31 | *Syzygium cumini*—Summary forest plot.

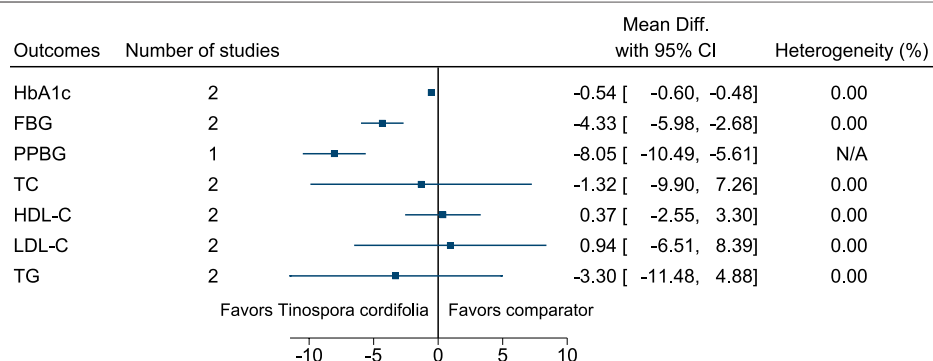
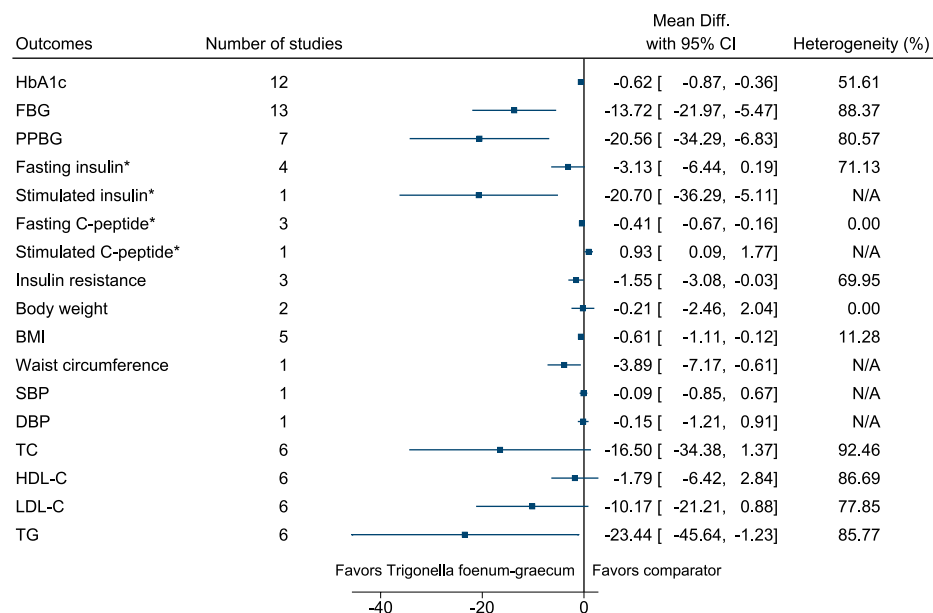
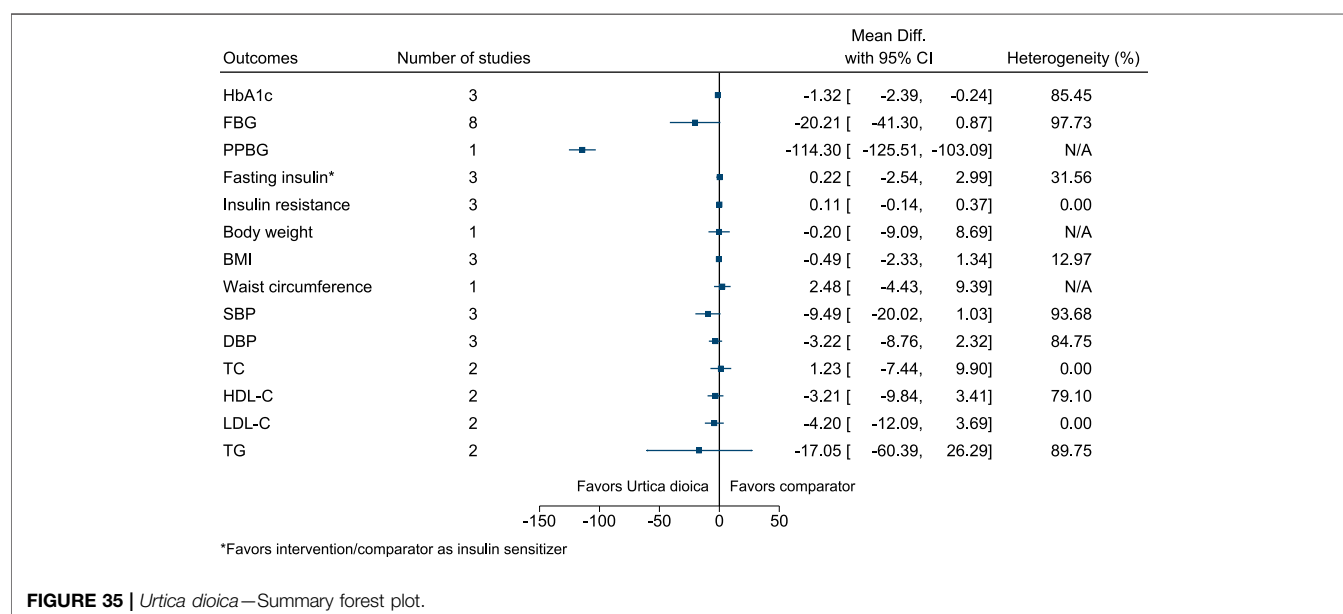
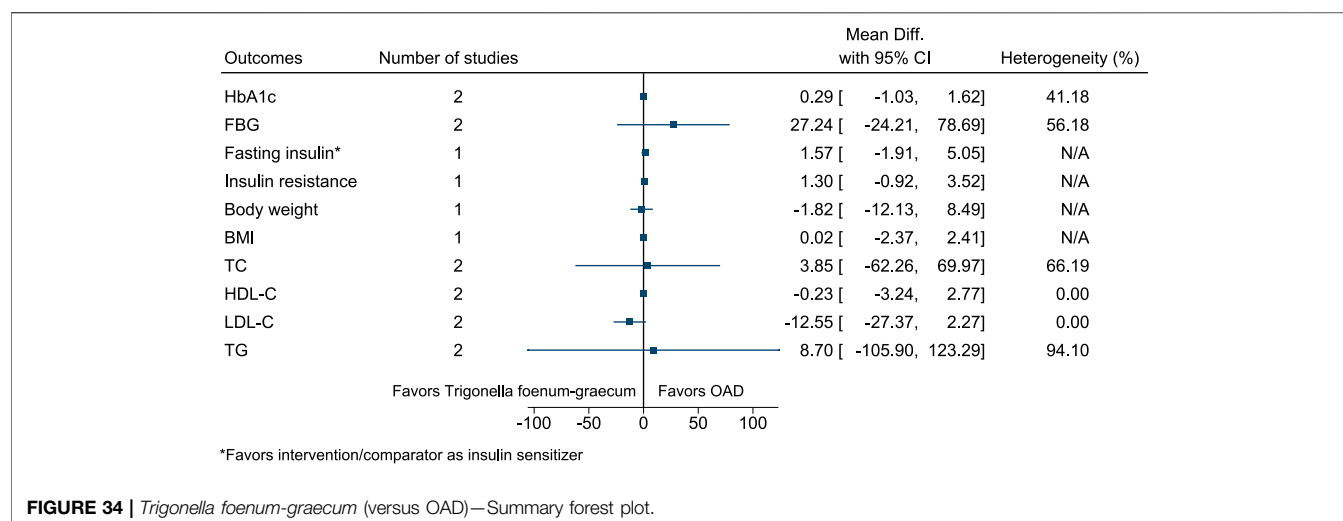


FIGURE 32 | *Tinospora cordifolia*—Summary forest plot.



*Favors intervention/comparator as insulin sensitizer

FIGURE 33 | *Trigonella foenum-graecum*—Summary forest plot.



Ismail, 2009; Ansari et al., 2011; Raftar et al., 2014; Suchitra and Parthasarathy, 2015; Kaur et al., 2016; Singh et al., 2016; Verma et al., 2016; Ranade and Mudgalkar, 2017; Gholaman and Gholami, 2018; Kandhare et al., 2018; Hassani et al., 2019; Hota et al., 2019; Rashid et al., 2019; Hadi et al., 2020) Publication bias was detected in the funnel plot for HbA1c but not for FBG. In the funnel plot for HbA1c, there was an absence of smaller sized studies showing a larger positive effect, which could imply the effect may be larger than that reported from the meta-analysis. In the sensitivity analysis, *Trigonella foenum-graecum* significantly reduced HbA1c and FBG even after excluding a publication that was not peer-reviewed. In the country subgroup analysis for HbA1c, no statistically significant difference was found between subgroups ($p = 0.44$). However, for FBG, a statistically significant difference was found between subgroups ($p <$

0.001). In the comparator subgroup analysis for HbA1c and FBG, a statistically significant difference was found between subgroups ($p = 0.04$ and $p < 0.001$, respectively).

5.5.33 *Trigonella foenum-graecum* L. (versus OAD)

Figure 34 shows the summary forest plot for *Trigonella foenum-graecum* (versus OAD). (Singh et al., 2016; Najdi et al., 2019).

5.5.34 *Urtica dioica* L.

Urtica dioica significantly reduced HbA1c (-1.3% ; -2.4 to -0.2) and PPBG (-114 mg/dl; -126 to -103) (see Figure 35). (Namazi et al., 2011; Esfanjani et al., 2012a; Esfanjani et al., 2012b; Kianbakht et al., 2013; Khajeh-Mehrizi et al., 2014; Dabagh and Nikbakht, 2016; Hassani et al., 2016; Dadvar et al., 2017; Ghalavand et al., 2017; Korani et al., 2017; Mohammadnia and Hassani, 2017).

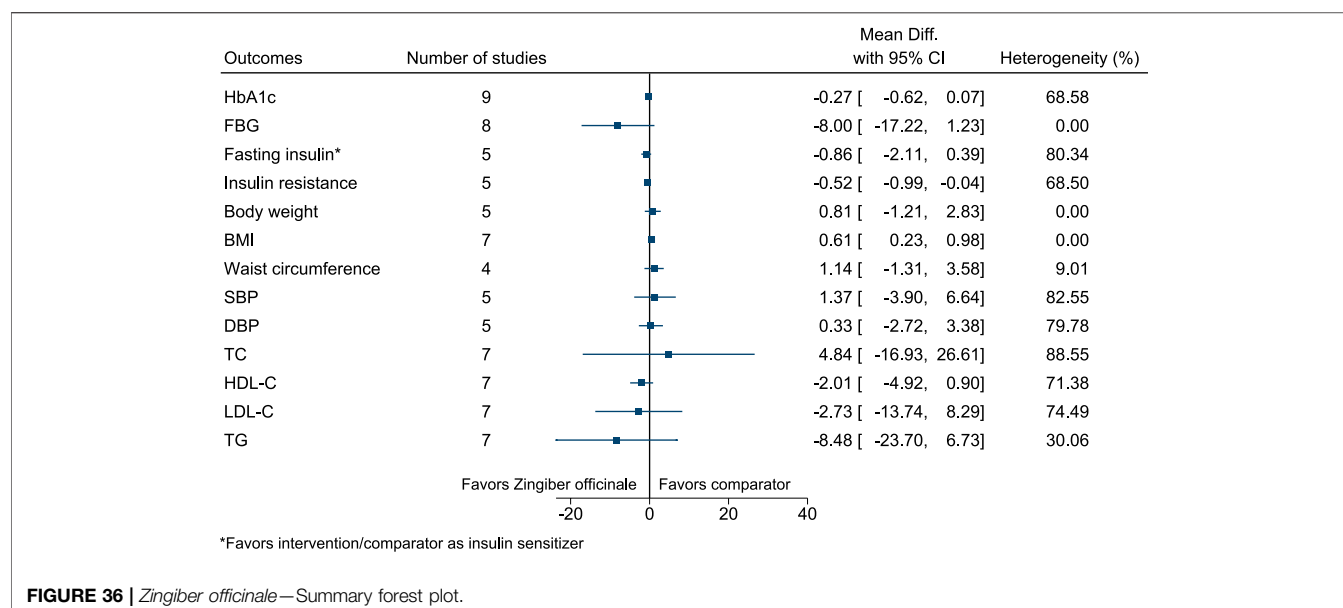


FIGURE 36 | *Zingiber officinale*—Summary forest plot.

5.5.35 *Zingiber officinale* Roscoe

Zingiber officinale significantly increased BMI (0.6 kg/m²; 0.2–1) (see Figure 36). (Mahluji et al., 2013; Arablou et al., 2014a; Arablou et al., 2014b; Azimi et al., 2014; Mozaffari-Khosravi et al., 2014; Shidfar et al., 2015; Azimi et al., 2016; Arzati et al., 2017; Talaei et al., 2017b; Mohammadi et al., 2017; Talaei et al., 2018; Zarezadeh et al., 2018; Mohammadi and Avandi, 2019; Carvalho et al., 2020; Gholinezhad et al., 2020).

The following 65 Ayurvedic medicines, administered either as a single medicine or in combination with other Ayurvedic medicines, could not be included in any meta-analyses due to being assessed in single studies: *Abelmoschus esculentus* (L.) Moench, *Acacia Senegal* (L.) Willd., *Acalypha indica* L., *Allium cepa* L., Asanadi Ghana Vati, AYUBES, *Berberis aristata* DC, BGR-34, Bilvadi Churna, *Capparis spinosa* L., CardiPro, *Cichorium intybus* L., Cogent db, *Convolvulus prostratus* Forssk., Darvyadi Kwatha, DCBT 2345, Diabetea tea, *Eclipta prostrata* (L.) L., *Emblica officinalis* Gaertn., combination of *Emblica officinalis* and *Withania somnifera* (L.) Dunal, Herbal combination, *Hibiscus sabdariffa* L., Hyponidd, Inolter, Kalpit, Khadira-Kramuka Kashaya Ghanavati, Kiratadi Churna, *Linum usitatissimum* L., Lodhradi Kashaya Ghana Vati, Madhumeha Nashini Gutika, Madhumehari Vati, Mamajjaka Ghana Vati, *Mangifera indica* L., Mehagni, *Murraya koenigii* (L.) Spreng., *Musa sapientum* O.Kuntze, Mustadi Kwatha Ghana Vati, combination of Naga Bhasma and Nishamalaki, combination of *Nigella sativa* and *Trigonella foenum-graecum*, Nisha Katakadi Kashaya, Nishamalaki, combination of Nishamalaki and *Hordeum vulgare* L., combination of Nishamalaki and Shilajit, *Ocimum tenuiflorum* L., Pancreas tonic, *Phyllanthus amarus* Schumach. & Thonn., Polyherbal formulation, Salasaradi Kashaya, Swarnamakshika Bhasma, Talapotaka Churna, Tejashiladi Vati, *Terminalia chebula* Retz., combination of *Tinospora cordifolia* and *Azadirachta indica*, *Tribulus terrestris*

L., combination of *Trigonella foenum-graecum* and *Ocimum tenuiflorum*, Trikatu Gutika, *Triticum aestivum* L., Trivanga Bhasma, *Vernonia cinerea* (L.) Less., Vidangadi Yoga, Vijaysaradi Ghana Vati, *Withania coagulans* (Stocks) Dunal, *Withania somnifera*, Yashad Bhasma, and *Ziziphus mauritiana* Lam. (See Supplementary Appendix S7 for 89 comparisons of Ayurvedic medicines which could not be included in meta-analyses).

5.6 Safety of Interventions

Supplementary Appendix S8 reports the adverse events and dropouts/withdrawals/discontinued interventions due to adverse events in the included studies. Adverse events were not reported in many studies. If reported, these were mostly none to mild and predominately related to the gastrointestinal tract. However, in the majority of cases, the relationship between the intervention and adverse events was not provided.

6 DISCUSSIONS

Beneficial effects of several Ayurvedic medicines on T2DM-related outcomes, including blood glucose, were found. The reduction in HbA1c of at least 0.3% or 0.4% is considered to be clinically meaningful, (US Food and Drug Administration, 2008) and a number of Ayurvedic medicines were found to bring such reduction such as *Aegle marmelos* (L.) Corrêa, *Boswellia serrata* Roxb., *Gynostemma pentaphyllum* (Thunb.) Makino, *Momordica charantia* L., *Nigella sativa* L., *Plantago ovata* Forssk., *Tinospora cordifolia* (Willd.) Hook.f. & Thomson, *Trigonella foenum-graecum* L., and *Urtica dioica* L. compared to control. Similarly, FBG was reduced by 4–56 mg/dl for a range of Ayurvedic medicines. However, the majority of studies did not assess HRQoL, an important patient-reported outcome. Adverse

events were not reported in many studies. If reported, these were mostly none to mild and predominantly related to the gastrointestinal tract. The findings are consistent with several systematic reviews conducted on single herbs as well as Ayurveda as a whole system. (Hardy et al., 2001; Yeh et al., 2003; Shekelle et al., 2005; Nahas and Moher, 2009; Shojaii et al., 2011; Sridharan et al., 2011; Suksomboon et al., 2011; Akilen et al., 2012; Allen et al., 2013; Gibb et al., 2015; Namazi et al., 2019; Peter et al., 2019; Jalali et al., 2020; Jamali et al., 2020) It should be noted that the majority of these Ayurvedic medicines are already in use in many countries, and many are used as dietary ingredients such as spices or foods. In many countries, Ayurvedic medicines are available over-the-counter (which includes online shopping) and are considered as dietary supplements. (Chattopadhyay et al., 2020b) Ayurveda is now recognized in 17 countries, including in and beyond South Asia. (Press Information Bureau, 2021) The integration of Ayurveda and Western medicine has been done in India. (Priya and Shweta, 2010) Many single herbs included in this review are not restricted to Ayurveda but are also used in other traditional therapies around the world such as Iranian traditional medicine and traditional Chinese medicine. Similarly, many traditional therapies use multi-ingredient medicines such as Unani (Graeco-Arabic), Siddha (from Southern part of India), traditional Chinese medicine, and Russian traditional medicine. (Chattopadhyay and Bochenek, 2008; Li et al., 2014; Shikov et al., 2021).

The Cochrane systematic review was conducted a decade ago and focused on multiherbal formulations and Ayurveda as a whole system and excluded single herbs and their extracts. (Sridharan et al., 2011) In this review, classical and proprietary Ayurvedic medicines in any form were included (containing plant- as well as mineral-origin ingredients–single or in combination). Many Ayurveda experts and Ayurvedic practitioners may view the inclusion of herb extracts and proprietary Ayurvedic medicines in this review as a deviation from the classical style of management. However, in reality, many Ayurvedic practitioners prescribe, and many people consume these types of medicines. Similarly, Ayurveda experts and Ayurvedic practitioners may view the exclusion of Ayurvedic detoxifying and purifying therapies (e.g., Panchakarma) in this review as a deviation from the classical style of management. However, considering the feasibility and practicality of the review work, these were beyond the scope of this review. The focus of this review was on Ayurvedic medicines, as these are commonly prescribed and consumed. Having said that, the future review work should consider synthesizing evidence on the effectiveness and safety of such complex interventions.

Overall, the methodology was not adequately reported in the studies, and this resulted in poor methodological quality scoring. The assessment of methodological quality is subjective to a large extent, and the reviewers were strict. For example, other systematic reviewers might be satisfied if the differences between study arms in terms of their follow-up are described. However, the reviewers went a step further and were expecting these to be analyzed. The strictness is one of the reasons for poor methodological quality scoring. In addition, if the funding statement was provided, it was mostly brief and difficult to

determine the level of support received from pharmaceutical companies. For example, it was not always clear if a pharmaceutical company provided the trial medicines for free or these were purchased. Therefore, it was difficult to determine the funding bias i.e., the tendency of a study to support the interests of the study's financial sponsor.

This systematic review has several strengths and weaknesses. To the best of our knowledge, this was the first comprehensive systematic review on any traditional medicine including Ayurveda, and which included a wide range of classical and proprietary Ayurvedic medicines in any form (containing plant- as well as mineral-origin ingredients–single or in combination). A large number of sources and databases were searched, without any date or language restrictions. An extensively robust methodology was followed to conduct this review. Although the information provided in the studies was at times confusing, the reviewers tried their best to extract the correct information. Two independent reviewers were involved throughout the process, and a third reviewer cross-checked everything. The kappa statistic was within the acceptable range i.e., 0.67 and 0.57 for the title and abstract screening and full text screening, respectively. A multi-disciplinary team was involved in the review, with expertise in Ayurveda, medicinal plants, diabetes, systematic reviewing, and statistics. The initial plan was to perform a range of sensitivity and subgroup analyses. However, many of these could not be performed. For example, complete information on commercial funding or other support was needed to correctly conduct the sensitivity analysis by excluding commercially funded studies. However, it was unclear in 43% of RCTs. Some of the issues were outside the scope of this review, and the evidence should be synthesized in future reviews to decide the optimal option. For example, comparison of two or more drug manufacturing processes, forms or timings of administration, doses, and Anupans of the same Ayurvedic medicine. Similarly, many other factors, such as patients' age, sex, ethnicity, lifestyle (e.g., diet and physical activity), chronicity and severity of T2DM, and comorbidities, can influence the outcomes. However, due to limited data for some comparison, we were not able to conduct separate subgroup analyses to explore the potential influence of these factors. Apart from the issues highlighted in this review, there are some basic issues which were beyond its scope and need addressing as well. For example, standardization and quality control of Ayurvedic medicines. (Chattopadhyay and Bochenek, 2008)

7 CONCLUSION

The current evidence suggests the benefit of a range of Ayurvedic medicines in improving glycemic control in T2DM patients. This evidence base and more specifically the Summary of Findings table will be used to develop a clinical guideline for managing T2DM by Ayurvedic practitioners. Given the limitations of the available evidence and to strengthen the evidence base, high-quality RCTs should be conducted and reported.

8 RECOMMENDATIONS FOR PRACTICE

There is a need to develop, evaluate, and implement need-sensitive, evidence-based interventions to manage T2DM among different population groups. (Chattopadhyay and Leonardi-Bee, 2021) Based on the best available evidence as found in this systematic review and more specifically the Summary of Findings table, a clinical guideline for managing T2DM by Ayurvedic practitioners will now be systematically developed. The next steps will be guided by the GRADE approach, the United Kingdom's National Institute for Health and Care Excellence (NICE) manual for developing guidelines and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument. (Brouwers et al., 2010; Schünemann et al., 2013; National Institute for Health and Care Excellence, 2014) Clinical guidelines for managing T2DM by Ayurvedic practitioners exist. (Central Council for Research in Ayurvedic Sciences, 2011; Ministry of Ayush, 2016; Ministry of Health and Family Welfare, 2016; Central Council for Research in Ayurvedic Sciences, 2017; Central Council for Research in Ayurvedic Sciences and Directorate General of Health Services, 2018) However, their quality is questionable due to several factors, including whether the best available evidence was considered. Low-quality clinical guidelines can lead to the use of ineffective interventions, inefficient use of scarce resources, and most importantly, harm to patients. (Institute of Medicine, 2011) The goal is to deter the usage of Ayurvedic medicines of no, minimal, or questionable value and promote the usage of effective and safe Ayurvedic medicines.

9 RECOMMENDATIONS FOR RESEARCH

In terms of recommendation for research, the future RCTs must address the following issues to strengthen the evidence base: 1) true randomization should be used to assign participants to study arms; 2) allocation concealment should be done to conceal the allocation to study arms; 3) adequate blinding should be done after considering who will be blinded and how blinding will be performed; 4) if placebo is used then it should be identical to the intervention, not only look and texture wise but also taste and smell wise, so that it is hard to differentiate from the intervention; 5) study arms should be treated identically other than the intervention of interest; 6) outcomes should be measured in the same way for study arms; 7) the sample size should be calculated based on appropriate components, such as primary outcome and *minimum* clinically important difference, and the trial should be adequately powered; 8) data should be analysed properly (including ITT analysis and post-intervention difference in outcomes between study arms); and 9) differences between study arms in terms of their follow-up should be described as well as analyzed. It should be noted that comprehensive and transparent reporting of the trial methods, funding, and results is important after designing and conducting a high-quality RCT. Clinical trial registration and prior publication of the trial protocol are also important. In order to update the clinical

guideline in the future, robust RCTs should be conducted not only on those Ayurvedic medicines that were included in meta-analyses but also on those on which meta-analysis was not possible. It would be beneficial if the comparison is also made with the standard treatment (i.e., OAD). T2DM is a chronic condition, and so, long-term studies are needed to determine the effectiveness and safety of these Ayurvedic medicines, especially in terms of preventing macro- or micro-vascular complications of T2DM and death. In addition, a sufficiently detailed description of the botanical and phytochemical aspects of the study material should be provided.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

KC conceptualized and designed the systematic review with the help of JP, MH, SL, SG, NT, TB, SK, and JL-B. KC, HW, JK, GN, AA, BK, and JL-B conducted the systematic review. KC wrote the first draft of the manuscript. HW, JK, GN, AA, BK, JP, MH, SL, SG, NT, TB, SK, and JL-B contributed significantly to the revision of the manuscript. All authors read and approved the final manuscript.

FUNDING

This systematic review was part of a project "Introduction of a clinical guideline to manage type-2 diabetes by Ayurvedic practitioners in Nepal: intervention development and feasibility study," funded by a grant from the United Kingdom's Department of Health and Social Care; Foreign, Commonwealth and Development Office; Medical Research Council; and Wellcome Trust Joint Global Health Trials (MR/T003537/1). The funding agencies had no role in designing the study or in writing the paper.

ACKNOWLEDGMENTS

Douglas Grindlay, information specialist at the University of Nottingham (United Kingdom), for contributing to the search strategies.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2022.821810/full#supplementary-material>

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor AS and reviewer ONP declared a past co-authorship with the author MH.

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Summary of Findings

Aegle marmelos (L.) Corrêa compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Aegle marmelos*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 1.6 % lower (3 lower to 0.3 lower)	210 (2 RCTs)	⊕⊕⊕○ MODERATE ^a	
FBG	MD 56 mg/dL lower (104 lower to 9 lower)	228 (3 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported 0 adverse event. Exact details were not provided in the other 2 studies.	(3 RCTs)	⊕⊕○○ LOW ^{a,d}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Small sample size.

b. Attrition bias.

c. Statistical heterogeneity.

d. Selective outcome reporting.

Allium sativum L. compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Allium sativum*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.4 % lower (0.9 lower to 0.1 higher)	272 (3 RCTs)	⊕⊕○○ LOW ^{a,b}	
FBG	MD 1 mg/dL lower (14 lower to 11 higher)	316 (4 RCTs)	⊕○○○ VERY LOW ^{a,b}	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported 0 adverse event in the intervention arm. 2 studies reported gastrointestinal tract related adverse event.	(3 RCTs)	⊕⊕○○ LOW ^{b,c}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

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Explanations

a. Statistical heterogeneity.

b. Small sample size.

c. Selective outcome reporting.

Aloe vera L. compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: Aloe vera

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.9 % lower (2.1 lower to 0.3 higher)	137 (3 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	
FBG	MD 11 mg/dL lower (32 lower to 10 higher)	197 (4 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported 0 adverse event. The other study reported 0 adverse event in the intervention arm and gastrointestinal tract related adverse event in the comparator arm.	(2 RCTs)	⊕⊕○○ LOW ^{c,d}	

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Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Statistical heterogeneity.

c. Small sample size.

d. Selective outcome reporting.

Anethum graveolens L. compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Anethum graveolens*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	N _e of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c - not reported	-	-	-	
FBG	MD 12 mg/dL lower (30 lower to 7 higher)	94 (2 RCTs)	⊕○○○ VERY LOW ^{a,b}	
HRQoL - not reported	-	-	-	
Adverse events - not reported	-	-	-	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

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Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Small sample size.

Azadirachta indica A.Juss. compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Azadirachta indica*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 1 % lower (1.2 lower to 0.8 lower)	78 (1 RCT)	⊕○○○ VERY LOW ^{a,b}	
FBG	MD 8 mg/dL lower (13 lower to 4 lower)	118 (2 RCTs)	⊕⊕⊕○ MODERATE ^b	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported gastrointestinal tract related adverse event.	(1 RCT)	⊕○○○ VERY LOW ^{b,c}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

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Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Small sample size.

c. Selective outcome reporting.

***Boswellia serrata* Roxb. compared to comparator for T2DM management**

Patient or population: T2DM management

Intervention: *Boswellia serrata*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.5 % lower (0.7 lower to 0.4 lower)	127 (2 RCTs)	⊕⊕⊕○ MODERATE ^a	
FBG	MD 24 mg/dL lower (28 lower to 21 lower)	127 (2 RCTs)	⊕⊕⊕○ MODERATE ^a	
HRQoL - not reported	-	-	-	
Adverse events	2 studies reported 0 adverse event (this includes 1 study which reported 0 adverse event in the intervention arm).	(2 RCTs)	⊕⊕○○ LOW ^{a,b}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Small sample size.

b. Selective outcome reporting.

Camellia sinensis (L.) Kuntze compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Camellia sinensis*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	N _e of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.1 % lower (0.4 lower to 0.2 higher)	317 (6 RCTs)	⊕⊕○○ LOW ^{a,b}	
FBG	MD 11 mg/dL lower (26 lower to 5 higher)	237 (4 RCTs)	⊕⊕○○ LOW ^{a,b}	
HRQoL - Physical health	SMD 0.01 SD higher (0.36 lower to 0.38 higher)	108 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	
HRQoL - Psychological	SMD 0.12 SD higher (0.25 lower to 0.5 higher)	108 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	
HRQoL - Social relationships	SMD 0.02 SD higher (0.35 lower to 0.39 higher)	108 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	
HRQoL - Environment	SMD 0.11 SD lower (0.62 lower to 0.41 higher)	108 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	
Adverse events	3 studies mainly reported gastrointestinal tract related adverse events and hypoglycemia (this includes 1 study which reported 0 adverse event in the comparator arm).	(3 RCTs)	⊕⊕○○ LOW ^{b,c}	

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Small sample size.

c. Selective outcome reporting.

Cinnamomum aromaticum Nees compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Cinnamomum aromaticum*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.2 % lower (0.5 lower to 0.1 higher)	794 (10 RCTs)	⊕⊕⊕○ MODERATE ^a	
FBG	MD 1 mg/dL higher (6 lower to 9 higher)	692 (9 RCTs)	⊕⊕⊕⊕ HIGH	
HRQoL - not reported	-	-	-	
Adverse events	3 studies reported 0 adverse event (this includes 1 study which reported 0 adverse event in the intervention arm). 2 studies reported gastrointestinal tract and skin related adverse events (this includes 1 study which reported 0 adverse event in the intervention arm and 1 study which reported 0 adverse event in the comparator arm).	(5 RCTs)	⊕⊕⊕○ MODERATE ^b	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

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Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Publication bias detected in the funnel plot.

b. Selective outcome reporting.

Cinnamomum verum J.Presl compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Cinnamomum verum*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	N _e of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.1 % lower (0.5 lower to 0.3 higher)	403 (6 RCTs)	⊕⊕○○ LOW ^{a,b}	
FBG	MD 11 mg/dL lower (19 lower to 3 lower)	403 (6 RCTs)	⊕⊕⊕○ MODERATE ^a	
HRQoL - not reported	-	-	-	
Adverse events	4 studies reported 0 adverse event (this includes 1 study which reported 0 adverse event in the intervention arm). 1 study reported an adverse event (this study reported 0 adverse event in the intervention arm).	(5 RCTs)	⊕⊕○○ LOW ^{c,d}	

CI: Confidence interval; **MD:** Mean difference

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Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Statistical heterogeneity.

c. Selective outcome reporting.

d. Small sample size.

***Citrullus colocynthis* (L.) Schrad. compared to comparator for T2DM management**

Patient or population: T2DM management

Intervention: *Citrullus colocynthis*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.2 % lower (0.7 lower to 0.4 higher)	120 (2 RCTs)	⊕⊕⊕○ MODERATE ^a	
FBG	MD 3 mg/dL lower (18 lower to 12 higher)	120 (2 RCTs)	⊕⊕⊕○ MODERATE ^a	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported 0 adverse event in the intervention arm. The other study reported gastrointestinal tract related adverse event.	(2 RCTs)	⊕⊕○○ LOW ^{a,b}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

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Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Small sample size.

b. Selective outcome reporting.

Coccinia grandis (L.) Voigt compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Coccinia grandis*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.5 % lower (1.1 lower to 0)	217 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	
FBG	MD 22 mg/dL lower (25 lower to 19 lower)	217 (2 RCTs)	⊕⊕⊕○ MODERATE ^b	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported 0 adverse event. The other study mainly reported gastrointestinal tract related adverse events and hypoglycemia.	(2 RCTs)	⊕⊕○○ LOW ^{b,c}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

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Explanations

a. Statistical heterogeneity.

b. Small sample size.

c. Selective outcome reporting.

Crocus sativus L. compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Crocus sativus*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.2 % higher (0.1 lower to 0.4 higher)	277 (4 RCTs)	⊕⊕○○ LOW ^{a,b}	
FBG	MD 9 mg/dL lower (26 lower to 8 higher)	334 (5 RCTs)	⊕⊕○○ LOW ^{a,b}	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported 0 adverse event in the intervention arm.	(1 RCT)	⊕○○○ VERY LOW ^{b,c}	

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Explanations

a. Attrition bias.

b. Small sample size.

c. Selective outcome reporting.

Cuminum cyminum L. compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Cuminum cyminum*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 1.5 % lower (3.7 lower to 0.7 higher)	140 (2 RCTs)	⊕○○○ VERY LOW ^{a,b}	
FBG	MD 14 mg/dL lower (35 lower to 6 higher)	290 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported 0 adverse event in the intervention arm.	(1 RCT)	⊕○○○ VERY LOW ^{b,c}	

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Explanations

a. Statistical heterogeneity.

b. Small sample size.

c. Selective outcome reporting.

Curcuma longa L. compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Curcuma longa*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.2 % lower (0.7 lower to 0.4 higher)	593 (6 RCTs)	⊕⊕○○ LOW ^{a,b}	
FBG	MD 10 mg/dL lower (15 lower to 5 lower)	593 (6 RCTs)	⊕⊕⊕○ MODERATE ^a	
HRQoL - not reported	-	-	-	
Adverse events	3 studies reported 0 adverse event (this includes 1 study which reported 0 adverse event in the comparator arm). 3 studies mainly reported gastrointestinal tract related adverse events.	(6 RCTs)	⊕⊕⊕○ MODERATE ^c	

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Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Statistical heterogeneity.

c. Selective outcome reporting.

Cyamopsis tetragonoloba (L.) Taub. compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Cyamopsis tetragonoloba*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 1 % lower (2 lower to 0)	39 (1 RCT)	⊕⊕○○ LOW ^a	
FBG	MD 7 mg/dL lower (58 lower to 44 higher)	56 (2 RCTs)	⊕○○○ VERY LOW ^{a,b}	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported gastrointestinal tract related adverse events. Exact details were not provided in the other study.	(2 RCTs)	⊕○○○ VERY LOW ^{a,c}	

CI: Confidence interval; MD: Mean difference

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Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Small sample size.

b. Statistical heterogeneity.

c. Selective outcome reporting.

***Elettaria cardamomum* (L.) Maton compared to comparator for T2DM management**

Patient or population: T2DM management

Intervention: *Elettaria cardamomum*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.2 % higher (0.2 lower to 0.5 higher)	164 (2 RCTs)	⊕⊕⊕○ MODERATE ^a	
FBG	MD 1 mg/dL higher (9 lower to 12 higher)	164 (2 RCTs)	⊕⊕⊕○ MODERATE ^a	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported 0 adverse event in the intervention arm. The other study reported adverse events (this study reported 0 adverse event in the comparator arm).	(2 RCTs)	⊕⊕⊕○ MODERATE ^a	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Small sample size.

***Enicostemma axillare* (Lam.) Raynal compared to OAD for T2DM management**

Patient or population: T2DM management

Intervention: *Enicostemma axillare*

Comparison: OAD

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.4 % lower (1.6 lower to 0.7 higher)	32 (1 RCT)	⊕○○○ VERY LOW ^{a,b}	
FBG	MD 23 mg/dL higher (20 lower to 66 higher)	101 (2 RCTs)	⊕○○○ VERY LOW ^{b,c}	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported 0 adverse event in the intervention arm.	(1 RCT)	⊕○○○ VERY LOW ^{b,d}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Small sample size.

c. Statistical heterogeneity.

d. Selective outcome reporting.

Gynostemma pentaphyllum (Thunb.) Makino compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Gynostemma pentaphyllum*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Ne of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 1 % lower (1.5 lower to 0.6 lower)	49 (2 RCTs)	⊕⊕○○ LOW ^a	
FBG	MD 29 mg/dL lower (43 lower to 15 lower)	49 (2 RCTs)	⊕⊕○○ LOW ^a	
HRQoL - not reported	-	-	-	
Adverse events	2 studies reported 0 adverse event.	(2 RCTs)	⊕⊕○○ LOW ^a	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Small sample size.

***Ipomoea batatas* (L.) Lam. compared to comparator for T2DM management**

Patient or population: T2DM management

Intervention: *Ipomoea batatas*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.2 % lower (0.5 lower to 0.1 higher)	122 (2 RCTs)	⊕⊕⊕○ MODERATE ^a	
FBG	MD 8 mg/dL lower (13 lower to 3 lower)	122 (2 RCTs)	⊕⊕⊕○ MODERATE ^a	
HRQoL - not reported	-	-	-	
Adverse events	Exact details were not provided in 2 studies but mainly reported gastrointestinal tract related adverse events.	(2 RCTs)	⊕⊕○○ LOW ^{a,b}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Small sample size.

b. Selective outcome reporting.

Juglans regia L. compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Juglans regia*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.3 % lower (0.6 lower to 0)	285 (5 RCTs)	⊕⊕○○ LOW ^{a,b}	
FBG	MD 14 mg/dL lower (24 lower to 4 lower)	285 (5 RCTs)	⊕⊕○○ LOW ^{a,b}	
HRQoL - not reported	-	-	-	
Adverse events	2 studies reported 0 adverse event (this includes 1 study which reported 0 adverse event in the intervention arm). 2 studies mainly reported gastrointestinal tract related adverse events (this includes 1 study which reported 0 adverse event in the comparator arm).	(4 RCTs)	⊕⊕○○ LOW ^{b,c}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Small sample size.

c. Selective outcome reporting.

Momordica charantia L. compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Momordica charantia*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.3 % lower (0.4 lower to 0.1 lower)	404 (7 RCTs)	⊕⊕⊕○ MODERATE ^a	
FBG	MD 14 mg/dL lower (23 lower to 4 lower)	360 (7 RCTs)	⊕⊕○○ LOW ^{a,b}	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported 0 adverse event. 5 studies mainly reported gastrointestinal tract related adverse events (this includes 1 study which reported 0 adverse event in the comparator arm).	(6 RCTs)	⊕⊕○○ LOW ^{b,c}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Small sample size.

c. Selective outcome reporting.

Momordica charantia L. compared to OAD for T2DM management

Patient or population: T2DM management

Intervention: *Momordica charantia*

Comparison: OAD

Outcomes	Absolute effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.4 % higher (0.2 higher to 0.7 higher)	201 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	
FBG	MD 14 mg/dL higher (9 higher to 19 higher)	198 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	
HRQoL - not reported	-	-	-	
Adverse events	1 study mainly reported gastrointestinal tract related adverse events. Exact details were not provided in the other study.	(2 RCTs)	⊕⊕○○ LOW ^{b,c}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Small sample size.

c. Selective outcome reporting.

***Nigella sativa* L. compared to comparator for T2DM management**

Patient or population: T2DM management

Intervention: *Nigella sativa*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.4 % lower (0.6 lower to 0.1 lower)	325 (4 RCTs)	⊕⊕⊕○ MODERATE ^a	
FBG	MD 15 mg/dL lower (30 lower to 0)	458 (7 RCTs)	⊕⊕⊕○ MODERATE ^b	
HRQoL - not reported	-	-	-	
Adverse events	3 studies reported 0 adverse event (this includes 1 study which reported 0 adverse event in the intervention arm). 2 studies reported gastrointestinal tract related adverse events (this includes 1 study which reported 0 adverse event in the comparator arm and exact details were not provided in the other study).	(5 RCTs)	⊕⊕○○ LOW ^{a,c}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Small sample size.

b. Statistical heterogeneity.

c. Selective outcome reporting.

***Plantago ovata* Forssk. compared to comparator for T2DM management**

Patient or population: T2DM management

Intervention: *Plantago ovata*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.9 % lower (1.4 lower to 0.3 lower)	106 (3 RCTs)	⊕⊕○○ LOW ^{a,b}	
FBG	MD 32 mg/dL lower (40 lower to 23 lower)	106 (3 RCTs)	⊕⊕○○ LOW ^{a,b}	
HRQoL - not reported	-	-	-	
Adverse events	1 study mainly reported gastrointestinal tract related adverse events. Exact details were not provided in the other study but hypoglycemia was reported.	(2 RCTs)	⊕○○○ VERY LOW ^{b,c}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Small sample size.

c. Selective outcome reporting.

***Portulaca oleracea* L. compared to comparator for T2DM management**

Patient or population: T2DM management

Intervention: *Portulaca oleracea*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.5 % higher (0 to 1 higher)	63 (1 RCT)	⊕⊕○○ LOW ^a	
FBG	MD 10 mg/dL lower (34 lower to 14 higher)	123 (3 RCTs)	⊕⊕⊕○ MODERATE ^a	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported adverse events.	(1 RCT)	⊕○○○ VERY LOW ^{a,b}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Small sample size.

b. Selective outcome reporting.

***Pterocarpus marsupium* Roxb. compared to OAD for T2DM management**

Patient or population: T2DM management

Intervention: *Pterocarpus marsupium*

Comparison: OAD

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.2 % higher (0.2 lower to 0.6 higher)	90 (1 RCT)	⊕○○○ VERY LOW ^{a,b}	
FBG	MD 16 mg/dL higher (7 lower to 39 higher)	409 (2 RCTs)	⊕⊕○○ LOW ^{a,c}	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported 0 adverse event in the intervention arm. The other study reported gastrointestinal tract related adverse event.	(2 RCTs)	⊕⊕⊕○ MODERATE ^d	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Small sample size.

c. Statistical heterogeneity.

d. Selective outcome reporting.

***Punica granatum* L. compared to comparator for T2DM management**

Patient or population: T2DM management

Intervention: *Punica granatum*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.1 % lower (0.5 lower to 0.4 higher)	312 (6 RCTs)	⊕⊕○○ LOW ^{a,b}	
FBG	MD 8 mg/dL lower (16 lower to 1 higher)	312 (6 RCTs)	⊕⊕○○ LOW ^{a,b}	
HRQoL - not reported	-	-	-	
Adverse events	2 studies reported 0 adverse event (this includes 1 study which reported 0 adverse event in the intervention arm). 1 study mainly reported gastrointestinal tract related adverse events.	(3 RCTs)	⊕⊕○○ LOW ^{b,c}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Small sample size.

c. Selective outcome reporting.

Sesamum indicum L. compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Sesamum indicum*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.7 % lower (1.4 lower to 0)	90 (2 RCTs)	⊕○○○ VERY LOW ^{a,b}	
FBG	MD 46 mg/dL lower (116 lower to 25 higher)	90 (2 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	
HRQoL - not reported	-	-	-	
Adverse events - not reported	-	-	-	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Small sample size.

c. Statistical heterogeneity.

Shilajit compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: Shilajit

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.3 % lower (0.7 lower to 0.2 higher)	132 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	
FBG	MD 4 mg/dL lower (18 lower to 9 higher)	92 (1 RCT)	⊕○○○ VERY LOW ^{b,c}	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported adverse events.	(1 RCT)	⊕○○○ VERY LOW ^{b,d}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Statistical heterogeneity.

b. Small sample size.

c. Attrition bias.

d. Selective outcome reporting.

Syzygium cumini (L.) Skeels compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Syzygium cumini*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.1 % lower (1.5 lower to 1.3 higher)	124 (2 RCTs)	⊕⊕○○ LOW ^{a,b}	
FBG	MD 5 mg/dL lower (40 lower to 29 higher)	124 (2 RCTs)	⊕○○○ VERY LOW ^{a,b}	
HRQoL - not reported	-	-	-	
Adverse events - not reported	-	-	-	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Statistical heterogeneity.

b. Small sample size.

***Tinospora cordifolia* (Willd.) Hook.f. & Thomson compared to comparator for T2DM management**

Patient or population: T2DM management

Intervention: *Tinospora cordifolia*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.5 % lower (0.6 lower to 0.5 lower)	159 (2 RCTs)	⊕⊕⊕○ MODERATE ^a	
FBG	MD 4 mg/dL lower (6 lower to 3 lower)	140 (2 RCTs)	⊕⊕⊕○ MODERATE ^a	
HRQoL - not reported	-	-	-	
Adverse events	2 studies reported 0 adverse event (this includes 1 study which reported 0 adverse event in the intervention arm).	(2 RCTs)	⊕⊕⊕○ MODERATE ^a	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Small sample size.

***Trigonella foenum-graecum* L. compared to comparator for T2DM management**

Patient or population: T2DM management

Intervention: *Trigonella foenum-graecum*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.6 % lower (0.9 lower to 0.4 lower)	1095 (12 RCTs)	⊕⊕⊕○ MODERATE ^a	
FBG	MD 14 mg/dL lower (22 lower to 5 lower)	1069 (13 RCTs)	⊕⊕⊕○ MODERATE ^{a,b}	
HRQoL - not reported	-	-	-	
Adverse events	5 studies reported 0 adverse event (this includes 2 studies which reported 0 adverse event in the intervention arm). 5 studies reported different body systems related adverse events but mainly gastrointestinal tract related and hypoglycemia (this includes 1 study which reported 0 adverse event in the comparator arm). Exact details were not provided in 1 study.	(11 RCTs)	⊕⊕⊕○ MODERATE ^c	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Publication bias.

b. Statistical heterogeneity.

c. Selective outcome reporting.

Trigonella foenum-graecum L. compared to OAD for T2DM management

Patient or population: T2DM management

Intervention: *Trigonella foenum-graecum*

Comparison: OAD

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.3 % higher (1 lower to 1.6 higher)	49 (2 RCTs)	⊕○○○ VERY LOW ^{a,b}	
FBG	MD 27 mg/dL higher (24 lower to 79 higher)	49 (2 RCTs)	⊕○○○ VERY LOW ^{a,b}	
HRQoL - not reported	-	-	-	
Adverse events	2 studies mainly reported gastrointestinal tract related adverse events and hypoglycemia (this includes 1 study which reported 0 adverse event in the comparator arm).	(2 RCTs)	⊕⊕○○ LOW ^b	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Lack of blinding.

b. Small sample size.

Urtica dioica L. compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Urtica dioica*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 1.3 % lower (2.4 lower to 0.2 lower)	181 (3 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	
FBG	MD 20 mg/dL lower (41 lower to 1 higher)	376 (8 RCTs)	⊕○○○ VERY LOW ^{a,b,c}	
HRQoL - not reported	-	-	-	
Adverse events	1 study reported 0 adverse event. The other study reported skin related adverse event (this study reported 0 adverse event in the comparator arm).	(2 RCTs)	⊕⊕○○ LOW ^{c,d}	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Statistical heterogeneity.

c. Small sample size.

d. Selective outcome reporting.

Zingiber officinale Roscoe compared to comparator for T2DM management

Patient or population: T2DM management

Intervention: *Zingiber officinale*

Comparison: comparator (i.e., no medicine, no additional medicine, or placebo)

Outcomes	Absolute effect (95% CI)	N _e of participants (studies)	Certainty of the evidence (GRADE)	Comments
HbA1c	MD 0.3 % lower (0.6 lower to 0.1 higher)	561 (9 RCTs)	⊕⊕⊕○ MODERATE ^a	
FBG	MD 8 mg/dL lower (17 lower to 1 higher)	517 (8 RCTs)	⊕⊕⊕○ MODERATE ^a	
HRQoL - not reported	-	-	-	
Adverse events	3 studies reported 0 adverse event (this includes 2 studies which reported 0 adverse event in the intervention arm). 2 studies reported gastrointestinal tract related adverse events.	(5 RCTs)	⊕⊕⊕○ MODERATE ^b	

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Attrition bias.

b. Selective outcome reporting.

Appendix S1: Search strategies.

MEDLINE (Ovid) (1946-16 January 2021): 2042 records

1. exp Diabetes mellitus, type 2/
2. (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw.
3. ((Late or maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)).tw.
4. ((Ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)).tw.
5. ((Non-insulin* or non insulin* or noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw.
6. (NIDDM or T2DM or T2D).tw.
7. Prameha.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8. Madhumeha.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9. or/1-8
10. exp Medicine, Ayurvedic/
11. Ayurved*.tw,ot.
12. *Medicine, traditional/
13. exp Complementary medicine/tu [Therapeutic use]
14. ((Plant* or herb* or medicin* or drug* or therap* or intervention* or extract* or formulation* or preparation* or supplement*) adj6 (Ayurved* or Hindu or Indian)).tw,ot.
15. exp Plants, medicinal/tu [Therapeutic use]
16. exp Plant extracts/tu [Therapeutic use]
17. exp Plants/tu [Therapeutic use]
18. ((Plant* or herb*) adj6 (medicin* or drug* or therap* or intervention* or extract* or formulation* or preparation* or supplement*)).tw,ot.
19. exp Ethnobotany/
20. exp Ethnopharmacology/
21. (Ethnobotan* or ethno botan* or ethnopharmacolog* or ethno pharmacolog*).tw,ot.
22. *Phytotherapy/
23. (Phytotherap* or phyto therap*).tw,ot.
24. exp Acanthaceae/
25. exp Aegle/
26. exp Aloe/
27. exp Artocarpus/
28. exp Azadirachta/
29. exp Butea/
30. exp Cassia/
31. exp Catharanthus/
32. exp Cinnamomum/
33. exp Cinnamomum aromaticum/
34. exp Cinnamomum zeylanicum/
35. exp Clerodendrum/
36. exp Cucurbitaceae/
37. exp Curcuma/
38. exp Cyamopsis/
39. exp Ficus/
40. exp Garlic/
41. exp Ginger/
42. exp Gymnema/
43. exp Gymnema sylvestre/

44. exp Ipomoea batatas/
45. exp Momordica charantia/
46. exp Murraya/
47. exp Nigella sativa/
48. exp Ocimum sanctum/
49. exp Onions/
50. exp Phyllanthus/
51. exp Phyllanthus emblica/
52. exp Piper/
53. exp Plantago/
54. exp Psyllium/
55. exp Pterocarpus/
56. exp Punicaceae/
57. exp Salacia/
58. exp Solanum/
59. exp Syzygium/
60. exp Tamarindus/
61. exp Tinospora/
62. exp Trigonella/
63. exp Lead/
64. exp Tin/
65. (Aegle marmelos or Crateva marmelos or Allium cepa or Allium sativum or Aloe vera or Artocarpus heterophyllus or Azadirachta indica or Melia azadirachta or Butea monosperma or Cassia auriculata or Catharanthus roseus or Vinca rosea or Cinnamomum aromaticum or Cinnamomum cassia or Cinnamomum tamala or Cinnamomum verum or Cinnamomum zeylanicum or Clerodendrum phlomides or Coccinia grandis or Coccinia cordifolia or Coccinia indica or Curcuma longa or Cyamopsis tetragonoloba or Emblica officinalis or Phyllanthus emblica or Enicostemma axillare or Enicostemma littorale or Ficus carica or Gymnema lactiferum or Gymnema sylvestre or Hygrophila schulli or Asteracantha longifolia or Ipomoea batatas or Momordica charantia or Murraya koenigii or Nigella sativa or Ocimum tenuiflorum or Ocimum sanctum or Phyllanthus amarus or Phyllanthus niruri or Piper longum or Plantago arenaria or Plantago psyllium or Pterocarpus marsupium or Pterocarpus santalinus or Punica granatum or Salacia chinensis or Salacia reticulata or Solanum torvum or Syzygium cumini or Eugenia jambolana or Syzygium jambolanum or Syzygium jambos or Eugenia jambos or Tamarindus indica or Tinospora cordifolia or Trigonella foenum-graecum or Zingiber officinale).tw,ot.
66. (Lead or Tin or Black bitumen or Black asphalt*).tw,ot.
67. (Arogyavardhini* or Arogyavardhini* or Ayaskriti or Chandrakant* or Chandraprabh* or Devdarvarisht* or Devdarvarist* or Dhanvantar* or Gokshuradi* or Goksuradi* or Jambudaryisht* or Jambudaryist* or Katakakhadiradi* or Kathakakhadiradi* or Kshirabal* or Ksirabal* or Lodhrasav* or Mamajjak* or Nag* or Naag* or Nimbadi* or Nimadi* or Nishamalak* or Nisamalak* or Nishamlak* or Nisamlak* or Nishakathakadi* or Nisakathakadi* or Phalatrikadi* or Falatrikadi* or Rajanyamalakadi* or Rajanyamlakadi* or Saptamrit* or Shaptamrit* or Saptargangyadi* or Shilajit* or Silajit* or Shilajat* or Silajat* or Shilajeet* or Silajeet* or Siva* or Shiva* or Somnath* or Shomnath* or Triphal* or Trifal* or Trivang* or Tribang* or Vang* or Bang* or Vasant Kusumakar* or Vashant Kushumakar* or Vasanta Kusumakar* or Vashanta Kushumakar* or Vasantkusumakar* or Vashantkushumakar* or Vasantakusumakar* or Vashantakushumakar* or Basant Kusumakar* or Bashant Kushumakar* or Basanta Kusumakar* or Bashanta Kushumakar* or Basantkusumakar* or Bashantkushumakar* or Basantakusumakar* or Bashantakushumakar* or Vijayasaradi* or Vijayasharadi* or Vijaysaradi* or Vijaysharadi* or Bijayasaradi* or Bijayasharadi* or Bijaysaradi* or Bijaysharadi* or Vyoshadi* or Vyosadi* or Byoshadi* or Byosadi*).tw,ot.
68. (Ayush 82 or Ayush-82 or Cogent DB or Diabecon or D 400 or D-400 or GS4 or Gurmar or Hyponidd or Inolter or M 93 or M-93 or MA 471 or MA-471 or Nosulin or Pancreas Tonic).tw,ot.

69. or/10-68
70. Randomized controlled trial.pt.
71. Controlled clinical trial.pt.
72. Clinical trial.pt.
73. exp Clinical trials as Topic/
74. Placebos/
75. Random allocation/
76. Double-blind method/
77. Single-blind method/
78. Cross-over studies/
79. ((Random\$ or control\$ or clinical\$) adj3 (trial\$ or stud\$)).tw.
80. (Random\$ adj3 allocat\$).tw.
81. Placebo\$.tw.
82. ((Singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).tw.
83. (Crossover\$ or (cross adj over\$)).tw.
84. or/70-83
85. 9 and 69 and 84

Embase (Ovid) (1974-16 January 2021): 13989 records

1. exp Diabetes mellitus, type 2/
2. (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw.
3. ((Late or maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)).tw.
4. ((Ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)).tw.
5. ((Non-insulin* or non insulin* or noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw.
6. (NIDDM or T2DM or T2D).tw.
7. Prameha.mp.
8. Madhumeha.mp.
9. or/1-8
10. exp Medicine, Ayurvedic/
11. Ayurved*.tw,ot.
12. *Medicine, traditional/
13. exp Complementary medicine/tu [Therapeutic use]
14. ((Plant* or herb* or medicin* or drug* or therap* or intervention* or extract* or formulation* or preparation* or supplement*) adj6 (Ayurved* or Hindu or Indian)).tw,ot.
15. exp Plants, medicinal/tu [Therapeutic use]
16. exp Plant extracts/tu [Therapeutic use]
17. exp Plants/tu [Therapeutic use]
18. ((Plant* or herb*) adj6 (medicin* or drug* or therap* or intervention* or extract* or formulation* or preparation* or supplement*)).tw,ot.
19. exp Ethnobotany/
20. exp Ethnopharmacology/
21. (Ethnobotan* or ethno botan* or ethnopharmacolog* or ethno pharmacolog*).tw,ot.
22. *Phytotherapy/
23. (Phytotherap* or phyto therap*).tw,ot.
24. exp Acanthaceae/
25. exp Aegle/
26. Aloe.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
27. Artocarpus.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

28. Azadirachta.mp. or exp Azadirachta indica/
29. exp Butea monosperma/ or exp Butea/ or Butea.mp.
30. Cassia.mp. or cassia extract/ or Cinnamomum cassia/ or exp Cassia/ or Cinnamomum cassia extract/
31. exp Catharanthus/
32. Cinnamomum.mp. or Cinnamomum camphora/ or exp Cinnamomum/
33. exp Cinnamomum/
34. exp Cinnamomum aromaticum/
35. exp Cinnamomum zeylanicum/
36. exp Clerodendrum/
37. exp Cucurbitaceae/
38. exp Curcuma/
39. exp Cyamopsis/
40. exp Ficus/
41. exp Garlic/
42. exp Ginger/
43. exp Gymnema/
44. exp Gymnema sylvestre/
45. exp Ipomoea batatas/
46. exp Momordica charantia/
47. exp Murraya/
48. exp Nigella sativa/
49. exp Ocimum sanctum/
50. exp Phyllanthus/
51. exp Phyllanthus emblica/
52. exp Piper/
53. exp Plantago/
54. exp Psyllium/
55. exp Pterocarpus/
56. exp Punicaceae/
57. exp Salacia/
58. exp Solanum/
59. Syzygium cumini/ or Syzygium.mp. or exp Syzygium/ or Syzygium cumini extract/
60. Tamarindus.mp. or exp Tamarind/
61. Tinospora cordifolia/ or Tinospora.mp. or exp Tinospora/ or Tinospora cordifolia extract/
62. Fenugreek/ or Trigonella.mp. or Trigonella foenum graecum extract/ or nonhuman/ or exp Trigonella/ or plant extract/ or plant seed/
63. exp Lead/ or Lead.mp.
64. Tin derivative/ or Tin.mp. or exp Tin/
65. Onion extract/ or Onion.mp. or exp Onion/
66. Piper.mp. or exp "Piper (plant)"/
67. (Lead or Tin or Black bitumen or Black asphalt*).tw,ab,kw,ot.
68. (Aegle marmelos or Crateva marmelos or Allium cepa or Allium sativum or Aloe vera or Artocarpus heterophyllus or Azadirachta indica or Melia azadirachta or Butea monosperma or Cassia auriculata or Catharanthus roseus or Vinca rosea or Cinnamomum aromaticum or Cinnamomum cassia or Cinnamomum tamala or Cinnamomum verum or Cinnamomum zeylanicum or Clerodendrum phlomides or Coccinia grandis or Coccinia cordifolia or Coccinia indica or Curcuma longa or Cyamopsis tetragonoloba or Emblica officinalis or Phyllanthus emblica or Enicostemma axillare or Enicostemma littorale or Ficus carica or Gymnema lactiferum or Gymnema sylvestre or Hygrophila schulli or Asteracantha longifolia or Ipomoea batatas or Momordica charantia or Murraya koenigii or Nigella sativa or Ocimum tenuiflorum or Ocimum sanctum or Phyllanthus amarus or Phyllanthus niruri or Piper longum or Plantago arenaria or Plantago psyllium or Pterocarpus marsupium or Pterocarpus santalinus or Punica granatum or Salacia chinensis or Salacia reticulata or Solanum torvum or Syzygium cumini or Eugenia jambolana or Syzygium jambolanum or Syzygium jambos or Eugenia jambos or

Tamarindus indica or Tinospora cordifolia or Trigonella foenum-graecum or Zingiber officinale).tw,ab,kw,ti.

69. (Arogyavardhini* or Arogyavardhini* or Ayaskriti or Chandrakant* or Chandraprabh* or Devdarvarisht* or Devdarvarist* or Dhanvantar* or Gokshuradi* or Goksuradi* or Jambudaryisht* or Jambudaryist* or Katakakhadiradi* or Kathakakhadiradi* or Kshirabal* or Ksirabal* or Lodhrasav* or Mamajjak* or Nag* or Naag* or Nimbadi* or Nimadi* or Nishamalak* or Nisamalak* or Nishamlak* or Nisamlak* or Nishakathakadi* or Nisakathakadi* or Phalatrikadi* or Falatrikadi* or Rajanyamalakadi* or Rajanyamlakadi* or Saptamrit* or Shaptamrit* or Saptargangyadi* or Shilajit* or Silajit* or Shilajat* or Silajat* or Shilajeet* or Silajeet* or Siva* or Shiva* or Somnath* or Shomnath* or Triphal* or Trifal* or Trivang* or Tribang* or Vang* or Bang* or Vasant Kusumakar* or Vashant Kushumakar* or Vasanta Kusumakar* or Vashanta Kushumakar* or Vasantkusumakar* or Vashantkushumakar* or Vasantakusumakar* or Vashantakushumakar* or Basant Kusumakar* or Bashant Kushumakar* or Basanta Kusumakar* or Bashanta Kushumakar* or Basantkusumakar* or Bashantkushumakar* or Basantakusumakar* or Bashantakushumakar* or Vijayasaradi* or Vijayasharadi* or Vijaysaradi* or Vijaysharadi* or Bijayasaradi* or Bijayasharadi* or Bijaysaradi* or Bijaysharadi* or Vyoshadi* or Vyosadi* or Byoshadi* or Byosadi*).tw,ot,ab,kw,ti.

70. or/10-69

71. Clinical trial/

72. Randomized controlled trial/

73. Randomization/

74. Single blind procedure/

75. Double blind procedure/

76. Crossover procedure/

77. Placebo/

78. Randomized controlled trial\$.tw.

79. RCT.tw.

80. Random allocation.tw.

81. Randomly allocated.tw.

82. Allocated randomly.tw.

83. (Allocated adj2 random).tw.

84. Single blind\$.tw.

85. Double blind\$.tw.

86. ((Treble or triple) adj blind\$.tw.

87. Placebo\$.tw.

88. Prospective study/

89. or/71-88

90. Case study/

91. Case report.tw.

92. Abstract report/ or letter/

93. or/90-92

94. 89 not 93

95. 9 and 70 and 94

CINAHL (EBSCOhost) (1937-16 January 2021): 193 records

(MH "medicine, Ayurvedic" OR Ayurved*) AND (MH "diabetes mellitus, type 2" OR diabet* OR NIDDM OR T2DM OR T2D OR Madhumeh* OR Prameh*)

PsycINFO (Ovid) (1806-16 January 2021): 595 records

1. exp Diabetes mellitus/

2. (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw.

3. ((Late or maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)).tw.

4. ((Ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)).tw.

5. ((Non-insulin* or non insulin* or noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw.
6. (NIDDM or T2DM or T2D).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. Ayurvedic medicine.mp.
9. Ayurved*.tw,ot.
10. Traditional medicine.mp.
11. exp Complementary medicine/
12. ((Plant* or herb* or medicin* or drug* or therap* or intervention* or extract* or formulation* or preparation* or supplement*) adj6 (Ayurved* or Hindu or Indian)).tw,ot.
13. exp "Medicinal herbs and plants"/
14. Plant extracts.mp.
15. Plants.mp.
16. ((Plant* or herb*) adj6 (medicin* or drug* or therap* or intervention* or extract* or formulation* or preparation* or supplement*)).tw,ot.
17. Ethnobotany.mp.
18. Ethnopharmacology.mp.
19. (Ethnobotan* or ethno botan* or ethnopharmacolog* or ethno pharmacolog*).tw,ot.
20. Phytotherapy.mp.
21. (Phytotherap* or phyto therap*).tw,ot.
22. Acanthaceae.mp.
23. Aegle.mp.
24. Aloe.mp.
25. Artocarpus.mp.
26. Azadirachta.mp.
27. Butea.mp.
28. Cassia.mp.
29. Cinnamomum.mp.
30. Cinnamomum zeylanicum.mp.
31. Clerodendrum.mp.
32. Cucurbitaceae.mp.
33. Curcuma.mp.
34. Ficus.mp.
35. Garlic.mp.
36. Ginger.mp.
37. Gymnema.mp.
38. Ipomoea batatas.mp.
39. Momordica charantia.mp.
40. Murraya.mp.
41. Nigella sativa.mp.
42. Ocimum sanctum.mp.
43. Onions.mp.
44. Piper.mp.
45. Plantago.mp.
46. Psyllium.mp.
47. Pterocarpus.mp.
48. Salacia.mp.
49. Solanum.mp.
50. Syzygium.mp.
51. Tamarindus.mp.
52. Tinospora.mp.
53. Trigonella.mp.
54. Lead.mp.
55. Tin.mp.
56. (Aegle marmelos or Crateva marmelos or Allium cepa or Allium sativum or Aloe vera or Artocarpus heterophyllus or Azadirachta indica or Melia azadirachta or Butea monosperma or

Cassia auriculata or Catharanthus roseus or Vinca rosea or Cinnamomum aromaticum or Cinnamomum cassia or Cinnamomum tamala or Cinnamomum verum or Cinnamomum zeylanicum or Clerodendrum phlomides or Coccinia grandis or Coccinia cordifolia or Coccinia indica or Curcuma longa or Cyamopsis tetragonoloba or Emblica officinalis or Phyllanthus emblica or Enicostemma axillare or Enicostemma littorale or Ficus carica or Gymnema lactiferum or Gymnema sylvestre or Hygrophila schulli or Asteracantha longifolia or Ipomoea batatas or Momordica charantia or Murraya koenigii or Nigella sativa or Ocimum tenuiflorum or Ocimum sanctum or Phyllanthus amarus or Phyllanthus niruri or Piper longum or Plantago arenaria or Plantago psyllium or Pterocarpus marsupium or Pterocarpus santalinus or Punica granatum or Salacia chinensis or Salacia reticulata or Solanum torvum or Syzygium cumini or Eugenia jambolana or Syzygium jambolanum or Syzygium jambos or Eugenia jambos or Tamarindus indica or Tinospora cordifolia or Trigonella foenum-graecum or Zingiber officinale).tw,ot.

57. (Lead or Tin or Black bitumen or Black asphalt*).tw,ot.

58. (Arogyavardhini* or Arogyavardhini* or Ayaskriti or Chandrakant* or Chandraprabh* or Devdarvarisht* or Devdarvarist* or Dhanvantar* or Gokshuradi* or Goksuradi* or Jambudaryisht* or Jambudaryist* or Katakakhadiradi* or Kathakakhadiradi* or Kshirabal* or Ksirabal* or Lodhrasav* or Mamajjak* or Nag* or Naag* or Nimbadi* or Nimadi* or Nishamalak* or Nisamalak* or Nishamlak* or Nisamlak* or Nishakathakadi* or Nisakathakadi* or Phalatrikadi* or Falatrikadi* or Rajanyamalakadi* or Rajanyamlakadi* or Saptamrit* or Shaptamrit* or Saptargangyadi* or Shilajit* or Silajit* or Shilajat* or Silajat* or Shilajeet* or Silajeet* or Siva* or Shiva* or Somnath* or Shomnath* or Triphal* or Trifal* or Trivang* or Tribang* or Vang* or Bang* or Vasant Kusumakar* or Vashant Kushumakar* or Vasanta Kusumakar* or Vashanta Kushumakar* or Vasantkusumakar* or Vashantkushumakar* or Vasantakusumakar* or Vashantakushumakar* or Basant Kusumakar* or Bashant Kushumakar* or Basanta Kusumakar* or Bashanta Kushumakar* or Basantkusumakar* or Bashantkushumakar* or Basantakusumakar* or Bashantakushumakar* or Vijayasaradi* or Vijayasharadi* or Vijaysaradi* or Vijaysharadi* or Bijayasaradi* or Bijayasharadi* or Bijaysaradi* or Bijaysharadi* or Vyoshadi* or Vyosadi* or Byoshadi* or Byosadi*).tw,ot.

59. (Ayush 82 or Ayush-82 or Cogent DB or Diabecon or D 400 or D-400 or GS4 or Gurmar or Hyponidd or Inolter or M 93 or M-93 or MA 471 or MA-471 or Nosulin or Pancreas Tonic).tw,ot.

60. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59

61. 7 and 60

Search strategy included only disease and treatment domains. Study design domain was removed.

Web of Science (1900-16 January 2021): 44 records

#1 TI= ("Type 2 diabetes mellitus" OR (type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)) OR ((Late or maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)) OR ((ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)) OR ((non-insulin* or non insulin* or noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)) OR (NIDDM or T2DM or T2D) OR (Prameh* OR Madhumeh*))

#2 TI= ("Ayurvedic medicine" OR Ayurved* OR "traditional medicine" OR "complementary medicine" OR ((plant* or herb* or medicin* or drug* or therap* or intervention* or extract* or formulation* or preparation* or supplement*) adj6 (Ayurved* or Hindu or Indian)) OR "medicinal plants" OR "plant extracts" OR plants OR ((plant* or herb*) adj6 (medicin* or drug* or therap* or intervention* or extract* or formulation* or preparation* or supplement*)) OR ethnobotany OR ethnopharmacology OR (ethnobotan* or ethno botan* or ethnopharmacolog*)

or ethno pharmacolog*) OR phytotherapy OR (phytotherap* or phyto therap*) OR Acanthaceae OR Aegle OR Aloe OR Artocarpus OR azadirachta OR Butea OR Cassia OR Catharanthus OR Cinnamomum OR "Cinnamomum aromaticum" OR "Cinnamomum zeylanicum" OR Clerodendrum OR Cucurbitaceae OR Curcuma OR Cyamopsis OR Ficus OR Garlic OR Ginger OR Gymnema OR "Gymnema sylvestre" OR "Ipomoea batatas" OR Momordica charantia OR Murraya OR "Nigella sativa" OR "Ocimum sanctum" OR Onions OR Phyllanthus OR Phyllanthus emblica OR Piper OR Plantago OR Psyllium OR Pterocarpus OR Punicaceae OR Salacia OR Solanum OR Syzygium OR Tamarindus OR Tinospora OR Trigonella OR Lead OR Tin OR (Aegle marmelos or Crateva marmelos or Allium cepa or Allium sativum or Aloe vera or Artocarpus heterophyllus or "Azadirachta indica" or "Melia azadirachta" or "Butea monosperma" or "Cassia auriculata" or "Catharanthus roseus" or "Vinca rosea" or "Cinnamomum aromaticum" or "Cinnamomum cassia" or "Cinnamomum tamala" or "Cinnamomum verum" or "Cinnamomum zeylanicum" or "Clerodendrum phlomides" or "Coccinia grandis" or Coccinia cordifolia or Coccinia indica or "Curcuma longa" or "Cyamopsis tetragonoloba" or "Emblica officinalis" or "Phyllanthus emblica" or "Enicostemma axillare" or "Enicostemma littorale" or "Ficus carica" or "Gymnema lactiferum" or "Gymnema sylvestre" or "Hygrophila schulli" or "Asteracantha longifolia" or "Ipomoea batatas" or "Momordica charantia" or "Murraya koenigii" or "Nigella sativa" or "Ocimum tenuiflorum" or "Ocimum sanctum" or "Phyllanthus amarus" or "Phyllanthus niruri" or "Piper longum" or "Plantago Arenaria" or "Plantago psyllium" or "Pterocarpus marsupium" or "Pterocarpus santalinus" or "Punica granatum" or "Salacia chinensis" or "Salacia reticulata" or "Solanum torvum" or "Syzygium cumini" or "Eugenia jambolana" or "Syzygium jambolanum" or "Syzygium jambos" or "Eugenia jambos" or "Tamarindus indica" or "Tinospora cordifolia" or "Trigo") OR (Arogyavardhini* or Arogyvardhini* or Ayaskriti or Chandrakant* or Chandraprabh* or Devdarvarisht* or Devdarvarist* or Dhanvantar* or Gokshuradi* or Goksuradi* or Jambudaryisht* or Jambudaryist* or Katakakhadiradi* or Kathakakhadiradi* or Kshirabal* or Ksirabal* or Lodhrasav* or Mamajjak* or Nag* or Naag* or Nimbadi* or Nimadi* or Nishamalak* or Nisamalak* or Nishamlak* or Nisamlak* or Nishakathakadi* or Nisakathakadi* or Phalatrikadi* or Falatrikadi* or Rajanyamalakadi* or Rajanyamlakadi* or Saptamrit* or Shaptamrit* or Saptargangyadi* or Shilajit* or Silajit* or Shilajat* or Silajat* or Shilajeet* or Silajeet* or Siva* or Shiva* or Somnath* or Shomnath* or Triphal* or Trifal* or Trivang* or Tribang* or Vang* or Bang* or Vasant Kusumakar* or Vashant Kushumakar* or Vasanta Kusumakar* or Vashanta Kushumakar* or Vasantkusumakar* or Vashantkushumakar* or Vasantakusumakar* or Vashantakushumakar* or Basant Kusumakar* or Bashant Kushumakar* or Basanta Kusumakar* or Bashanta Kushumakar* or Basantkusumakar* or Bashantkushumakar* or Basantakusumakar* or Bashantakushumakar* or Vijayasaradi* or Vijayasharadi* or Vijaysaradi* or Vijaysharadi* or Bijayasaradi* or Bijayasharadi* or Bijaysaradi* or Bijaysharadi* or Vyoshadi* or Vyosadi* or Byoshadi* or Byosadi*) OR (Ayush 82 or Ayush-82 or Cogent DB or Diabecon or "D 400" or "D-400" or GS4 or Gurmar or Hyponidd or Inolter or "M 93" or "M-93" or "MA 471" or "MA-471" or Nosulin or "Pancreas Tonic"))

#3 ALL= ("Randomized controlled trial" OR "controlled clinical trial" OR "clinical trial" OR "clinical trials" OR placebos OR "random allocation" OR "double-blind method" OR "single-blind method" OR "cross-over studies" OR ((random\$ or control\$ or clinical\$) adj3 (trial\$ or stud\$)) OR (random\$ adj3 allocat\$) OR placebo\$ OR ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)) OR (crossover\$ or (cross adj over\$)))

#1 AND #2 AND #3

Cochrane Central Register of Controlled Trials (CENTRAL) (1996-16 January 2021): 9442 records

#1 MeSH descriptor: [Diabetes mellitus, type 2] explode all trees and with qualifier(s): [diagnosis - DI]

- #2 Diabet* in Trials
- #3 (NIDDM or T2DM or T2D) in Trials
- #4 Ketosis resistant diabete or ketosis resistant diabetic or stable diabete or stable diabetic in Trials
- #5 ((Non-insulin* or non insulin* or noninsulin*) adj3 depend* adj3 (diabete* or diabetic*))
- #6 ((Late or maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*))
- #7 Prameh* in Trials
- #8 Madhumeh* in Trials
- #9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 in Trials
- #10 MeSH descriptor: [Diabetes mellitus, type 1] explode all trees and with qualifier(s): [diagnosis - DI]
- #11 Diabet* insipidus in Trials
- #12 #10 OR #11 in Trials
- #13 #9 NOT #12
- #14 MeSH descriptor: [Medicine, traditional] explode all trees
- #15 MeSH descriptor: [Medicine, Ayurvedic] explode all trees
- #16 MeSH descriptor: [Complementary therapies] explode all trees
- #17 MeSH descriptor: [Plants, medicinal] explode all trees
- #18 MeSH descriptor: [Phytotherapy] explode all trees
- #19 MeSH descriptor: [Ethnobotany] explode all trees
- #20 MeSH descriptor: [Ethnopharmacology] explode all trees
- #21 (Ethnobotan*):ti,ab,kw (Word variations have been searched)
- #22 (Ethnopharmacolog*):ti,ab,kw (Word variations have been searched) in Trials
- #23 MeSH descriptor: [Aloe] explode all trees
- #24 (Ezadirachta):ti,ab,kw (Word variations have been searched) in Trials
- #25 ("Aegle"):ti,ab,kw (Word variations have been searched) in Trials
- #26 ("Artocarpus"):ti,ab,kw (Word variations have been searched)
- #27 (Butea*):ti,ab,kw (Word variations have been searched)
- #28 MeSH descriptor: [Cassia] explode all trees
- #29 ("Cassia"):ti,ab,kw (Word variations have been searched) in Trials
- #30 ("Cinnamomum"):ti,ab,kw (Word variations have been searched)
- #31 (Cinnamomum zeylanicum):ti,ab,kw (Word variations have been searched)
- #32 ("Cucurbita"):ti,ab,kw (Word variations have been searched)
- #33 (Curcuma):ti,ab,kw (Word variations have been searched)
- #34 MeSH descriptor: [Trigonella] explode all trees
- #35 MeSH descriptor: [Ficus] explode all trees
- #36 MeSH descriptor: [Garlic] explode all trees
- #37 MeSH descriptor: [Ginger] explode all trees
- #38 MeSH descriptor: [Zingiberales] explode all trees
- #39 MeSH descriptor: [Gymnema] explode all trees
- #40 ("Gymnema sylvestre"):ti,ab,kw (Word variations have been searched)
- #41 ("Ipomoea batatas"):ti,ab,kw (Word variations have been searched)
- #42 ("Momordica charantia"):ti,ab,kw (Word variations have been searched)
- #43 (Murraya):ti,ab,kw (Word variations have been searched)
- #44 ("Nigella sativa"):ti,ab,kw (Word variations have been searched)
- #45 ("Ocimum sanctum"):ti,ab,kw (Word variations have been searched)
- #46 MeSH descriptor: [Onions] explode all trees
- #47 MeSH descriptor: [Allium] explode all trees
- #48 ("Piper"):ti,ab,kw (Word variations have been searched)
- #49 MeSH descriptor: [Tinospora] explode all trees
- #50 ("Tinospora"):ti,ab,kw (Word variations have been searched)
- #51 ("Tamarindus"):ti,ab,kw (Word variations have been searched)
- #52 ("Salacia") (Word variations have been searched)
- #53 (Lead):ti,ab,kw (Word variations have been searched)
- #54 (Tin):ti,ab,kw (Word variations have been searched)

#55 (Arogyavardhini* or Arogyvardhini* or Ayaskriti or Chandrakant* or Chandraprabh* or Devdarvarisht* or Devdarvarist* or Dhanvantar* or Gokshuradi* or Goksuradi* or Jambudyarisht* or Jambudyarist* or Katakakhadiradi* or Kathakakhadiradi* or Kshirabal* or Ksirabal* or Lodhrasav* or Mamajjak* or Nag* or Naag* or Nimbadi* or Nimadi* or Nishamalak* or Nisamalak* or Nishamlak* or Nisamlak* or Nishakathakadi* or Nisakathakadi* or Phalatrikadi* or Falatrikadi* or Rajanyamalakadi* or Rajanyamlakadi* or Saptamrit* or Shaptamrit* or Saptargangyadi* or Shilajit* or Silajit* or Shilajat* or Silajat* or Shilajeet* or Silajeet* or Siva* or Shiva* or Somnath* or Shomnath* or Triphal* or Trifal* or Trivang* or Tribang* or Vang* or Bang* or Vasant Kusumakar* or Vashant Kushumakar* or Vasanta Kusumakar* or Vashanta Kushumakar* or Vasantkusumakar* or Vashantkushumakar* or Vasantakusumakar* or Vashantakushumakar* or Basant Kusumakar* or Bashant Kushumakar* or Basanta Kusumakar* or Bashanta Kushumakar* or Basantkusumakar* or Bashantkushumakar* or Basantakusumakar* or Bashantakushumakar* or Vijayasaradi* or Vijayasharadi* or Vijaysaradi* or Vijaysharadi* or Bijayasaradi* or Bijayasharadi* or Bijaysaradi* or Bijaysharadi* or Vyoshadi* or Vyosadi* or Byoshadi* or Byosadi*) (Word variations have been searched)

#56 (Ayush 82 or Ayush-82 or Cogent DB or Diabecon or D 400 or D-400 or GS4 or Gurmar or Hyponidd or Inolter or M 93 or M-93 or MA 471 or MA-471 or Nosulin or Pancreas Tonic) (Word variations have been searched)

#57 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 in Trials

#58 #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR 29 #32

#59 #57 OR #58

#60 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42

#61 #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52

#62 #60 OR #61

#63 #53 OR #54 OR #55 OR #56

#64 #59 OR #62 OR #63

#65 #13 AND #64

Allied and Complementary Medicine Database (AMED) (Ovid) (1985-16 January 2021): 474 records

1. exp Diabetes mellitus type 2/
2. (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw.
3. ((Late or maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)).tw.
4. ((Ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)).tw.
5. ((Non-insulin* or non insulin* or noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw.
6. (NIDDM or T2DM or T2D).tw.
7. Prameha.mp.
8. Madhumeh*.mp.
9. or/1-8
10. exp Ayurvedic medicine/
11. Ayurved*.tw,ti,ab.
12. exp Traditional medicine/
13. exp Complementary medicine/
14. ((Plant* or herb* or medicin* or drug* or therap* or intervention* or extract* or formulation* or preparation* or supplement*) adj6 (Ayurved* or Hindu or Indian)).tw,ti,ab.
15. exp Ethnopharmacology/
16. Ethnobotany.mp.
17. (Ethnobotan* or ethno botan* or ethnopharmacolog* or ethno pharmacolog*).tw,ti,ab.
18. exp Phytotherapy/
19. (Phytotherap* or phyto therap*).tw,ti,ab.
20. Acanthaceae.mp.
21. Aegle.mp.
22. exp Aloe/

23. exp Artocarpus/
24. exp Azadirachta/
25. Butea.mp.
26. Cassia.mp.
27. Catharanthus.mp.
28. exp Cinnamomum/
29. Cinnamomum zeylanicum.mp.
30. Clerodendrum.mp.
31. Cucurbitaceae.mp.
32. exp Curcuma/
33. exp Cyamopsis/
34. exp Ficus/
35. Garlic.mp.
36. exp Zingiber officinale/
37. exp Allium sativum/
38. Gymnema.mp.
39. Gymnema sylvestre.mp.
40. exp Ipomoea/
41. exp Ipomoea/ or Ipomoea batatas.mp.
42. exp Momordica charantia/
43. exp Momordica/
44. Curry.mp.
45. Murraya koenigii.mp.
46. exp Nigella sativa/
47. Ocimum sanctum.mp.
48. Onions.mp.
49. exp Allium cepa/
50. exp Phyllanthus/
51. Emblic.mp.
52. Amla.mp.
53. Myrobalan.mp.
54. exp Piper/
55. Piper longum.mp.
56. Plantago.mp.
57. Psyllium.mp.
58. Pterocarpus.mp.
59. exp Punicaceae/
60. Salacia.mp.
61. Syzgium.mp.
62. Tamarindus.mp.
63. Tinospora.mp.
64. Tinospora cordifolia.mp.
65. Guduchi.mp.
66. exp Trigonella/
67. Fenugreek.mp.
68. exp Lead/
69. exp Tin/
70. (Lead or Tin or Black bitumen or Black asphalt*).tw,ab,ti.
71. (Aegle marmelos or Crateva marmelos or Allium cepa or Allium sativum or Aloe vera or Artocarpus heterophyllus or Azadirachta indica or Melia azadirachta or Butea monosperma or Cassia auriculata or Catharanthus roseus or Vinca rosea or Cinnamomum aromaticum or Cinnamomum cassia or Cinnamomum tamala or Cinnamomum verum or Cinnamomum zeylanicum or Clerodendrum phlomides or Coccinia grandis or Coccinia cordifolia or Coccinia indica or Curcuma longa or Cyamopsis tetragonoloba or Emblica officinalis or Phyllanthus emblica or Enicostemma axillare or Enicostemma littorale or Ficus carica or Gymnema

lactiferum or Gymnema sylvestre or Hygrophila schulli or Asteracantha longifolia or Ipomoea batatas or Momordica charantia or Murraya koenigii or Nigella sativa or Ocimum tenuiflorum or Ocimum sanctum or Phyllanthus amarus or Phyllanthus niruri or Piper longum or Plantago arenaria or Plantago psyllium or Pterocarpus marsupium or Pterocarpus santalinus or Punica granatum or Salacia chinensis or Salacia reticulata or Solanum torvum or Syzygium cumini or Eugenia jambolana or Syzygium jambolanum or Syzygium jambos or Eugenia jambos or Tamarindus indica or Tinospora cordifolia or Trigonella foenum-graecum or Zingiber officinale).tw,ti,ab.

72. (Arogyavardhini* or Arogyavardhini* or Ayaskriti or Chandrakant* or Chandraprabh* or Devdarvarisht* or Devdarvarist* or Dhanvantar* or Gokshuradi* or Goksuradi* or Jambudaryisht* or Jambudaryist* or Katakakhadiradi* or Kathakakhadiradi* or Kshirabal* or Ksirabal* or Lodhrasav* or Mamajjak* or Nag* or Naag* or Nimbadi* or Nimadi* or Nishamalak* or Nisamalak* or Nishamlak* or Nisamlak* or Nishakathakadi* or Nisakathakadi* or Phalatrikadi* or Falatrikadi* or Rajanyamalakadi* or Rajanyamlakadi* or Saptamrit* or Shaptamrit* or Saptargangyadi* or Shilajit* or Silajit* or Shilajat* or Silajat* or Shilajeet* or Silajeet* or Siva* or Shiva* or Somnath* or Shomnath* or Triphal* or Trifal* or Trivang* or Tribang* or Vang* or Bang* or Vasant Kusumakar* or Vashant Kushumakar* or Vasanta Kusumakar* or Vashanta Kushumakar* or Vasantkusumakar* or Vashantkushumakar* or Vasantakusumakar* or Vashantakushumakar* or Basant Kusumakar* or Bashant Kushumakar* or Basanta Kusumakar* or Bashanta Kushumakar* or Basantkusumakar* or Bashantkushumakar* or Basantakusumakar* or Bashantakushumakar* or Vijayasaradi* or Vijayasharadi* or Vijaysaradi* or Vijayasharadi* or Bijayasaradi* or Bijayasharadi* or Bijaysaradi* or Bijayasharadi* or Vyoshadi* or Vyosadi* or Byoshadi* or Byosadi*).tw,ti,ab.

73. (Ayush 82 or Ayush-82 or Cogent DB or Diabecon or D 400 or D-400 or GS4 or Gurmar or Hyponidd or Inolter or M 93 or M-93 or MA 471 or MA-471 or Nosulin or Pancreas Tonic).tw,ti,ab.

74. or/10-73

75. 9 and 74

Search strategy included only disease and treatment domains. Study design domain was removed.

International Pharmaceutical Abstracts (Ovid) (1970-16 January 2021): 286 records

1. Diabetes mellitus.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
2. (Type* adj3 ("2" or "II" or two*) adj3 (diabete* or diabetic*)).tw.
3. ((Late or maturit* or adult* or slow*) adj3 onset* adj3 (diabete* or diabetic*)).tw.
4. ((Ketosis-resistant* or stable*) adj3 (diabete* or diabetic*)).tw.
5. ((Non-insulin* or non insulin* or noninsulin*) adj3 depend* adj3 (diabete* or diabetic*)).tw.
6. (NIDDM or T2DM or T2D).tw.
7. Prameh*.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
8. Madhume*.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. Ayurvedic medicine.mp.
11. Ayurved*.tw.
12. Traditional medicine.mp.
13. Complementary medicine.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
14. ((Plant* or herb* or medicin* or drug* or therap* or intervention* or extract* or formulation* or preparation* or supplement*) adj6 (Ayurved* or Hindu or Indian)).tw.
15. Medicinal plant.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]

16. Plant extracts.mp.
17. Plants.mp.
18. ((Plant* or herb*) adj6 (medicin* or drug* or therap* or intervention* or extract* or formulation* or preparation* or supplement*)).tw.
19. Ethnobotany.mp.
20. Ethnopharmacology.mp.
21. (Ethnobotan* or ethno botan* or ethnopharmacolog* or ethno pharmacolog*).tw.
22. Phytotherapy.mp.
23. (Phytotherap* or phyto therap*).tw.
24. Acanthaceae.mp.
25. Aegle.mp.
26. Aloe.mp.
27. Artocarpus.mp.
28. Azadirachta.mp.
29. Butea.mp.
30. Cassia.mp.
31. Cinnamomum.mp.
32. Cinnamomum aromaticum.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
33. Cinnamomum zeylanicum.mp.
34. Clerodendrum.mp.
35. Cucurbitaceae.mp.
36. Curcuma.mp.
37. Cyamopsis.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
38. Ficus.mp.
39. Garlic.mp.
40. Ginger.mp.
41. Gymnema.mp.
42. Gymnema sylvestre.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
43. Ipomoea batatas.mp.
44. Momordica charantia.mp.
45. Murraya.mp.
46. Nigella sativa.mp.
47. Ocimum sanctum.mp.
48. Onions.mp.
49. Phyllanthus.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
50. Phyllanthus emblica.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
51. Piper.mp.
52. Plantago.mp.
53. Psyllium.mp.
54. Pterocarpus.mp.
55. Punicaceae.mp. [mp=title, subject heading word, registry word, abstract, trade name/generic name]
56. Salacia.mp.
57. Solanum.mp.
58. Syzygium.mp.
59. Tamarindus.mp.
60. Tinospora.mp.
61. Trigonella.mp.
62. Lead.mp.
63. Tin.mp.

64. (Aegle marmelos or Crateva marmelos or Allium cepa or Allium sativum or Aloe vera or Artocarpus heterophyllus or Azadirachta indica or Melia azadirachta or Butea monosperma or Cassia auriculata or Catharanthus roseus or Vinca rosea or Cinnamomum aromaticum or Cinnamomum cassia or Cinnamomum tamala or Cinnamomum verum or Cinnamomum zeylanicum or Clerodendrum phlomides or Coccinia grandis or Coccinia cordifolia or Coccinia indica or Curcuma longa or Cyamopsis tetragonoloba or Emblica officinalis or Phyllanthus emblica or Enicostemma axillare or Enicostemma littorale or Ficus carica or Gymnema lactiferum or Gymnema sylvestre or Hygrophila schulli or Asteracantha longifolia or Ipomoea batatas or Momordica charantia or Murraya koenigii or Nigella sativa or Ocimum tenuiflorum or Ocimum sanctum or Phyllanthus amarus or Phyllanthus niruri or Piper longum or Plantago arenaria or Plantago psyllium or Pterocarpus marsupium or Pterocarpus santalinus or Punica granatum or Salacia chinensis or Salacia reticulata or Solanum torvum or Syzygium cumini or Eugenia jambolana or Syzygium jambolanum or Syzygium jambos or Eugenia jambos or Tamarindus indica or Tinospora cordifolia or Trigonella foenum-graecum or Zingiber officinale).tw.

65. (Lead or Tin or Black bitumen or Black asphalt*).tw.

66. (Arogyavardhini* or Arogyavardhini* or Ayaskriti or Chandrakant* or Chandraprabh* or Devdarvarisht* or Devdarvarist* or Dhanvantari* or Gokshuradi* or Goksuradi* or Jambudaryisht* or Jambudaryist* or Katakakhadiradi* or Kathakakhadiradi* or Kshirabal* or Ksirabal* or Lodhrasav* or Mamajjak* or Nag* or Naag* or Nimbadi* or Nimadi* or Nishamalak* or Nisamalak* or Nishamlak* or Nisamlak* or Nishakathakadi* or Nisakathakadi* or Phalatrikadi* or Falatrikadi* or Rajanyamalakadi* or Rajanyamlakadi* or Saptamrit* or Shaptamrit* or Saptargangyadi* or Shilajit* or Silajit* or Shilajat* or Silajat* or Shilajeet* or Silajeet* or Siva* or Shiva* or Somnath* or Shomnath* or Triphal* or Trifal* or Trivang* or Tribang* or Vang* or Bang* or Vasant Kusumakar* or Vashant Kushumakar* or Vashant Kushumakar* or Vasantkusumakar* or Vashantkusumakar* or Vasantkusumakar* or Vashantkusumakar* or Basant Kusumakar* or Bashant Kushumakar* or Basanta Kusumakar* or Bashanta Kushumakar* or Basantkusumakar* or Bashantkusumakar* or Basantkusumakar* or Bashantkusumakar* or Vijayasaradi* or Vijayasharadi* or Vijaysaradi* or Vijaysharadi* or Bijayasaradi* or Bijayasharadi* or Bijaysaradi* or Bijaysharadi* or Vyoshadi* or Vyosadi* or Byoshadi* or Byosadi*).tw.

67. (Ayush 82 or Ayush-82 or Cogent DB or Diabecon or D 400 or D-400 or GS4 or Gurmar or Hyponid or Inolter or M 93 or M-93 or MA 471 or MA-471 or Nosulin or Pancreas Tonic).tw.

68. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67

69. Randomised controlled trial.mp.

70. Random allocation.mp.

71. Double-blind method.mp.

72. Single-blind method.mp.

73. Cross-over studies.mp.

74. ((Random\$ or control\$ or clinical\$) adj3 (trial\$ or stud\$)).tw.

75. (Random\$ adj3 allocat\$).tw.

76. Placebo\$.tw.

77. ((Singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).tw.

78. (Crossover\$ or (cross adj over\$)).tw.

79. 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78

80. 9 and 68 and 79

Turning Research Into Practice (TRIP) (1997-16 January 2021): 186 records

(Diabet* OR NIDDM OR T2DM OR T2D OR Prameh* OR Madhumeh*) AND Ayurved*

AYUSH Research Portal (16 January 2021): 292 records

Searched with AYUSH terminology -> Selected medical system - Ayurveda -> Selected disease from the list –

Madhumeha (283 records)

Madhumeha – (9 records)

Digital Helpline for Ayurveda Research Articles (DHARA) (16 January 2021): 1230 records

Single search terms were used.

Diabetes (662 records)

Diabetic (436 records)

Diabetics (30 records)

NIDDM (15 records)

T2DM (3 records)

T2D (3 records)

Madhumeha (31 records)

Prameha (50 records)

A Bibliography of Indian medicine (ABIM) (16 January 2021): 3015 records

Single search terms were used.

Diabetes (1404 records)

Diabetic (1404 records)

Diabetics (23 records)

NIDDM (29 records)

T2DM (0 records)

T2D (0 records)

Madhumeha (113 records)

Prameha (42 records)

CAM-QUEST (16 January 2021): 29 records

Selected disease pattern - metabolic disorders -> Selected disease - diabetes mellitus -> Selected therapy - Ayurveda

Directory of Open Access Journals (16 January 2021): 191 records

Three different searches were run.

Diabet* AND Ayurved* [All fields] (171 records)

Prameha [All fields] (11 records)

Madhumeha [All fields] (9 records)

EthOS (16 January 2021): 18 records

Ayurveda [any word] OR Ayurvedic [any word]

OpenGrey (16 January 2021): 22 records

Ayurved*

ProQuest Dissertations and Theses (16 January 2021): 400 records

Three different searches were run.

Ti(Diabet* OR NIDDM OR T2DM OR T2D) AND Ayurved* (111 records)

Prameh* (165 records)

Madhumeh* (124 records)

Appendix S2: Excluded studies with reasons for exclusion.

Ineligible participants (includes impossible to extract data on T2DM participants) (n=1)

1. Hsu P, Pan FF, Hsieh C. mclRBP-19 of bitter melon peptide effectively regulates diabetes mellitus (DM) patients' blood sugar levels. *Nutrients*. 2020;12(5):1252.

Ineligible interventions (includes unclear interventions) (n=8)

1. Mohan V. Evaluation of D-400 (Diabecon) as anti-diabetic agent: A double blind placebo controlled trial in NIDDM patients with secondary failure to oral drugs. *Indian Journal of Clinical Practice*. 1998;8(9):18-21.
2. Elder C, Aickin M, Bauer V, Cairns J, Vuckovic N. Randomized trial of a whole-system Ayurvedic protocol for type 2 diabetes. *Altern Ther Health Med*. 2006;12(5):24-30.
3. Yin J, Xing H, Ye J. Efficacy of berberine in patients with type 2 diabetes mellitus. *Metabolism*. 2008;57(5):712-7.
4. Sharma RK, Patki PS. Double-blind, placebo-controlled clinical evaluation of an Ayurvedic formulation (Glucocare capsules) in non-insulin dependent diabetes mellitus. *J Ayurveda Integr Med*. 2010;1(1):45-51.
5. Agrawal RP, Goyal S, Chopra A, Jain S, Agarwal V, Khatri MP, *et al*. A randomized placebo controlled trial of herbal medicine (Sugaradik) in the treatment of type 2 diabetes. *Indian Medical Gazette*. 2014;148(4):142-8.
6. Kurian GA, Manjusha V, Nair SS, Varghese T, Padikkala J. Short-term effect of G-400, polyherbal formulation in the management of hyperglycemia and hyperlipidemia conditions in patients with type 2 diabetes mellitus. *Nutrition*. 2014;30(10):1158-64.
7. Mirfeizi M, Tourzani ZM, Mirfeizi SZ, Jafarabadi MA, Rezvani HR, Afzali M. Controlling type 2 diabetes mellitus with herbal medicines: A triple-blind randomized clinical trial of efficacy and safety. *J Diabetes*. 2016;8(5):647-56.
8. Venkatesan H, Karthi SA. Hypoglycaemic effect of alcoholic extracts of the leaves of *Abroma augusta* and *Gymnema sylvestre* plants in type II diabetes mellitus patients. *Indian Journal of Public Health Research and Development*. 2020;11(7):293-9.

Ineligible outcomes (includes inadequate data and/or timings) (n=19)

1. Khan AK, Akhtar S, Mahtab H. Treatment of diabetes mellitus with *Coccinia indica*. *Br Med J*. 1980;280(6220):1044.
2. Niemi MK, Keinänen-Kiukaanniemi SM, Salmela PI. Long-term effects of guar gum and microcrystalline cellulose on glycaemic control and serum lipids in type 2 diabetes. *Eur J Clin Pharmacol*. 1988;34(4):427-9.
3. Lalor BC, Bhatnagar D, Winocour PH, Ishola M, Arrol S, Brading M, *et al*. Placebo-controlled trial of the effects of guar gum and metformin on fasting blood glucose and serum lipids in obese, type 2 diabetic patients. *Diabet Med*. 1990;7(3):242-5.
4. Agrawal P, Rai V, Singh RB. Randomized placebo-controlled, single blind trial of holy basil leaves in patients with noninsulin-dependent diabetes mellitus. *Int J Clin Pharmacol Ther*. 1996;34(9):406-9.
5. Anderson JW, Allgood LD, Turner J, Oeltgen PR, Daggy BP. Effects of psyllium on glucose and serum lipid responses in men with type 2 diabetes and hypercholesterolemia. *Am J Clin Nutr*. 1999;70(4):466-73.
6. Yadav RK, Mishra R, Chhipa RP, Audichya KC. Clinical trial of an indigenous compound drug Nishaamalki in the management of madhumeha vis-a-vis diabetes mellitus. *Anc Sci Life*. 2001;21(1):18-24.

7. Arora D, Kumar M, Dubey SD, Sings U. Immunomodulating effects of rasayana drugs in diabetics: A clinical study. *Anc Sci Life*. 2002;22(2):42-8.
8. Ludvik BH, Mahdjoobian K, Waldhaeusl W, Hofer A, Prager R, Kautzky-Willer A, *et al*. The effect of *Ipomoea batatas* (caiao) on glucose metabolism and serum cholesterol in patients with type 2 diabetes: A randomized study. *Diabetes Care*. 2002;25(1):239-40.
9. John AJ, Cherian R, Subhash HS, Cherian AM. Evaluation of the efficacy of bitter gourd (*Momordica charantia*) as an oral hypoglycemic agent: A randomized controlled clinical trial. *Indian J Physiol Pharmacol*. 2003;47(3):363-5.
10. Jayawardena MH, de Alwis NM, Hettigoda V, Fernando DJ. A double blind randomized placebo controlled cross over study of a herbal preparation containing *Salacia reticulata* in the treatment of type 2 diabetes. *J Ethnopharmacol*. 2005;97(2):215-8.
11. Ryu OH, Lee J, Lee KW, Kim HY, Seo JA, Kim SG, *et al*. Effects of green tea consumption on inflammation, insulin resistance and pulse wave velocity in type 2 diabetes patients. *Diabetes Res Clin Pract*. 2006;71(3):356-8.
12. Inayat-ur-Rahman, Malik SA, Bashir M, Khan R, Iqbal M. Serum sialic acid changes in non-insulin-dependant diabetes mellitus (NIDDM) patients following bitter melon (*Momordica charantia*) and rosiglitazone (Avandia) treatment. *Phytomedicine*. 2009;16(5):401-5.
13. Ahmed F, Huded S, Urooj A. Antihyperglycemic activity of *Ficus racemosa* bark extract in type 2 diabetic individuals. *J Diabetes*. 2011;3(4):318-9.
14. Amarnath S, Shukla HM. Single blind placebo controlled clinical evaluation of Mamajjaka Ghanvati in prameha with special reference to diabetes mellitus. *Journal of Ayurveda and Holistic Medicine*. 2013;1(5):11-9.
15. Jani DK. Clinical effect of supplementation of *Solanum nigrum* in diabetic individuals. *International Journal of Pharmacy and Integrated Life Sciences*. 2014;2(4):76-84.
16. Behzadi AA, Kalalian-Moghaddam H, Ahmadi AH. Effects of *Urtica dioica* supplementation on blood lipids, hepatic enzymes and nitric oxide levels in type 2 diabetic patients: A double blind, randomized clinical trial. *Avicenna J Phytomed*. 2016;6(6):686-95.
17. Pachaghare M. Randomized open clinical study of Charakokta Mutrasangrahiya Mahakashay with special reference to madhumeh i.e. diabetes mellitus. *Deerghayu International*. 2016;32-02(126):254-8.
18. Sharma SD, Masand S, Sharma GD, Chaudhary V, Sharma SD. A randomized clinical study to evaluate the efficacy of an Ayurvedic formulation in the management of madhumeha with special reference to diabetes mellitus. *International Journal of Research in Ayurveda and Pharmacy*. 2016;7(6):33-8.
19. Hadi S, Mirmiran P, Daryabeygi-Khotbesara R, Hadi V. Effect of *Nigella sativa* oil extract on inflammatory cytokine response and oxidative stress among people with type 2 diabetes mellitus: A randomized, double-blind, placebo controlled trial. *Progress in Nutrition*. 2018;20(1-S):127-33.

Ineligible study designs (n=34)

1. Singh TN, Upadhyay BN, Tewari CM, Tripathi SN. Management of diabetes mellitus (prameha) with *Inula racemosa* and *Cinnamomum tamala*. *Anc Sci Life*. 1985;5(1):9-16.
2. Kohli KR, Naik S, Tripathi R, Zarapkar M, Kenkare D. Karnim: A herbal formulation in non-insulin dependent diabetes mellitus. *The Journal of General Medicine*. 1993;6(1):47-52.
3. Kohli KR, Singh RH. A clinical trial of jambu (*Eugenia jambolana*) in non-insulin dependant diabetes mellitus. *Journal of Research in Ayurveda and Siddha*. 1993;14(3-4):89-97.
4. Kamble SM, Jyotishi GS, Kamlakar PL, Vaidya SM. Efficacy of *Coccinia indica* W. and A. in diabetes mellitus. *Journal of Research in Ayurveda and Siddha*. 1996;17(1-2):77-84.

5. Sharma RD, Sarkar A, Hazra DK, Mishra B, Singh JB, Sharma SK, *et al.* Use of fenugreek seed powder in the management of non-insulin dependent diabetes mellitus. *Nutr Res.* 1996;16(8):1331-9.
6. Sharma RD, Sarkar A, Hazra DK, Misra B, Singh JB, Maheshwari BB, *et al.* Hypolipidaemic effect of fenugreek seeds: A chronic study in non-insulin dependent diabetic patients. *Phytother Res.* 1996;10(4):332-4.
7. Bordia A, Verma SK, Srivastava KC. Effect of ginger (*Zingiber officinale* Rosc.) and fenugreek (*Trigonella foenumgraecum* L.) on blood lipids, blood sugar and platelet aggregation in patients with coronary artery disease. *Prostaglandins Leukot Essent Fatty Acids.* 1997;56(5):379-84.
8. Chandra V, Aruna K. Glycaemic and cholesterolaemic effect of sprouted fenugreek on diabetic subjects. *The Indian Journal of Nutrition and Dietetics.* 1997;34(10):246-51.
9. Mehra PS, Singh RH. Clinical evaluation of the effect of Amrita-Pippali-Nimba Yoga in diabetes mellitus with special reference to the role of agni and ojas. *Journal of Research in Ayurveda and Siddha.* 2001;21(3-4):183-97.
10. Adhikari KS, Ojha JK, Dwivedi KN. A clinical study of Shilajatu Bijaka Yoga in ojomaha patients. *Journal of Research in Ayurveda and Siddha.* 2003;24(1-2):62-70.
11. Pandey AK, Singh RH. A study of the immune status in patients of diabetes mellitus and their management with certain naimittika rasayana drugs. *Journal of Research in Ayurveda and Siddha.* 2003;24(3-4):48-61.
12. Islas IL, Nuevo JJ, Saab NG, Guerra AF. Onion consumption as an adjuvant in glycemic control of type 2 diabetes. *Medicina Interna de Mexico.* 2005;21(1):44-7.
13. Andallu B, Ramya V. Anti-hyperglycemic, cholesterol-lowering and HDL-raising effects of cumin (*Cuminum cyminum*) seeds in type 2 diabetes. *Journal of Natural Remedies.* 2007;7(1):142-9.
14. Joshi A. Studies on the impact of phytochemical rich fruit supplementation amla *Embilica officinalis* in the management of diabetes mellitus and efficacy of interpersonal counselling on the knowledge and lifestyle related risk factors in type 2 diabetes mellitus [dissertation on the internet]. Baroda: Maharaja Sayajirao University of Baroda; 2008.
15. Mitra A. Preparation and effects of cheap salad oil in the management of type 2 rural Indian diabetics. *Journal of Human Ecology.* 2008;23(1):27-38.
16. Kochhar A, Sharma N, Sachdeva R. Effect of supplementation of tulsi (*Ocimum sanctum*) and neem (*Azadirachta indica*) leaf powder on diabetic symptoms, anthropometric parameters and blood pressure of non insulin dependent male diabetics. *Studies on Ethno-Medicine.* 2009;3(1):5-9.
17. Radha R, Amrithaveni M. Role of medicinal plant *Salacia reticulata* in the management of type II diabetic subjects. *Anc Sci Life.* 2009;29(1):14-6.
18. Sartore G, Reitano R, Barison A, Magnanini P, Cosma C, Burlina S, *et al.* The effects of psyllium on lipoproteins in type II diabetic patients. *Eur J Clin Nutr.* 2009;63(10):1269-71.
19. Kumar SN, Mani UV, Mani I. An open label study on the supplementation of *Gymnema sylvestre* in type 2 diabetics. *J Diet Suppl.* 2010;7(3):273-82.
20. Venugopal S, Iyer UM. Management of diabetic dyslipidemia with subatmospheric dehydrated barley grass powder. *International Journal of Green Pharmacy.* 2010;4(4):251-6.
21. Anas M, Mohsin M, Siddiqui M, Mannan A. Therapeutic evaluation of a polyherbal formulation in type 2 diabetes mellitus. *Indian Journal of Traditional Knowledge.* 2011;10(4):711-5.
22. Nath P, Dubey SD, Ojha JK. Study on ojah kshaya WSR to madhumeha hara dravyas in Samhitas. *Journal of Research in Ayurveda and Siddha.* 2011;32(3-4):87-100.
23. Tanna I, Chandola HM, Joshi JR. Clinical efficacy of Mehamudgara Vati in type 2 diabetes mellitus. *Ayu.* 2011;32(1):30-9.

24. Upadhyay BN, Gupta V. A clinical study on the effect of Rishyagandha (*Withania coagulans*) in the management of prameha (type II diabetes mellitus). *Ayu*. 2011;32(4):507-11.
25. Hoehn AN, Stockert AL. The effects of *Cinnamomum cassia* on blood glucose values are greater than those of dietary changes alone. *Nutr Metab Insights*. 2012;5:77–83.
26. Singh U, Kochhar A. Effect of supplementation of bael (*Aegle marmelos* L.) and nutrition counseling on blood glucose, lipid profile and blood pressure of non-insulin dependent diabetics. *Journal of Pharma Research*. 2012;1(2):1-6.
27. Kim HM, Kim J. The effects of green tea on obesity and type 2 diabetes. *Diabetes Metab J*. 2013;37(3):173-5.
28. Sharma P, Sharma AK, Dwivedi KN. Clinical study on antidiabetic activity of karanja (*Pongamia pinnata*). *International Journal of Pharmaceutical Research and Bio-Science*. 2013;2(5):438-51.
29. Tayyab F, Lal SS. Antidiabetic hypolipidemic and antioxidant activity of *Momordica charantia* on type-II diabetic patient in Allahabad India. *International Journal of Pharma and Bio Sciences*. 2013;4(4):932-40.
30. Choudhary M, Kochhar A, Sangha J. Hypoglycemic and hypolipidemic effect of *Aloe vera* L. in non-insulin dependent diabetics. *J Food Sci Technol*. 2014;51(1):90-6.
31. Mathew R, Radhakrishnan VN, Babu NS. Effect of Katakakhadiradi Kasaya in type 2 diabetes mellitus associated with hypercholesterolemia. *Aryavaidyan*. 2014;28(1):27-30.
32. Balavenkata KS, Bulusu S. A critical study of pramehahara effect of Dhaatri Nishe WSR to diabetes mellitus. *International Journal of Ayurvedic Medicine*. 2018;9(3):196-201.
33. Boston C, Wong N, Ganga T, Chandradatt K, Rosales J, Singh J, et al. Comparison and effectiveness of complementary and alternative medicine as against conventional medicine in the treatment and management of type 2 diabetes. *Journal of Complementary and Alternative Medical Research*. 2019;7(2):1-8.
34. Sehgal S, Huddar VG, Rao MV. Efficacy of prakriti specific herbal tea in diabetes: A randomized controlled trial. *International Journal of Ayurvedic Medicine*. 2020;11(3):524-35.

Ineligible participants (includes impossible to extract data on T2DM participants)+ineligible study designs (n=7)

1. Rajasekharan S, Tuli SN. Vijaysar (*Pterocarpus marsupium*) in the treatment of madhumeha (diabetes mellitus): A clinical trial. *Journal of Research Indian Medicine, Yoga and Homoeopathy*. 1976;11:9-14.
2. Shaw BP, Tripathy PC. Evaluation of Svarnamakshika (copper pyrites) as an oral hypoglycaemic agent (clinical trials). *Nagarjun*. 1980;23(1-9):195-7.
3. Mishra SK, Pandey SK, Sharma SH, Singh GD. Effect of Amalaki-Haridra on madhumeha. *Nagarjun*. 1983;26(1-5):105-7.
4. Chaube A, Nagraja TN, Dixit SK, Agrawal JK, Kumar M, Prakash B. A novel Ayurvedic anti diabetic medicine. *Anc Sci Life*. 1995;15(2):153-5.
5. Rajagopalan K, Sasidharan K. Evaluation of the clinical management of prameha roga (diabetes mellitus). *Aryavaidyan*. 2000;14(1):33-43.
6. Kanthi VG, Sarashetti RS, Bidari RC. Management of madhumeha (diabetes mellitus) with herbomineral compound preparations. *Journal of Research in Ayurveda and Siddha*. 2004;25(3-4):47-56.
7. Gaikwad S, Kadam DB, Pawar PS. Role of Ayurvedic treatment in the management of diabetes. *Aryavaidyan*. 2009;22(4):202-5.

Ineligible interventions (includes unclear interventions)+ineligible study designs (n=4)

1. Maji D, Singh AK. Clinical trial of D-400, a herbomineral preparation in diabetes mellitus. *Journal of the Diabetic Association of India*. 1995;35(1):1-4.

2. Mitra SK, Hemavathi TS, Mohan AR, Rajesha. Anti-diabetic effect of D-400, an Ayurvedic herbal preparation in non-insulin dependent diabetes mellitus patients. *The Antiseptic*. 1995;92(9):342-5.
3. Mitra SK, Sessaiah V, Agarwal JK, Maji D, Yajnik VH, Prasanna Kumar KM, *et al*. Multicentric trial of Diabecon (D-400): A herbomineral preparation on lipid profile in diabetes mellitus. *Int J Diabetes Dev Ctries*. 1996;16:87-9.
4. Geetha B, Shivananda N, Manjula S. Management of newly diagnosed type 2 diabetes by *Trigonella foenum-graecum*. *International Journal of Research in Ayurveda and Pharmacy*. 2011;2(4):1231-4.

Ineligible outcomes (includes inadequate data and/or timings)+ineligible study designs (n=11)

1. Ojha JK, Bajpai HS, Sharma PV. Hypoglycemic effect of *Pterocarpus marsupium* Roxb (vijaysar). *Journal of Research Indian Medicine, Yoga and Homoeopathy*. 1978;13(4):12-6.
2. Chandola HM, Tripathi SN, Udupa KN. Hypoglycaemic response of *C. tamala* in patients of maturity onset (insulin independent) diabetes. *Journal of Research in Ayurveda and Siddha*. 1980;1:275-90.
3. Chandola HM, Tripathi SN, Udupa KN. Effect of *C. tamala* on plasma insulin vis-à-vis blood sugar in patients of diabetes mellitus. *Journal of Research in Ayurveda and Siddha*. 1980;1(3):345-57.
4. Jain AK, Shaw BP. Effect of herbal compound on maturity onset diabetes. *Anc Sci Life*. 1987;7(1):12-6.
5. Kumar N, Kumar A. A clinical trial of M-93 compound in the management of madhumeha (diabetes mellitus). *Journal of Research in Ayurveda and Siddha*. 1995;16(3-4):102-7.
6. Nanda GC, Chopra KK, Sahu DP, Padhi MM. Nishamalaki in madhumeha (NIDDM): A clinical study. *Journal of Research in Ayurveda and Siddha*. 1998;19(1-2):34-40.
7. Kumar N, Kumar A, Sharma ML. Clinical evaluation of single and herbo-mineral compound drugs in the management of madhumeha. *Journal of Research in Ayurveda and Siddha*. 1999;20(1-2):1-9.
8. Mudra M, Ercan-Fang N, Zhong L, Furne J, Levitt M. Influence of mulberry leaf extract on the blood glucose and breath hydrogen response to ingestion of 75 g sucrose by type 2 diabetic and control subjects. *Diabetes Care*. 2007;30(5):1272-4.
9. Date KA, Dwivedi LK, Sharma RP, Rao KS. Comparative study of Ganesayagokta Havanasamagribhasma and Silabhrarasa with Madhumeharicurna with special reference to its anti-hyperglycemic effect. *Aryavaidyan*. 2014;28(1):47-51.
10. Kumari M, Jain S, Dave R. Babul (*Acacia nilotica*): A potential source of tannin and its suitability in management of type II diabetes. *Nutrition and Food Science*. 2014;44(2):119-26.
11. Kapoor S. Impact of indigenous food (Methi dana, Kale til and Kali jiri) on blood glucose level of middle aged NIDDM patients [dissertation on the internet]. Indore: Devi Ahilya Vishwavidyalaya; 2015.

Ineligible participants (includes impossible to extract data on T2DM participants)+ineligible outcomes (includes inadequate data and/or timings)+ineligible study designs (n=3)

1. Atique A, Iqbal M, Ghouse AK. Use of *Annona squamosa* and *Piper nigrum* against diabetes. *Fitoterapia*. 1985;56(3):190-2.
2. Fernando MR, Wickramasinghe SM, Thabrew MI, Ariyananda PL, Karunanayake EH. Effect of *Artocarpus heterophyllus* and *Asteracanthus longifolia* on glucose tolerance in normal human subjects and in maturity-onset diabetic patients. *J Ethnopharmacol*. 1991;31(3):277-82.

3. Karnick CR. A clinical trial of a composite herbal drugs in the treatment of diabetic mellitus (madhumeha). *Aryavaidyan*. 1991;5(1):36-46.

Ineligible interventions (includes unclear interventions)+ineligible outcomes (includes inadequate data and/or timings)+ineligible study designs (n=1)

1. Khan SK. South Asian and Chinese medical systems: Ayurveda and traditional Chinese medicine treatments for diabetes mellitus, type 2 [dissertation on the internet]. New York: City University of New York; 2006.

Ineligible participants (includes impossible to extract data on T2DM participants)+ineligible comparators+ineligible outcomes (includes inadequate data and/or timings)+ineligible study designs (n=1)

1. Shaw BP, Gupta S. A clinical study of bimbi (*Coccinia indica*) in the treatment of madhumeha (diabetes mellitus). *Nagarjun*. 1981;14(6):24-6.

Full text unavailable (n=1)

1. Bhimani S. Clinical study of efficacy of Glycoban cap in patients of non-insulin dependent diabetes (NIDDM) mellitus. *The Antiseptic*. 2005;102(2):71-5.

Appendix S3: Potentially eligible ongoing RCTs.

Trial registry number	Scientific study title	Country
CTRI/2015/03/005660	A comparative clinical study to evaluate the efficacy of Phalendradhi Yogam with and without Yashada Bhasma in the management of madhumeha (type 2 DM)	India
CTRI/2015/06/005891	A randomised, prospective single blind clinical trial of anti diabetic polyherbal formulation (DiaKure)	India
CTRI/2017/05/008451	Pharmaceutical development of trinshati and shashti puti Naga Bhasma and their comparative clinical efficacy in the management of madhumeha (type 2 diabetes)	India
CTRI/2017/05/008461	Open labelled, controlled, randomized evaluation of the effect of Dhatri Nisha Yoga in management of prameha vis a vis diabetes mellitus (type II)	India
CTRI/2017/08/009575	Role of Vijaysaradi capsule in the management of insulin dependent type 2 diabetes: An open labelled standard controlled clinical trial	India
CTRI/2018/04/013415	Clinical evaluation of the effect of Phalatrikadi Kwath and Madhumeha-har Vati Kalpit Yoga in madhumeh (diabetes mellitus II)	India
CTRI/2018/09/015829	A comparative pharmaceutico-analytical and clinical study of Indravati and Vangeshwara Rasa in madhumeha	India
CTRI/2019/02/017474	Efficacy and safety of <i>Curcuma longa</i> as an add-on therapy in type 2 diabetes mellitus: A randomized, double blind, placebo controlled trial	India
CTRI/2019/02/017500	A randomised control trial for the mechanism of action of yoga and Ayurveda with yoga in type-2 diabetes mellitus	India
CTRI/2019/02/017609	Randomized controlled clinical study on the efficacy of Vidangadi Lauha on sthula madhumeha with special reference to type II diabetes mellitus	India
CTRI/2019/02/017755	A clinical study to evaluate the efficacy of pathya, shodhana, shamana and rasayana chikitsa in the management of madhumeha WSR to type II diabetes mellitus	India

CTRI/2019/04/018729	A comparative clinical study to evaluate the efficacy of Nyagrodhadi Churna and B-S Patra Ghana Vati in the management of madhumeha WSR type-2 diabetes mellitus	India
CTRI/2019/05/019370	An open label double arm clinical trial to determine the efficacy of D 4 combination along with ongoing conventional medicine in managing diabetes mellitus (type 2)	India
CTRI/2019/05/019452	A randomized, multi-center, open labeled, comparative, prospective clinical study to evaluate efficacy and safety of Yesaka liquid as an add-on therapy to oral hypoglycemic agent (OHA) in type 2 diabetic patients	India
CTRI/2019/06/019636	An open-label, prospective, observational, multiple-dose, controlled, two armed, relative study of bio active liquid curcumin 5mg/50ml (5 drops in 50 ml of water) of oral dose (TDS dose) along with conventional pharmaceutical treatment (only prescribed diabetic medicine) in diabetic, adult, human patients to evaluate the safety and efficacy	India
CTRI/2020/01/023027	A double blind randomised placebo controlled evaluation of adjuvant effect of Kimshukatvagadi Ghana capsule in prameha with special reference to diabetes mellitus type II	India
CTRI/2020/02/023118	A comparative control clinico-biochemical study of Ayurvedic formulation in the patients of type 2 diabetes mellitus WSR madhumeha	India
CTRI/2020/03/023876	An open label randomised clinical trial to determine the efficacy of Rohitakadi Churna along with Triphaladi granules in the management of madhumeha with special reference to diabetes mellitus (type 2)	India
CTRI/2020/06/025922	Efficacy of vamana, virechana and basti followed by shamana in the management of sthula pramehi WSR to type 2 diabetes: An open labelled randomized standard controlled clinical trial	India
CTRI/2020/07/026465	Association study between sharir prakriti and type 2 diabetes (madhumeha) and its Ayurvedic management along with lifestyle modifications	India
CTRI/2020/10/028201	An open labelled randomized controlled clinical study to evaluate the anti-hyperglycemic activity of novel Ayurvedic Choorna in the management of prameha vis-a-vis type 2 diabetes mellitus	India
CTRI/2020/12/029806	Study the effect of Nisha-amalaki (as an adjuvant drug) in uncontrolled type II diabetes mellitus: A pragmatic, randomized controlled trial	India
IRCT2016042717254N5	The effects of green cardamom supplementation on blood glucose, lipids profile, oxidative stress, sirtuin-1 and irisin in type 2 diabetic patients: A study protocol for a randomized placebo-controlled clinical trial The effects of green cardamom supplementation on blood pressure and endothelium function in type 2 diabetic patients: A study protocol for a randomized controlled clinical trial	Iran
NCT03151837	A randomized, double-blind, placebo-controlled trial to evaluate the hypoglycemic efficacy of greenyn <i>Momordica charantia</i> extracts in diabetic subjects	Taiwan
NCT04023539	Evaluation of the effect of <i>Cinnamomum zeylanicum</i> on glycemic levels of Mexican adult patients with type 2 diabetes at 3 months: Randomized clinical trial	Mexico
NCT04259606	Effect of Cassia Cinnamon on arterial stiffness parameters in patients with type 2 diabetes mellitus	Mexico

RBR-2KKB6D	Analysis of the effectiveness of cinnamon (<i>Cinnamomum verum</i>) in the reduction of glycemic and lipidic levels of adults with type 2 diabetes: A study protocol	Brazil
SLCTR/2017/010	Effectiveness of <i>Cinnamomum zeylanicum</i> (Ceylon cinnamon) in lowering blood glucose in type 2 diabetes mellitus: A randomized double blind placebo controlled clinical trial	Sri Lanka

Appendix S4: Characteristics of included studies.

Author and year	Country	T2DM patients (duration of T2DM if existing cases [mean, years])	Comorbidities/ complications of T2DM	Participants /eligible arm (n)	Age (mean, years)	Female s (n)	HbA1c (mean, %)	FBG (mean, mg/dL)	Any commercial funding/other support
Ayurvedic medicine- single plant- or mineral-origin ingredient									
<i>Abelmoschus esculentus</i>									
Moradi 2020	Iran	Existing cases (4.3)/on OAD		A1=30, A2=30	53.8	44	7.8	183.0	Unclear
<i>Acacia Senegal</i>									
Babiker 2017, Babiker 2018	Sudan	Existing cases (5.1Ω)/on OAD		A1=50, A2=50	50.1Ω	73Ω	9.4Ω	182.1Ω	Unclear
<i>Aegle marmelos</i>									
Sankhla 2009	India¥	Existing cases (NS)/on OAD		A1=10, A2=10	NS	0	NS	135.0Ω	Unclear
Sharma 2013	India	Newly diagnosed/treatment naïve		A1=100☼, A2=50	NS	88	8.7	225.0	Unclear
Nigam 2019	India	Existing cases (6.6Ω)/on OAD		A1=31, A2=34	51.4Ω	35Ω	9.2Ω	171.5Ω	No?
<i>Allium sativum</i>									
Ashraf 2005	Pakistan	Existing cases (NS)/on OAD	Dyslipidemia	A1=35, A2=35	59.0	38	NS	NS	Unclear
Ashraf 2011a	Pakistan ¥	Existing cases (2.8)/on OAD?		A1=150☼, A2=30, A3=30	45.0	88	6.6	127.4	Unclear
Ashraf 2011b	Pakistan ¥	Newly diagnosed/treatment naïve		A1=30, A2=30	37.5	27	NS	120.6	Unclear
Kumar 2013	India	Existing cases (NS)/on OAD	Obesity	A1=30, A2=30	53.3	NS	7.5	158.7	Unclear
<i>Aloe vera</i>									
Arora 2009	India	Existing cases (NS)/on OAD		A1=14, A2=12	NS	NS	8.7Ω	180.4Ω	Unclear
Huseini 2012a, Huseini 2012b	Iran	Existing cases (9.9?)/on OAD		A1=35?, A2=35?	54.0?	38?	7.2?	181.1?	No
Zarrintan 2015	Iran	Existing cases (NS)/on OAD		A1=22, A2=22	52.6	19	8.6	175.4	Unclear
<i>Anethum graveolens</i>									
Mobasserri 2014	Iran	Existing cases (NS)/on OAD		A1=30, A2=30	53.1Ω	28Ω	NS	141.2Ω	No
Haidari 2020	Iran	Existing cases (8.3Ω)/on OAD	Gastrointestinal symptoms	A1=24, A2=24	50.5Ω	30Ω	NS	147.2Ω	No
<i>Azadirachta indica</i>									
Usharani 2020	India	Existing cases (NS)/on OAD		A1=60☼, A2=20	53.6	34	7.4Ω	119.3Ω	Yes
<i>Berberis aristata</i>									

Author and year	Country	T2DM patients (duration of T2DM if existing cases [mean, years])	Comorbidities/ complications of T2DM	Participants /eligible arm (n)	Age (mean, years)	Female s (n)	HbA1c (mean, %)	FBG (mean, mg/dL)	Any commercial funding/other support
Sharma 2017	India	Existing cases (NS)/on OAD	Dyslipidemia	A1=68?♂, A2=35?	NS	NS	NS	163.4Ω	Unclear
<i>Boswellia serrata</i>									
Azadmehr 2014	Iran	Existing cases (5.7)/on OAD		A1=37, A2=34	51.1	29	7.3	156.5	No
Mehrzadi 2018	Iran	Existing cases (11.1)/on OAD		A1=27, A2=29	54.9	30	8.2	167.0	No
<i>Camellia sinensis</i>									
MacKenzie 2007	US	Existing cases (7.0Ω)/on OAD		A1=36♂, A2=18♂	65.4Ω	28Ω	7.1Ω	NS	Yes?
Mirzaei 2009	Iran	Existing cases (5.7)/on OAD		A1=26, A2=46	54.6	58?	7.7	170.4	No
Hsu 2011	Taiwan	Existing cases (4.2Ω)/on OAD	Obesity	A1=40, A2=40	51.4Ω	44Ω	8.4Ω	172.8Ω	No
Lasaita 2014	Lithuania	Existing cases (8.1Ω)/on OAD and/or insulin	Diabetic retinopathy, nephropathy, or neuropathy?	A1=83?, A2=84?	57.0Ω	NS	8.0Ω	NS	Yes?
Liu 2014	Taiwan	Existing cases (4.7Ω)/on OAD	Dyslipidemia	A1=46, A2=46	54.3Ω	45Ω	7.6Ω	145.7Ω	No
Quezada-Fernandez 2019	Mexico	Existing cases (6.0Ω)/on OAD		A1=12, A2=13	53.2Ω	10Ω	7.5Ω	169.0Ω	Unclear
<i>Capparis spinosa</i>									
Huseini 2013	Iran	Existing cases (6.9Ω)/on OAD		A1=30, A2=30	53.9Ω	NS	8.3Ω	180.2Ω	No
<i>Cichorium intybus</i>									
Chandra 2020	India	Existing cases (4.6Ω)/on OAD		A1=56, A2=55	47.0Ω	45Ω	8.6Ω	197.0Ω	Yes
<i>Cinnamomum aromaticum</i>									
Mang 2006	Germany	Existing cases (7.0Ω)/on OAD		A1=40?, A2=39?	63.3Ω	21Ω	6.8Ω	162.0Ω	Yes
Suppakitporn 2006	Thailand	Existing cases (4.5)/on OAD		A1=20, A2=40	59.2	32	8.1	149.3	Unclear
Blevins 2007	US	Existing cases (NS)/on OAD		A1=30, A2=30	60.8Ω	29Ω	7.2Ω	138.8Ω	No
Crawford 2009	US\$	Existing cases (NS)/on OAD and/or insulin		A1=55, A2=54	60.2	45	8.4	NS	No?
Akilen 2010	UK\$	Existing cases (5.8)/on OAD		A1=30, A2=28	54.7	32	8.4	158.4	Yes
Wainstein 2011	Israel	Existing cases (8.2)/on OAD		A1=29, A2=30	63.1	24	7.6	155.0	Unclear
Lu 2012	China	Existing cases (NS)/on OAD?		A1=46?♂, A2=23?	60.4Ω	44	8.9Ω	174.6Ω	Unclear

Author and year	Country	T2DM patients (duration of T2DM if existing cases [mean, years])	Comorbidities/ complications of T2DM	Participants /eligible arm (n)	Age (mean, years)	Female s (n)	HbA1c (mean, %)	FBG (mean, mg/dL)	Any commercial funding/other support
Sharma 2012	India	Newly diagnosed/treatment naïve		A1=100♂, A2=50	NS	56	8.4	223.5	Unclear
Hasanzade 2013	Iran	Newly diagnosed/treatment naïve?		A1=35, A2=36	54.2	47	8.7	168.0	No
Tangvarasittic hai 2015, Sengsuk 2016	Thailand	Existing cases (8.6Ω)/on OAD		A1=54?, A2=60?	57.2?Ω	74?Ω	7.9?▼Ω	145.8? ▼Ω	No
<i>Cinnamomum verum</i>									
Vafa 2012	Iran	Existing cases (6.5Ω)/on OAD		A1=22, A2=22	54.9Ω	24Ω	7.3Ω	137.8Ω	No
Zahmatkesh 2012♂	Iran	Both (7.5)		A1=31, A2=30	54.7	45	9.1Ω	185.0Ω	Unclear
Talaei 2017	Iran	Existing cases (NS)/on OAD		A1=22, A2=22	57.6Ω	24Ω	10.2Ω	187.2Ω	No
Zare 2019	Iran	Existing cases (5.4Ω)/on OAD		A1=70♂, A2=70♂	52.7Ω	63Ω	7.4Ω	161.0Ω	Unclear
Mirmiranpour 2020	Iran	Existing cases (NS)/on OAD		A1=34, A2=34	58.5Ω	31Ω	NS	NS	No?
<i>Citrullus colocynthis</i>									
Huseini 2009	Iran	Existing cases (4.9)/on OAD		A1=25, A2=25	54.2	38	9.8	180.6	No
Barghamdi 2016	Iran	Existing cases (7.5)/on OAD		A1=35, A2=35	53.0	40	8.1	164.9	No
<i>Coccinia grandis</i>									
Kuriyan 2008, Kurpad 2008	India	Newly diagnosed/treatment naïve		A1=30, A2=30	47.1Ω	26Ω	6.6Ω	128.7Ω	Yes
Quamri 2017	India	Existing cases (NS)/on OAD	Dyslipidemia	A1=20, A2=20	44.1	21	NS	NS	No
Wasana 2021	Sri Lanka	Newly diagnosed/treatment naïve		A1=79, A2=79	48.6	96	6.4	133.7	Unclear
<i>Convolvulus prostratus</i>									
Patel 2012	India	Existing cases (NS)/on OAD		A1=45, A2=48	NS	NS	NS	182.4Ω	Unclear
<i>Crocus sativus</i>									
Milajerdi 2018	Iran	Existing cases (NS)/on OAD	Anxiety and depression?	A1=27, A2=27	54.6	42	6.6Ω	162.0Ω	Yes
Aleali 2019	Iran	Existing cases (6.3Ω)/on OAD		A1=38, A2=38	53.0Ω	45Ω	8.9Ω	175.2Ω	No
Ebrahimi 2019	Iran	Existing cases (7.2Ω)/on OAD		A1=45, A2=45	54.1Ω	44Ω	7.7Ω	163.8Ω	Unclear
Mobasserri 2020	Iran	Existing cases (NS)/on OAD		A1=30, A2=30	51.1Ω	NS	NS	135.1Ω	No
<i>Cuminum cyminum</i>									

Author and year	Country	T2DM patients (duration of T2DM if existing cases [mean, years])	Comorbidities/ complications of T2DM	Participants /eligible arm (n)	Age (mean, years)	Female s (n)	HbA1c (mean, %)	FBG (mean, mg/dL)	Any commercial funding/other support
Jafari 2017	Iran	Existing cases (NS)/on OAD		A1=66♂, A2=33	47.3Ω	62Ω	7.0Ω	166.6Ω	Unclear
Hendre 2020	India	Existing cases (NS)/on OAD		A1=100, A2=100	NS	NS	NS	151	No
<i>Curcuma longa</i>									
Usharani 2008	India	Existing cases (NS)/on OAD		A1=24?, A2=24?	52.6Ω	21Ω	7.9Ω	158.1Ω	Yes
Na 2013	China	Existing cases (7.7Ω)/on OAD and/or insulin	Obesity	A1=55, A2=54	55.1Ω	51Ω	7.7Ω	153.0Ω	Unclear
Chuengsamarn 2014	Thailand	Newly diagnosed/treatment naïve		A1=120, A2=120	59.4Ω	116Ω	7.0Ω	141.5Ω	No
Panahi 2017, Panahi 2018	Iran	Both (NS)		A1=61, A2=57	42.0Ω	49Ω	7.5Ω	168.5Ω	Yes
Adab 2019	Iran	Existing cases (NS)/on OAD	Dyslipidemia	A1=40, A2=40	55.2Ω	39Ω	6.9Ω	131.9Ω	No
Adibian 2019	Iran	Existing cases (8.0Ω)/on OAD		A1=25, A2=28	59.0Ω	22Ω	NS	NS	Unclear
Srinivasan 2019	India	Existing cases (3.9Ω)/on OAD		A1=69, A2=67	50.6Ω	85Ω	NS	NS	Yes
de Sousa 2020	Brazil¥	Existing cases (NS)/on OAD		A1=47, A2=46	62.6Ω	47Ω	7.9Ω	171.4Ω	No
<i>Cyamopsis tetragonoloba</i>									
Uusitupa 1984	Finland	Newly diagnosed/treatment naïve		A1=10, A2=9	62.0Ω	18	NS	174.8Ω	Unclear
Uusitupa 1989	Finland	Existing cases (9.4)/on OAD		A1=20, A2=19	60.1	26	9.1	225.0	Unclear
<i>Eclipta prostrata</i>									
Sazia 2015a, Sazia 2015b	India	Newly diagnosed/treatment naïve		A1=24, A2=24, A3=24	NS	NS	NS	127.1Ω	No?
<i>Elettaria cardamomum</i>									
Aghasi 2019	Iran	Existing cases (7.7)/on OAD		A1=41, A2=42	53.6	39	8.0	157.0	No?
<i>Embllica officinalis</i>									
Usharani 2013	India	Existing cases (NS)/on OAD		A1=44?♂, A2=22?	57.4Ω	20Ω	7.7Ω	NS	Yes
<i>Enicostemma axillare</i>									
Shankarrao 2017	India	Newly diagnosed/treatment naïve	Obesity	A1=20, A2=20	NS	NS	NS	NS	Unclear
<i>Gynostemma pentaphyllum</i>									
Huyen 2010	Vietnam ¥	Newly diagnosed/treatment naïve		A1=12, A2=12	60.4	7	8.8	174.6	No
Huyen 2012	Vietnam ¥	Newly diagnosed/treatment naïve		A1=12, A2=13	55.0	10	8.9	167.4	No

Author and year	Country	T2DM patients (duration of T2DM if existing cases [mean, years])	Comorbidities/ complications of T2DM	Participants /eligible arm (n)	Age (mean, years)	Female s (n)	HbA1c (mean, %)	FBG (mean, mg/dL)	Any commercial funding/other support
<i>Hibiscus sabdariffa</i>									
Sarbini 2019	Indonesia	Both (7.4Q)		A1=30, A2=30	55.1Q	40Q	NS	150.6Q	Unclear
<i>Ipomoea batatas</i>									
Ludvik 2004	Switzerland	Both (NS)?		A1=30, A2=31	55.4	27	7.1	144.0	Yes
Ludvik 2008	Austria?, Germany?	Both (3.9Q)?		A1=44?, A2=44?	59.2Q	29Q	6.4Q	138.5Q	Yes
<i>Juglans regia</i>									
Hosseini 2014a	Iran	Existing cases (5.7Q)/on OAD		A1=31, A2=31	57.2Q	37	8.4Q	166.5Q	No
Hosseini 2014b	Iran	Existing cases (6.4)/on OAD		A1=32, A2=29	55.1	33	8.4	166.5	No
Abdoli 2017	Iran	Existing cases (7.1Q)/on OAD		A1=25, A2=25	55.8Q	25Q	8.0Q	160.8Q	No
Zibaeenezhad 2016, Zibaeenezhad 2017	Iran	Existing cases (NS)/on OAD	Dyslipidemia?	A1=50?, A2=50?	54.8Q	47Q	7.0Q	156.2Q	No
Rabiei 2018	Iran	Existing cases (NS)/on OAD		A1=25, A2=25	50.2	37	9.7	200.1	No
<i>Linum usitatissimum</i>									
Barre 2008	Canada	Existing cases (NS)/on OAD?		A1=20, A2=20	60.1Q	20	7.1Q	145.0Q	Yes
Hashemzadeh 2017	Iran	Existing cases (NS)/on OAD?	Coronary heart disease	A1=30, A2=30	59.6	NS	NS	NS	Yes
<i>Momordica charantia</i>									
Dans 2007	Philippines	Both (NS)		A1=20, A2=20	59.2	25	8.0	149.4	Yes
Zänker 2012	Germany	Both (NS)?		A1=44, A2=45	62.5Q	18Q	6.5Q	NS	Yes
Trakoon-osot 2013	Thailand	Existing cases (7.5)/on OAD		A1=19, A2=19	58.0	27	7.4	118.0	No
Rahman 2015	Pakistan	Newly diagnosed/treatment naïve		A1=65, A2=30	52.0Q	31Q	NS	143.7Q	Unclear
Suthar 2016a	India	Existing cases (NS)/on OAD		A1=64, A2=21	41.3Q	30Q	7.9Q	149.4Q	Yes
Suthar 2016b	India	Both (NS)		A1=83, A2=40	48.6	54	8.2	151.5	Yes
Cortez-Navarrete 2018	Mexico	Newly diagnosed/treatment naïve?		A1=12, A2=12	48.6	16	7.7	138.6	Unclear

Author and year	Country	T2DM patients (duration of T2DM if existing cases [mean, years])	Comorbidities/ complications of T2DM	Participants /eligible arm (n)	Age (mean, years)	Female s (n)	HbA1c (mean, %)	FBG (mean, mg/dL)	Any commercial funding/other support
Kumari 2018	India	Existing cases (NS)/on OAD		A1=50♣, A2=25	NS	NS	7.3	152.9	Unclear
Amini 2020♣	Iran	Existing cases (9.3Ω)/on OAD		A1=12, A2=12	51.8Ω	0	NS	190.6Ω	Unclear
Kim 2020	Republic of Korea	Existing cases (NS)/on OAD		A1=66, A2=30	59.2Ω	40Ω	7.0Ω	138.5Ω	Unclear
<i>Nigella sativa</i>									
Najmi 2012	India	Newly diagnosed/treatment naïve	Metabolic syndrome	A1=40, A2=40	NS	38	7.9	154.9	Unclear
Hosseini 2013	Iran	Existing cases (6.2)/on OAD		A1=35, A2=35	49.7	40	8.8	180.0	No
Hadi 2015	Iran	Existing cases (5.3Ω)/on OAD		A1=25, A2=25	53.7Ω	23Ω	NS	172.1Ω	Unclear
Heshmati 2015	Iran	Existing cases (7.0)/on OAD		A1=36, A2=36	46.4	38	8.3	192.6	Unclear
Kaatabi 2015	Saudi Arabia	Existing cases (6.6)/on OAD		A1=57, A2=57	46.5	51	8.4	188.4	No?
Moustafa 2019	Egypt	Newly diagnosed/treatment naïve		A1=29, A2=36?	NS	47	7.5Ω	154.4Ω	Unclear
Kooshki 2020	Iran	Existing cases (7.5)/on OAD		A1=27, A2=23	54.1	34	NS	195.8	Unclear
Jangjo-Borazjani 2021	Iran	Existing cases (NS)/on OAD		A1=20♣, A2=20♣	43.6	40	NS	135.9	Unclear
<i>Plantago ovata</i>									
Ziai 2005	Iran	Existing cases (NS)/on OAD		A1=27, A2=22	52.8Ω	NS	9.8Ω	193.7Ω	Unclear
Feinglos 2013	US¥	Both (NS)		A1=29♣, A2=8	61.0	12	7.5	200.1	Yes
Abutair 2016	Palestine¥	Existing cases (NS)/on OAD		A1=20, A2=20	NS	20	8.5Ω	160.0Ω	No
<i>Portulaca oleracea</i>									
El-Sayed 2011	Yemen	Unclear	Obesity, dyslipidemia?, liver dysfunction?	A1=15, A2=15	40.0	10	NS	226.8	No?
Farzanegi 2014	Iran	Existing cases (NS)/on OAD		A1=14♣, A2=14♣	51.1	28	NS	174.1	Unclear
Dehghan 2016	Iran	Existing cases (8.0?)/on OAD		A1=16?♣, A2=16?♣	55.6	32?	NS	167.0	No
Wainstein 2016	Israel	Existing cases (NS)/on OAD?		A1=31, A2=32	55.4	22	7.5	174.0	Yes
<i>Pterocarpus marsupium</i>									

Author and year	Country	T2DM patients (duration of T2DM if existing cases [mean, years])	Comorbidities/ complications of T2DM	Participants /eligible arm (n)	Age (mean, years)	Females (n)	HbA1c (mean, %)	FBG (mean, mg/dL)	Any commercial funding/other support
Hariharan 2005	India	Newly diagnosed/treatment naïve		A1=182, A2=183	46.0	150	10.5	169.2	No
<i>Punica granatum</i>									
Faghihimani 2016	Iran	Existing cases (7.7)/on OAD		A1=40, A2=40	50.0	52	6.8	152.5	Unclear
Babaeian 2013	Iran	Existing cases (4.2)/on OAD		A1=25, A2=25	47.0	23	8.0	174.6	Unclear
Sohrab 2014, Sohrab 2015	Iran	Existing cases (6.2)/on OAD		A1=25, A2=25	56.0	21	8.0	154.5	Unclear
Khajebishak 2019a, Khajebishak 2019b	Iran	Existing cases (5.9)/on OAD	Obesity	A1=30, A2=30	44.8	30	7.6	159.0	Unclear
Grabež 2020	Republic of Srpska, Bosnia and Herzegovina	Existing cases (6.2)/on OAD		A1=19, A2=18	57.3	20	7.5	159.2	No
Hashemi 2020	Iran	Existing cases (5.7)/on OAD		A1=33, A2=32	62.1	31	7.2	145.7	No
<i>Sesamum indicum</i>									
Shahi 2017	Iran	Existing cases (NS)/on OAD		A1=24, A2=24	50.9	NS	8.0	159.0	No
Aslam 2018	Pakistan	Existing cases (NS)/on OAD		A1=30?, A2=30?	NS	NS	7.6	187.1	No
<i>Shilajit</i>									
Narasimha Raju 2016	India	Both (NS)?		A1=56, A2=54	NS	NS	7.6	193.4	Unclear
Niranjan 2016	India	Existing cases (NS)/on OAD		A1=20, A2=20	55.3	10	7.7	NS	Yes
<i>Syzygium cumini</i>									
Sahana 2010	India	Newly diagnosed/treatment naïve		A1=15, A2=5, A3=10	56.2	14	8.3	150.8	Yes
Sidana 2016, Sidana 2017	India	Existing cases (NS)/on OAD		A1=58, A2=55	NS	NS	8.8	142.0	No
<i>Terminalia chebula</i>									
Usharani 2020	India	Existing cases (NS)/on OAD	Endothelial dysfunction	A1=40, A2=20	54.3	21	7.4	121.5	Yes
<i>Tinospora cordifolia</i>									
Mishra 2015	India	Existing cases (NS)/on OAD		A1=50?, A2=50?	49.9	NS	8.2	149.8	No

Author and year	Country	T2DM patients (duration of T2DM if existing cases [mean, years])	Comorbidities/ complications of T2DM	Participants /eligible arm (n)	Age (mean, years)	Female s (n)	HbA1c (mean, %)	FBG (mean, mg/dL)	Any commercial funding/other support
Roy 2015	India	Existing cases (NS)/on OAD	Dyslipidemia	A1=30?, A2=30	NS	NS	7.8Ω	NS	No
<i>Tribulus terrestris</i>									
Samani 2016	Iran¥	Existing cases (8.2Ω)/on OAD		A1=50, A2=50	52.5Ω	100	7.7Ω	158.0Ω	No
<i>Trigonella foenum-graecum</i>									
Gupta 2001	India	Both (NS)?		A1=12, A2=13	51.0	6	8.3	142.9	Yes
Lu 2008	China	Existing cases (10.8)/on OAD		A1=46, A2=23	54.3	31	8.3	153.0	Unclear
Ansari 2011	Pakistan	Existing cases (NS)/on OAD		A1=102, A2=108	61.0Ω	82Ω	9.2Ω?	NS	Unclear
Rafraf 2014	Iran	Existing cases (5.9Ω)/on OAD		A1=45, A2=45	40.5Ω	78Ω	8.8Ω	179.5Ω	No
Suchitra 2015	India	Existing cases (7.1)/on OAD		A1=30, A2=30	50.2	23	7.9	NS	Unclear
Kaur 2016	India	Newly diagnosed/treatment naïve		A1=30, A2=30	53.1	24	8.1	163.1	No
Singh 2016	India	Both (NS)		A1=20, A2=20, A3=20	56.5	31	8.0	170.2	No
Verma 2016	India¥	Existing cases (NS)/on OAD		A1=77?, A2=77?	NS	46	NS	152.1	Yes
Ranade 2017	India	Existing cases (NS)/on OAD and/or insulin		A1=30, A2=30	47.1	15	7.6	157.2	No
Gholaman 2018	Iran	Existing cases (NS)/on OAD	Obesity	A1=10, A2=10	NS	20	NS	207.7	Unclear
Kandhare 2018	India¥	Existing cases (NS)/on OAD		A1=60, A2=59	51.5	66	8.5	180.2	Yes
Hassani 2019	Iran¥	Existing cases (6.6Ω)/on OAD		A1=72♣, A2=72♣	51.4Ω	71Ω	8.1Ω	160.5Ω	Unclear
Hota 2019\$	India	Existing cases (NS)/on OAD		A1=102, A2=102	52.6	65	8.1	144.8	Yes
Najdi 2019	Saudi Arabia	Existing cases (4.8)/on OAD		A1=6, A2=6	51.2	NS	8.2Ω	172.3Ω	Unclear
Rashid 2019	Pakistan	Newly diagnosed/treatment naïve		A1=32, A2=32	47.1	29	7.3	135.0	Unclear
Hadi 2020	Iran	Existing cases (4.7Ω)/on OAD		A1=25, A2=25	47.6Ω	25Ω	NS	141.7Ω	No
<i>Urtica dioica</i>									
Namazi 2011, Esfanjani 2012aα,	Iran	Existing cases (8.5?Ω)/on OAD		A1=25, A2=25	53.5Ω	21?Ω	7.4Ω	135.5Ω	Unclear

Author and year	Country	T2DM patients (duration of T2DM if existing cases [mean, years])	Comorbidities/ complications of T2DM	Participants /eligible arm (n)	Age (mean, years)	Females (n)	HbA1c (mean, %)	FBG (mean, mg/dL)	Any commercial funding/other support
Esfanjani 2012b ^a									
Kianbakht 2013	Iran	Existing cases (12.8 Ω)/on OAD		A1=52, A2=55	55.3 Ω	75 Ω	10.1 Ω	255.3 Ω	No
Khajeh-Mehrizi 2014	Iran	Existing cases (NS)/on OAD		A1=30, A2=30	54.7 Ω	28 Ω	NS	175.4 Ω	Unclear
Dabagh 2016	Iran	Existing cases (3.0)/on OAD		A1=20 $\oplus$, A2=20 $\oplus$	42.9	0	NS	147.5	No
Hassani 2016 ^a	Iran	Existing cases (NS)/on OAD		A1=15?, A2=13?	NS	28?	NS	177.9 Ω	Unclear
Dadvar 2017 ^a	Iran	Existing cases (2.9)/on OAD		A1=20 $\oplus$, A2=20 $\oplus$	45.6	40	NS	156.0	Unclear
Ghalavand 2017	Iran	Existing cases (2.7)/on OAD		A1=20 $\oplus$, A2=20 $\oplus$	42.1	0	NS	155.2	Unclear
Korani 2017	Iran	Existing cases (2.5 Ω)/on OAD		A1=30, A2=30	49.1 Ω	36 Ω	8.8 Ω	142.5 Ω	Yes
Mohammadnia 2017 ^a	Iran	Existing cases (NS)/on OAD		A1=15, A2=13	55.8 Ω	28	NS	NS	Unclear
<i>Vernonia cinerea</i>									
Sayeed 2013	Bangladesh	Existing cases (4.9)/on OAD		A1=24, A2=24	54.2	26	10.1	188.5	Unclear
<i>Withania coagulans</i>									
Hemalatha 2018	India	Existing cases (NS)/on OAD		A1=12, A2=12	NS	15	NS	185.0	Unclear
<i>Withania somnifera</i>									
Usharani 2014	India	Existing cases (NS)/on OAD		A1=44? $\oplus$, A2=22?	56.7 Ω	21 Ω	NS	NS	Yes
<i>Zingiber officinale</i>									
Mahluji 2013	Iran	Existing cases (NS)/on OAD		A1=32, A2=32	51.2 Ω	24 Ω	7.0 Ω	147.5 Ω	No
Arablou 2014a, Arablou 2014b ^a	Iran	Existing cases (3.9 Ω)/on OAD		A1=35, A2=35	52.3 Ω	48 Ω	8.3 Ω	130.0 Ω	No
Mozaffari-Khosravi 2014, Talaei 2017, Talaei 2018	Iran	Existing cases (NS)/on OAD		A1=44, A2=44	50.4 Ω	50 Ω	7.6 Ω	153.7 Ω	No?
Shidfar 2015	Iran	Existing cases (5.3 Ω)/on OAD		A1=25, A2=25	46.2 Ω	NS	7.4 Ω	158.5 Ω	No?

Author and year	Country	T2DM patients (duration of T2DM if existing cases [mean, years])	Comorbidities/ complications of T2DM	Participants /eligible arm (n)	Age (mean, years)	Female s (n)	HbA1c (mean, %)	FBG (mean, mg/dL)	Any commercial funding/other support
Arzati 2017, Zarezadeh 2018	Iran	Existing cases (NS)/on OAD		A1=25?, A2=25?	50.7Ω	34Ω	7.4Ω	165.5Ω	No
Mohammadi 2017 ^a , Mohammadi 2019 ^a	Iran	Existing cases (NS)/on OAD		A1=22 ⁺ , A2=22 ⁺	53.4	NS	8.9	NS	Unclear
Carvalho 2020	Brazil [¥]	Existing cases (NS)/on OAD		A1=72, A2=72	58.6Ω	72Ω	8.4Ω	194.4Ω	Unclear
Gholinezhad 2020	Iran [¥]	Existing cases (NS)/on OAD	Periodontitis	A1=25, A2=25	52.2Ω	23Ω	8.5Ω	180.0Ω	No
<i>Ziziphus mauritiana</i>									
Yazdanpanah 2017	Iran	Existing cases (3.6Ω)/on OAD		A1=58, A2=58	49.8Ω	69Ω	8.0Ω	148.5Ω	No
<i>Acalypha indica</i>/<i>Allium cepa</i>/<i>Allium sativum</i>/<i>Azadirachta indica</i>/<i>Mangifera indica</i>/<i>Murraya koenigii</i>/<i>Musa sapientum</i>/<i>Ocimum tenuiflorum</i>/<i>Phyllanthus amarus</i>/<i>Tinospora cordifolia</i>									
Balasubramaniam 2010	India	Newly diagnosed/treatment naïve		A1=20/group (total 200), A2=20/group (total 200)	50.8	184	NS	NS	Unclear
<i>Allium sativum</i>; <i>Cuminum cyminum</i>									
Mansouri 2018	Iran	Existing cases (NS)/on OAD	Hypertension	A1=25, A2=25, A3=25	52.9	41?	11.8	NS	Unclear
<i>Aloe vera</i>; <i>Pterocarpus marsupium</i>; <i>Aloe vera</i>+<i>Pterocarpus marsupium</i>									
Maurya 2017	India	Newly diagnosed/treatment naïve		A1=35, A2=35, A3=35, A4=35	51.7Ω	64Ω	7.0Ω	154.7Ω	No
<i>Cinnamomum verum</i>; <i>Crocus sativus</i>; <i>Elettaria cardamomum</i>; <i>Zingiber officinale</i>									
Azimi 2014, Azimi 2016	Iran	Existing cases (NS)/on OAD		A1=42?, A2=42?, A3=42?, A4=42?, A5=40?	54.3Ω	125Ω	7.8Ω	360.2Ω	No
<i>Enicostemma axillare</i>; Shilajit									
Kumar 2014	India	Both (NS)		A1=33?, A2=31?, A3=31?	NS	NS	8.1Ω	143.0Ω	Unclear
<i>Enicostemma axillare</i>+<i>Embllica officinalis</i>+<i>Tinospora cordifolia</i>									
Sharma 2019	India [¥]	Existing cases (NS)/on OAD		A1=6071, A2=43	NS	NS	NS	146.2Ω	No?
<i>Linum usitatissimum</i>; <i>Plantago ovata</i>									

Author and year	Country	T2DM patients (duration of T2DM if existing cases [mean, years])	Comorbidities/ complications of T2DM	Participants /eligible arm (n)	Age (mean, years)	Female s (n)	HbA1c (mean, %)	FBG (mean, mg/dL)	Any commercial funding/other support
Ricklefs-Johnson 2017	US	Existing cases (NS)/on OAD		A1=10?, A2=9?	59.1Ω	8Ω	6.9Ω	125.1Ω	Yes
Syzygium cumini+Withania coagulans									
Siddiqui 2017	India	Unclear		A1=35?, A2=35?	NS	37Ω	8.5Ω	162.3Ω	Unclear
Trigonella foenum-graecum; Aegle marmelos; Trigonella foenum-graecum+Aegle marmelos									
Yaheya 2009	Oman?	Existing cases (NS)/on OAD		A1=20, A2=20, A3=20, A4=20	NS	NS	NS	NS	Unclear
Ayurvedic medicine- combination of plant- and/or mineral-origin ingredients§									
AYUBES									
Godatwar 2019§	India¥	Existing cases (NS)/on OAD		A1=39?, A2=39?	56.5Ω	NS	7.6Ω	160.1Ω	Yes
BGR-34									
Gupta 2018	India	Both (NS)?		A1=32, A2=32	48.8Ω	26Ω	9.7Ω	191.6Ω	Unclear
Bilvadi Churna; Kiratadi Churna									
Kumari 2016	India	Existing cases (NS)/on OAD	Stress	A1=20, A2=20, A3=20	NS	21	8.0	183.3	Unclear
CardiPro									
Fatima 2012	India	Existing cases (NS)/on OAD		A1=30, A2=30	52.2Ω	21Ω	NS	NS	Yes
Cogent db									
Shekhar 2002	Malaysia ¥	Existing cases (9.0)/on OAD		A1=39, A2=40	49.0Ω	27	9.9Ω	208.8Ω	Yes
DCBT 2345									
Mohan 2001	India	Existing cases (NS)/on OAD		A1=22?, A2=22?	55.0Ω	19Ω	9.4Ω	189.0Ω	Yes
Diabetea tea									
Mahmoud 2016	Kuwait	Existing cases (5.7Ω)/on OAD	Hypertension?	A1=30, A2=30	52.9Ω	22Ω	9.1Ω	156.6Ω	Unclear
Emblica officinalis; Withania somnifera; Emblica officinalis, Withania somnifera									
Usharani 2014	India	Existing cases (NS)/on OAD		A1=14?, A2=14?, A3=14?	58.7Ω	4Ω	NS	NS	Yes
Herbal combination									
Shokoohi 2017	Iran	Existing cases (6.2)/on OAD	Dyslipidemia	A1=43, A2=43	49.7	86	8.0	189.8	No
Hyponidd									
Poongothai 2002	India	Existing cases (NS)/on OAD		A1=20, A2=20	53.5Ω	11Ω	8.7Ω	177.5Ω	Yes
Inolter									

Author and year	Country	T2DM patients (duration of T2DM if existing cases [mean, years])	Comorbidities/ complications of T2DM	Participants /eligible arm (n)	Age (mean, years)	Female s (n)	HbA1c (mean, %)	FBG (mean, mg/dL)	Any commercial funding/other support
Agrawal 2002	India	Newly diagnosed/treatment naïve		A1=30, A2=30	46.1	14	10.1	218.5	Yes
Kalpita									
Agarwal 2013	India	Unclear	Obesity	A1=30, A2=30, A3=30	NS	NS	NS	168.4	Unclear
Khadira-Kramuka Kashaya Ghanavati; Nishamalaki, Shilajit; Khadira-Kramuka Kashaya Ghanavati+Nishamalaki, Shilajit									
Paliwal 2018\$	India	Both (NS)		A1=20?, A2=20?, A3=20?	NS	NS	8.0	160.3	Unclear
Lodhradi Kashaya Ghana Vati									
Bramhankar 2017	India	Newly diagnosed/treatment naïve?		A1=15, A2=15, A3=15	NS	NS	NS	176.8Ω	Unclear
Madhumeha Nashini Gutika; Darvyadi Kwatha; Madhumeha Nashini Gutika+Darvyadi Kwatha									
Bhawana 2015	India	Unclear		A1=20, A2=20, A3=20	NS	NS	NS	159.7	Unclear
Mamajaka Ghana Vati; Tejashiladi Vati									
Bhagat 2017\$	India	Both (NS)		A1=46, A2=44	NS	44	NS	209.7Ω	Unclear
Mamajaka Ghana Vati; Trikatu Gutika									
Kataria 2017\$	India	Both (NS)		A1=15, A2=15	NS	12	NS	170.6	Unclear
Mehagni									
Gopalakrishna 2017	India	Existing cases (NS)/on OAD		A1=20, A2=20	43.4	NS	9.4	156.3	Yes
Mustadi Kwatha Ghana Vati									
Kushwaha 2017	India	Existing cases (8.9)/on OAD		A1=50, A2=50	NS	50	NS	180.8	Unclear
Naga Bhasma, Nishamalaki; Nishamalaki, Hordeum vulgare									
Desale 2018\$	India	Both (NS)		A1=80⊕, A2=40	NS	56	NS	179.4Ω	Unclear
Nigella sativa, Trigonella foenum-graecum									
Memon 2010a, Memon 2010b, Memon 2012	Pakistan ¥	Existing cases (NS)/on OAD		A1=50, A2=50	49.5	60	NS	189.0	Unclear
Nisha Katakadi Kashaya; Yashad Bhasma; Nisha Katakadi Kashaya+Yashad Bhasma									
Srinivas 2018	India¥	Both (NS)?		A1=65?, A2=64?, A3=64?	NS	100Ω	7.1Ω	145.0Ω	Unclear
Pancreas tonic									

Author and year	Country	T2DM patients (duration of T2DM if existing cases [mean, years])	Comorbidities/ complications of T2DM	Participants /eligible arm (n)	Age (mean, years)	Female s (n)	HbA1c (mean, %)	FBG (mean, mg/dL)	Any commercial funding/other support
Hsia 2004	US¥	Existing cases (4.1Ω~)/on OAD		A1=31, A2=16	47.5Ω~	26Ω~	9.9Ω~	219.0Ω~	Unclear
Polyherbal formulation									
Awasthi 2015	India	Newly diagnosed/treatment naïve		A1=48, A2=45	45.6Ω	33Ω	7.6Ω	163.3Ω	No?
Salasaradi Kashaya+Shilajit+Trivanga Bhasma+Tinospora cordifolia, Azadirachta indica; Hyponidd									
Bhat 2012\$	India	Both (NS)		A1=25?, A2=25?	NS	8Ω	NS	137.8Ω	Yes?
Shilajit; Asanadi Ghana Vati									
Gupta 2016	India	Existing cases (NS)/on OAD	Diabetic neuropathy?	A1=45?, A2=45?	NS	29Ω	7.7Ω	168.5Ω	No
Swarnamakshika Bhasma									
Taviad 2016\$	India	Both (NS)		A1=54, A2=56	NS	65	NS	180.2Ω	Unclear
Talapotaka Churna									
Nille 2018	India	Unclear		A1=16?⊕, A2=12?, A3=8?	NS	NS	8.5Ω	150.7Ω	Unclear
Trigonella foenum-graecum, Ocimum tenuiflorum									
Mitra 2006	India	Newly diagnosed/treatment naïve	Dyslipidemia	A1=64⊕, A2=16	46.7	38	NS	183.6	Unclear
Triticum aestivum; Nishamalaki; Triticum aestivum+Nishamalaki									
Samagandi 2012	India	Existing cases (NS)/on OAD		A1=10, A2=10, A3=10	NS	NS	NS	172.6	Unclear
Vidangadi Yoga									
Deshpande 2018	India	Both (NS)		A1=31, A2=30	49.2Ω	32Ω	7.0Ω	149.4Ω	No
Vijaysaradi Ghana Vati; Madhumehari Vati									
Sharma 2018\$	India	Existing cases (NS)/on OAD		A1=29, A2=31	NS	19	8.1Ω	164.3Ω	Yes

A1, A2, A3, A4, A5=Eligible study arms, FBG=Fasting blood glucose, HbA1c=Glycated hemoglobin, NS=Not specified, OAD=Oral antidiabetic drug, T2DM=Type 2 diabetes mellitus

\$Not a journal publication.

⊕In Persian language.

¥Multicenter/site recruitment.

⊕Two or more study arms were pooled together.

▼Median.

ΩPer-protocol analysis.

~Prior to randomization (and not at the point of randomization).

§Some of the Ayurvedic medicines contain single plant- or mineral-origin ingredient.

Appendix S5: Details of the interventions.

Author and year	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Form and timing of administration of Ayurvedic medicine	Dose (g/day or otherwise mentioned) X duration (weeks) of Ayurvedic medicine	Anupan of Ayurvedic medicine
Ayurvedic medicine- single plant- or mineral-origin ingredient								
<i>Abelmoschus esculentus</i>								
Moradi 2020	<i>Abelmoschus esculentus</i> (fruit)	Placebo				A1=Powder, BD	A1=10 X 8	A1=Yogurt
<i>Acacia Senegal</i>								
Babiker 2017, Babiker 2018	<i>Acacia senegal</i> (gum)	Placebo				A1=Powder, OD	A1=30 X 13	A1=Water
<i>Aegle marmelos</i>								
Sankhla 2009	<i>Aegle marmelos</i> (leaf, leaf extract)	Placebo (green gram)				A1=Powder, BD	A1=4 X 8	
Sharma 2013	<i>Aegle marmelos</i> (leaf extract)☹	Placebo				A1=Capsule, OD☹	A1=0.25, 0.6 X 13☹	
Nigam 2019	<i>Aegle marmelos</i> (leaf)	No additional medicine?				A1=Juice, OD	A1=100(m l) X 8	
<i>Allium sativum</i>								
Ashraf 2005	<i>Allium sativum</i> (clove)	Placebo				A1=Tablet, BD	A1=0.6 X 12	
Ashraf 2011a	<i>Allium sativum</i> (clove)☹	OAD	Placebo			A1=Tablet, Unclear☹	A1=0.3, 0.6, 0.9, 1.2, 1.5 X 24☹	
Ashraf 2011b	<i>Allium sativum</i> (clove)	Placebo				A1=Tablet, TDS	A1=0.9 X 24	
Kumar 2013	<i>Allium sativum</i> (clove)	No additional medicine				A1=Capsule, BD	A1=0.5 X 12	
<i>Aloe vera</i>								
Arora 2009	<i>Aloe vera</i> (leaf?)	No additional medicine				A1=Juice, OD	A1=150(m l) X 13	
Huseini 2012a, Huseini 2012b	<i>Aloe vera</i> (leaf gel)	Placebo				A1=Capsule, BD	A1=0.6 X 9	

Author and year	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Form and timing of administration of Ayurvedic medicine	Dose (g/day or otherwise mentioned) X duration (weeks) of Ayurvedic medicine	Anupan of Ayurvedic medicine
Zarrintan 2015	<i>Aloe vera</i> (leaf? extract)	Placebo				A1=Tablet, OD	A1=1 X 9	
<i>Anethum graveolens</i>								
Mobasserri 2014	<i>Anethum graveolens</i> (leaf, stem)	Placebo				A1=Tablet, TDS	A1=3.3 X 8	
Haidari 2020	<i>Anethum graveolens</i> (leaf)	Placebo				A1=Capsule, TDS	A1=3 X 8	
<i>Azadirachta indica</i>								
Usharani 2020	<i>Azadirachta indica</i> (leaf+twig extract)☼	Placebo				A1=Capsule, BD☼	A1=0.25, 0.5, 1 X 12☼	A1=Water☼
<i>Berberis aristata</i>								
Sharma 2017	<i>Berberis aristata</i> (stem)☼	No additional medicine				A1=Powder, BD☼	A1=1.5, 3 X 39☼	
<i>Boswellia serrata</i>								
Azadmehr 2014	<i>Boswellia serrata</i> (gum resin)	Placebo				A1=Capsule, BD	A1=0.8 X 12	
Mehrziadi 2018	<i>Boswellia serrata</i> (gum resin)	Placebo				A1=Capsule, BD	A1=0.5 X 8	
<i>Camellia sinensis</i>								
MacKenzie 2007	<i>Camellia sinensis</i> (green and black tea; leaf extract; decaffeinated)☼	Placebo☼				A1=Capsule, OD☼	A1=0.375, 0.75 X 12☼	
Mirzaei 2009	<i>Camellia sinensis</i> (green tea; leaf extract)¶¶	Placebo				A1=Capsule, TDS	A1=1.5 X 8	
Hsu 2011	<i>Camellia sinensis</i> (green tea; leaf extract; decaffeinated)	Placebo				A1=Capsule, TDS	A1=1.5 X 16	
Lasaitte 2014	<i>Camellia sinensis</i> (green tea; leaf extract)	Placebo				A1=Capsule, BD to TDS	A1=0.4 to 0.6 X 78	
Liu 2014	<i>Camellia sinensis</i> (green tea; leaf extract; decaffeinated)	Placebo				A1=Capsule, TDS	A1=1.5 X 16	
Quezada-Fernandez 2019	<i>Camellia sinensis</i> (green tea; leaf extract; decaffeinated)	Placebo				A1=Capsule, Unclear	A1=0.4 X 12	
<i>Capparis spinosa</i>								
Huseini 2013	<i>Capparis spinosa</i> (fruit extract)¶¶	Placebo				A1=Capsule, TDS	A1=1.2 X 9	

Author and year	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Form and timing of administration of Ayurvedic medicine	Dose (g/day or otherwise mentioned) X duration (weeks) of Ayurvedic medicine	Anupan of Ayurvedic medicine
Cichorium intybus								
Chandra 2020	<i>Cichorium intybus</i> (seed extract)¶	Placebo				A1=Capsule, BD	A1=0.541 X 12	
Cinnamomum aromaticum								
Mang 2006	<i>Cinnamomum aromaticum</i> (bark extract)	Placebo				A1=Capsule, TDS	A1=0.336 X 17	
Suppapatiporn 2006	<i>Cinnamomum aromaticum</i> (bark)	Placebo				A1=Capsule, TDS	A1=4.5? X 12	
Blevins 2007	<i>Cinnamomum aromaticum</i> (bark)	Placebo (wheat)				A1=Capsule, BD	A1=1 X 13	
Crawford 2009	<i>Cinnamomum aromaticum</i> (bark)	No additional medicine				A1=Capsule, OD?	A1=1 X 13	
Akilen 2010	<i>Cinnamomum aromaticum</i> (bark)¶	Placebo				A1=Capsule, TDS	A1=2 X 12	
Wainstein 2011	<i>Cinnamomum aromaticum</i> (bark)	Placebo				A1=Capsule, TDS	A1=2.4 to 1.2 X 12	
Lu 2012	<i>Cinnamomum aromaticum</i> (bark extract)¶☼	Placebo				A1=Tablet, OD☼	A1=0.12, 0.36 X 13☼	
Sharma 2012	<i>Cinnamomum aromaticum?</i> (bark)☼	Placebo				A1=Capsule, TDS☼	A1=3, 6 X 13☼	
Hasanzade 2013	<i>Cinnamomum aromaticum</i> (bark)	Placebo				A1=Capsule, BD	A1=1 X 9	
Tangvarasittichai 2015, Sengsuk 2016	<i>Cinnamomum aromaticum</i> (bark)	Placebo				A1=Capsule, TDS	A1=1.5 X 9	
Cinnamomum verum								
Vafa 2012	<i>Cinnamomum verum</i> (bark)	Placebo (wheat)				A1=Capsule, TDS	A1=3 X 8	
Zahmatkesh 2012	<i>Cinnamomum verum</i> (bark)	Placebo				A1=Capsule, BD	A1=1 X 8?	
Talaei 2017	<i>Cinnamomum verum?</i> (bark)	Placebo				A1=Capsule, TDS	A1=3 X 8	
Zare 2019	<i>Cinnamomum verum?</i> (bark)¶☼	Placebo☼				A1=Capsule, BD☼	A1=1 X 13☼	

Author and year	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Form and timing of administration of Ayurvedic medicine	Dose (g/day or otherwise mentioned) X duration (weeks) of Ayurvedic medicine	Anupan of Ayurvedic medicine
Mirmiranpour 2020	<i>Cinnamomum verum</i> (bark)	Placebo (rice)				A1=Capsule, OD	A1=0.5 X 13	
<i>Citrullus colocynthis</i>								
Huseini 2009	<i>Citrullus colocynthis</i> (fruit)	Placebo				A1=Capsule, TDS	A1=0.3 X 9	
Barghamdi 2016	<i>Citrullus colocynthis</i> (fruit)	Placebo				A1=Capsule, OD	A1=0.125 X 9	
<i>Coccinia grandis</i>								
Kuriyan 2008, Kurpad 2008	<i>Coccinia grandis</i> (aerial parts extract)	Placebo				A1=Capsule, OD?	A1=1 X 13	
Quamri 2017	<i>Coccinia grandis</i> (leaf)	OAD				A1=Powder, BD	A1=15 X 8	
Wasana 2021	<i>Coccinia grandis</i> (leaf extract)¶	Placebo (corn)				A1=Capsule, OD	A1=0.5 X 13	
<i>Convolvulus prostratus</i>								
Patel 2012	<i>Convolvulus prostratus</i> (whole plant)	No additional medicine				A1=Capsule, TDS	A1=1.5 X 8	
<i>Crocus sativus</i>								
Milajerdi 2018	<i>Crocus sativus</i> (stigma extract)	Placebo				A1=Capsule, BD	A1=0.03 X 8	
Aleali 2019	<i>Crocus sativus</i> (stigma extract)	Placebo				A1=Capsule, Unclear	A1=0.03 X 12	
Ebrahimi 2019	<i>Crocus sativus</i> (stigma)	Placebo				A1=Tablet, BD	A1=0.1 X 12	A1=Water
Mobasserri 2020	<i>Crocus sativus</i> (stigma)	Placebo				A1=Capsule, OD	A1=0.1 X 8	
<i>Cuminum cyminum</i>								
Jafari 2017	<i>Cuminum cyminum</i> (seed oil)☞	Placebo				A1=Capsule, Unclear☞	A1=0.05, 0.1 X 8☞	
Hendre 2020	<i>Cuminum cyminum</i> (seed)	No additional medicine				A1=Capsule, OD	A1=0.5 X 13	
<i>Curcuma longa</i>								
Usharani 2008	<i>Curcuma longa</i> (rhizome extract)	Placebo				A1=Capsule, BD	A1=0.6 X 8	

Author and year	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Form and timing of administration of Ayurvedic medicine	Dose (g/day or otherwise mentioned) X duration (weeks) of Ayurvedic medicine	Anupan of Ayurvedic medicine
Na 2013	<i>Curcuma longa</i> (rhizome extract)	Placebo				A1=Capsule, BD	A1=0.3 X 13	
Chuengsamarn 2014	<i>Curcuma longa</i> (rhizome extract)	Placebo				A1=Capsule, BD	A1=1.5 X 26	
Panahi 2017, Panahi 2018	<i>Curcuma longa</i> (rhizome extract)	Placebo				A1=Capsule, Unclear	A1=1 X 12	
Adab 2019	<i>Curcuma longa</i> (rhizome)¶	Placebo (corn)				A1=Capsule, TDS	A1=2.1 X 8	
Adibian 2019	<i>Curcuma longa</i> (rhizome extract)	Placebo (rice)				A1=Capsule, TDS	A1=1.5 X 10	
Srinivasan 2019	<i>Curcuma longa</i> (rhizome)	Placebo				A1=Capsule, TDS	A1=1.2 X 12	
de Sousa 2020	<i>Curcuma longa</i> (rhizome)	Placebo				A1=Capsule, OD	A1=0.5 X 17	
<i>Cyamopsis tetragonoloba</i>								
Uusitupa 1984	<i>Cyamopsis tetragonoloba</i> (seed)	Placebo (wheat)				A1=Granule, TDS	A1=7.5 to 15 to 21 X 18	
Uusitupa 1989	<i>Cyamopsis tetragonoloba</i> (seed)	Placebo (wheat)				A1=Granule, TDS	A1=15 X 13	A1=Juice, milk, or water
<i>Eclipta prostrata</i>								
Sazia 2015a, Sazia 2015b	<i>Eclipta prostrata</i> (extract)	OAD	No medicine			A1=Capsule, TDS	A1=2.4 X 13	
<i>Elettaria cardamomum</i>								
Aghasi 2019	<i>Elettaria cardamomum</i> (seedpod?)¶	Placebo				A1=Capsule, TDS	A1=3 X 10	
<i>Emblica officinalis</i>								
Usharani 2013	<i>Emblica officinalis</i> (fruit extract)☼	Placebo				A1=Capsule, BD☼	A1=0.5, 1 X 12☼	
<i>Enicostemma axillare</i>								
Shankarrao 2017	<i>Enicostemma axillare</i>	OAD				A1=Powder, BD	A1=10 X 12	A1=Lukewarm water
<i>Gynostemma pentaphyllum</i>								

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Huyen 2010	<i>Gynostemma pentaphyllum</i> (whole plant extract)¶	Placebo (green tea)				A1=Powder, BD	A1=6 X 12	A1=Water
Huyen 2012	<i>Gynostemma pentaphyllum</i> (whole plant extract)¶	Placebo (green tea)				A1=Powder, BD	A1=6 X 8	A1=Water
<i>Hibiscus sabdariffa</i>								
Sarbini 2019	<i>Hibiscus sabdariffa</i> ¶	Placebo				A1=Capsule, BD	A1=1 X 8	
<i>Ipomoea batatas</i>								
Ludvik 2004	<i>Ipomoea batatas</i> (white variety; tuber skin extract)	Placebo				A1=Tablet?, OD	A1=4 X 12	
Ludvik 2008	<i>Ipomoea batatas</i> (white variety; tuber skin extract)	Placebo				A1=Tablet, OD	A1=4 X 22	
<i>Juglans regia</i>								
Hosseini 2014a	<i>Juglans regia</i> (leaf extract)	Placebo				A1=Tablet, BD	A1=0.4 X 9	
Hosseini 2014b	<i>Juglans regia</i> (leaf extract)¶	Placebo				A1=Capsule, BD	A1=0.2 X 13	
Abdoli 2017	<i>Juglans regia</i> (leaf extract)¶	Placebo				A1=Capsule, TDS	A1=0.75 X 13	
Zibaeenezh ad 2016, Zibaeenezh ad 2017	<i>Juglans regia</i> (seed oil)	Placebo?				A1=Capsule, TDS	A1=15 X 13	
Rabiei 2018	<i>Juglans regia</i> (leaf extract)¶	Placebo				A1=Capsule, OD to BD	A1=0.1 to 0.2 X 8	
<i>Linum usitatissimum</i>								
Barre 2008	<i>Linum usitatissimum</i> (seed oil)	Placebo (safflower oil)				A1=Capsule, Unclear	A1=10 X 13	
Hashemzadeh 2017	<i>Linum usitatissimum</i> (seed oil)	Placebo				A1=Capsule, BD	A1=2 X 12	
<i>Momordica charantia</i>								
Dans 2007	<i>Momordica charantia</i> (fruit+seed extract)	Placebo				A1=Capsule, TDS	A1=3? X 13	
Zänker 2012	<i>Momordica charantia</i> (fruit? extract)	Placebo				A1=Capsule, BD	A1=1 X 17	
Trakoonosot 2013	<i>Momordica charantia</i> (fruit pulp)¶	Placebo				A1=Capsule, TDS	A1=6 X 16	
Rahman 2015	<i>Momordica charantia</i> (fruit pulp)☉	OAD				A1=Capsule, Unclear☉	A1=2, 4 X 10☉	

Author and year	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Form and timing of administration of Ayurvedic medicine	Dose (g/day or otherwise mentioned) X duration (weeks) of Ayurvedic medicine	Anupan of Ayurvedic medicine
Suthar 2016a	<i>Momordica charantia</i> (fruit)	Placebo				A1=Capsule, BD	A1=1.2 X 13	
Suthar 2016b	<i>Momordica charantia</i> (fruit)	OAD				A1=Capsule, BD	A1=0.8 to 1.2 X 15	
Cortez-Navarrete 2018	<i>Momordica charantia</i> (fruit pulp)	Placebo				A1=Capsule, BD	A1=2 X 12	
Kumari 2018	<i>Momordica charantia</i> (fruit?)☼	Placebo				A1=Tablet, Unclear☼	A1=1, 1.5 X 8☼	
Amini 2020	<i>Momordica charantia</i> (fruit)	Placebo				A1=Capsule, BD	A1=2 X 8	
Kim 2020	<i>Momordica charantia</i> (fruit extract)¶	Placebo				A1=Capsule, BD	A1=2.38 X 12	
<i>Nigella sativa</i>								
Najmi 2012	<i>Nigella sativa</i> (seed)	No additional medicine				A1=Capsule, OD	A1=0.5 X 8	
Hosseini 2013	<i>Nigella sativa</i> (seed oil)	Placebo				A1=Oil, BD	A1=5(ml) X 13	
Hadi 2015	<i>Nigella sativa</i> (seed oil)	Placebo				A1=Capsule, BD	A1=1 X 8	
Heshmati 2015	<i>Nigella sativa</i> (seed oil)	Placebo (sunflower oil)				A1=Capsule, TDS	A1=3 X 12	
Kaatabi 2015	<i>Nigella sativa</i> (seed)	Placebo				A1=Capsule, BD	A1=2 X 52	
Moustafa 2019	<i>Nigella sativa</i> (seed oil)	OAD				A1=Capsule, TDS	A1=1.35 X 12	
Kooshki 2020	<i>Nigella sativa</i> (seed oil)	Placebo				A1=Capsule, BD	A1=1 X 8	
Jangjo-Borazjani 2021	<i>Nigella sativa</i> (seed)☼	Placebo☼				A1=Capsule, BD☼	A1=2 X 8☼	
<i>Plantago ovata</i>								
Ziai 2005	<i>Plantago ovata</i> (seed husk)	Placebo				A1=Fiber, BD	A1=10.2 X 8	A1=Water
Feinglos 2013	<i>Plantago ovata</i> (seed husk)☼	Placebo				A1=Fiber, BD☼	A1=6.8, 13.6 X 12☼	

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Abutair 2016	<i>Plantago ovata</i> (seed husk)	No additional medicine?				A1=Fiber, BD	A1=10.5 X 8	A1=Water
<i>Portulaca oleracea</i>								
El-Sayed 2011	<i>Portulaca oleracea</i> (seed)¶	OAD				A1=Powder, BD	A1=10 X 8	A1=Skimmed yogurt
Farzanegi 2014	<i>Portulaca oleracea</i> (seed)☼	Placebo☼				A1=Powder, BD☼	A1=7.5 X 8☼	A1=Skimmed yogurt☼
Dehghan 2016	<i>Portulaca oleracea</i> (seed)¶☼	Placebo☼				A1=Capsule, BD☼	A1=7.5 X 16☼	
Wainstein 2016	<i>Portulaca oleracea</i> (whole plant extract)	Placebo				A1=Capsule, OD?	A1=0.18 X 12	
<i>Pterocarpus marsupium</i>								
Hariharan 2005	<i>Pterocarpus marsupium</i> (heartwood extract)	OAD				A1=Capsule, BD	A1=2 to 4 X 36	
<i>Punica granatum</i>								
Faghihimani 2016	<i>Punica granatum</i> (seed oil)	Placebo				A1=Capsule, BD	A1=2 X 8	
Babaeian 2013	<i>Punica granatum</i> (fruit)	Placebo?				A1=Juice, OD?	A1=240(ml) X 8	
Sohrab 2014, Sohrab 2015	<i>Punica granatum</i> (fruit)	Placebo				A1=Juice, OD?	A1=250(ml) X 12	
Khajebishak 2019a, Khajebishak 2019b	<i>Punica granatum</i> (seed oil)	Placebo				A1=Capsule, TDS	A1=3 X 8	
Grabež 2020	<i>Punica granatum</i> (peel extract)	Placebo				A1=Capsule, BD	A1=0.5 X 8	
Hashemi 2020	<i>Punica granatum</i> (seed)	Placebo				A1=Infusion, BD	A1=10 X 8	A1=Hot water (infused in)
<i>Sesamum indicum</i>								
Shahi 2017	<i>Sesamum indicum</i> (seed extract)	Placebo				A1=Capsule, OD	A1=0.2 X 8	A1=Water
Aslam 2018	<i>Sesamum indicum</i> (seed oil)	Placebo				A1=Oil, Unclear	A1=30(ml) X 13	

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Shilajit								
Narasimha Raju 2016	Shilajit (<i>Asphaltum punjabianum</i>)	Placebo				A1=Capsule, BD	A1=2 X 9	A1=Salasar adi Gana Kashaya (<i>Acacia catechu</i> [resin], <i>Areca catechu</i> [fruit], <i>Gymnema sylvestre</i> [leaf], <i>Albizia lebbeck</i> [bark], <i>Terminalia arjuna</i> [bark], <i>Pongamia pinnata</i> [seed])
Niranjan 2016	Shilajit (<i>Asphaltum punjabianum</i> ; extract)	Placebo				A1=Capsule, BD	A1=0.5 X 12	A1=Water
<i>Syzygium cumini</i>								
Sahana 2010	<i>Syzygium cumini</i> (seed)¶	OAD	No medicine			A1=Powder, BD	A1=10 X 26	
Sidana 2016, Sidana 2017	<i>Syzygium cumini</i> (seed)	Placebo				A1=Powder, BD	A1=10 X 13	
<i>Terminalia chebula</i>								
Usharani 2020	<i>Terminalia chebula</i> (fruit extract)¶☞	Placebo				A1=Capsule, BD☞	A1=0.5, 1 X 12☞	
<i>Tinospora cordifolia</i>								
Mishra 2015	<i>Tinospora cordifolia</i> (extract)	No additional medicine				A1=Tablet, TDS	A1=1.5 X 26	
Roy 2015	<i>Tinospora cordifolia</i> (stem extract)	No additional medicine				A1=Capsule, BD	A1=0.5 X 9	
<i>Tribulus terrestris</i>								

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Samani 2016	<i>Tribulus terrestris</i> (extract)¶	Placebo				A1=Capsule, BD	A1=1 X 13	
<i>Trigonella foenum-graecum</i>								
Gupta 2001	<i>Trigonella foenum-graecum</i> (seed extract)	Placebo				A1=Capsule, BD	A1=1 X 9	
Lu 2008	<i>Trigonella foenum-graecum</i> (seed extract)¶	Placebo				A1=Capsule, TDS	A1=6.3 X 12	
Ansari 2011	<i>Trigonella foenum-graecum</i> (seed)	No additional medicine				A1=Powder, BD	A1=100 X 13	
Rafraf 2014	<i>Trigonella foenum-graecum</i> (seed)	Placebo (wheat)				A1=Powder, BD	A1=10 X 8	A1=Water
Suchitra 2015	<i>Trigonella foenum-graecum</i> (seed)	No additional medicine				A1=Seed, TDS	A1=30 X 8	
Kaur 2016	<i>Trigonella foenum-graecum</i> (seed)	No additional medicine				A1=Capsule, TDS	A1=3 X 12	
Singh 2016	<i>Trigonella foenum-graecum</i> (seed extract)	<i>Trigonella foenum-graecum</i> (seed extract)+OAD	OAD			A1=Capsule, OD, A2=Capsule, BD	A1=0.5 X 12, A2=1 X 12	
Verma 2016	<i>Trigonella foenum-graecum</i> (seed extract)¶	Placebo				A1=Capsule, BD	A1=1 X 13	
Ranade 2017	<i>Trigonella foenum-graecum</i> (seed)	No additional medicine				A1=Seed, OD	A1=10 X 26	A1=Hot water (soaked in)
Gholaman 2018	<i>Trigonella foenum-graecum</i> (seed)	Placebo				A1=Powder, TDS	A1=15 X 8	A1=Yogurt
Kandhare 2018	<i>Trigonella foenum-graecum</i> (seed extract)	Placebo				A1=Capsule, TDS	A1=2.1 X 12	
Hassani 2019	<i>Trigonella foenum-graecum</i> (seed?)¶☞	Placebo (wheat)☞				A1=Powder, BD☞	A1=10 X 8☞	
Hota 2019	<i>Trigonella foenum-graecum</i> (seed extract)¶	No additional medicine				A1=Capsule, BD	A1=1 X 12	
Najdi 2019	<i>Trigonella foenum-graecum</i> (seed)	OAD				A1=Capsule, TDS	A1=2 X 12	
Rashid 2019	<i>Trigonella foenum-graecum</i> (seed extract)¶	Placebo				A1=Capsule, OD	A1=1 X 12	
Hadi 2020	<i>Trigonella foenum-graecum</i> (seed)	No additional medicine				A1=Powder, TDS	A1=15 X 8	A1=Water
<i>Urtica dioica</i>								

Author and year	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Form and timing of administration of Ayurvedic medicine	Dose (g/day or otherwise mentioned) X duration (weeks) of Ayurvedic medicine	Anupan of Ayurvedic medicine
Namazi 2011, Esfanjani 2012a, Esfanjani 2012b	<i>Urtica dioica</i> (aerial parts extract)	Placebo				A1=Powder, TDS	A1=0.1(/kg) X 8	A1=Lukewarm water
Kianbakht 2013	<i>Urtica dioica</i> (leaf extract)¶	Placebo				A1=Capsule, TDS	A1=1.5 X 13	
Khajeh-Mehrizi 2014	<i>Urtica dioica</i> (extract)	Placebo				A1=Unclear, TDS	A1=0.1(/kg) X 8	
Dabagh 2016	<i>Urtica dioica</i> (leaf)☼	No additional medicine☼				A1=Powder, OD☼	A1=10 X 8☼	A1=Yogurt☼
Hassani 2016	<i>Urtica dioica</i> (extract)	Placebo				A1=Liquid, TDS	A1=6(ml) X 8	A1=Water
Dadvar 2017	<i>Urtica dioica</i> ☼	No additional medicine☼				A1=Powder, OD	A1=10 X 8	A1=Yogurt
Ghalavand 2017	<i>Urtica dioica</i> ☼	No additional medicine☼				A1=Unclear, TDS☼	A1=10 X 8☼	
Korani 2017	<i>Urtica dioica</i> (extract)	Placebo				A1=Unclear, TDS	A1=0.02(/kg) X 8	
Mohammadnia 2017	<i>Urtica dioica</i> (extract)	Placebo				A1=Liquid, TDS	A1=6(ml) X 8	A1=Water
<i>Vernonia cinerea</i>								
Sayeed 2013	<i>Vernonia cinerea</i> (root)	Placebo				A1=Tablet, TDS	A1=6 X 13	
<i>Withania coagulans</i>								
Hemalatha 2018	<i>Withania coagulans</i> (fruit)	Placebo				A1=Infusion, OD	A1=2-2.5 X 9	A1=Water (infused in)
<i>Withania somnifera</i>								
Usharani 2014	<i>Withania somnifera</i> (root extract)☼	Placebo				A1=Capsule, BD☼	A1=0.5, 1 X 12☼	
<i>Zingiber officinale</i>								
Mahluji 2013	<i>Zingiber officinale</i> (rhizome)	Placebo (corn)				A1=Tablet, BD	A1=2 X 8	
Arablou 2014a,	<i>Zingiber officinale</i> (rhizome)	Placebo (wheat)				A1=Capsule, BD	A1=1.6 X 12	

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Arablou 2014b								
Mozaffari-Khosravi 2014, Talaei 2017, Talaei 2018	<i>Zingiber officinale</i> (rhizome)	Placebo				A1=Capsule, TDS	A1=3 X 8	
Shidfar 2015	<i>Zingiber officinale</i> (rhizome)	Placebo				A1=Capsule, TDS?	A1=3 X 12	
Arzati 2017, Zarezadeh 2018	<i>Zingiber officinale</i> (rhizome)	Placebo (wheat)				A1=Capsule, BD	A1=2 X 10	
Mohammadi 2017, Mohammadi 2019	<i>Zingiber officinale</i> (rhizome)✱	Placebo✱				A1=Capsule, QDS?✱	A1=1 X 8✱	
Carvalho 2020	<i>Zingiber officinale</i> (rhizome extract)	Placebo				A1=Capsule, BD	A1=1.2 X 13	
Gholinezhad 2020	<i>Zingiber officinale</i> (rhizome)	Placebo (pea)				A1=Tablet, BD	A1=2 X 8	
<i>Ziziphus mauritiana</i>								
Yazdanpanah 2017	<i>Ziziphus mauritiana</i> (fruit pulp+peel)	No additional medicine				A1=Infusion, TDS	A1=30 X 12	A1=Hot water
<i>Acalypha indica</i>/<i>Allium cepa</i>/<i>Allium sativum</i>/<i>Azadirachta indica</i>/<i>Mangifera indica</i>/<i>Murraya koenigii</i>/<i>Musa sapientum</i>/<i>Ocimum tenuiflorum</i>/<i>Phyllanthus amarus</i>/<i>Tinospora cordifolia</i>								
Balasubramaniam 2010	<i>Acalypha indica</i> (whole plant extract)/ <i>Allium cepa</i> (bulb extract)/ <i>Allium sativum</i> (bulb extract)/ <i>Azadirachta indica</i> (leaf extract)/ <i>Mangifera indica</i> (stem bark extract)/ <i>Murraya koenigii</i> (leaf extract)/ <i>Musa sapientum</i> (flower extract)/ <i>Ocimum tenuiflorum</i> (leaf extract)/ <i>Phyllanthus amarus</i> (whole plant extract)/ <i>Tinospora cordifolia</i> (leaf extract)†	Placebo				A1=Decoction, OD?	A1=5(ml) X 9	
<i>Allium sativum</i>; <i>Cuminum cyminum</i>								
Mansouri 2018	<i>Allium sativum</i> (clove)	<i>Cuminum cyminum</i> (seed)	Placebo			A1=Capsule, TDS, A2=Capsule, BD	A1=0.9 X 9, A2=0.2 X 9	
<i>Aloe vera</i>; <i>Pterocarpus marsupium</i>; <i>Aloe vera</i>+<i>Pterocarpus marsupium</i>								
Maurya 2017	<i>Aloe vera</i> (leaf?)	<i>Pterocarpus marsupium</i> (heartwood?)	<i>Aloe vera</i> + <i>Pter</i>	OAD		A1=Capsule, BD,	A1=0.6 X 13, A2=2	

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			<i>ocarpus marsupium</i>			A2=Capsule, BD, A3=Capsule, OD+Capsule, BD	to 4 X 13, A3=0.3+1 to 3 X 13	
Cinnamomum verum; Crocus sativus; Elettaria cardamomum; Zingiber officinale								
Azimi 2014, Azimi 2016	<i>Cinnamomum verum</i> (bark)	<i>Crocus sativus</i> (flower stigma)	<i>Elettaria cardamomum</i> (seedpod)	<i>Zingiber officinale</i> (rhizome)	Placebo (black tea)	A1=Powder, TDS, A2=Powder, TDS, A3=Powder, TDS, A4=Powder, TDS	A1=3 X 8, A2=1 X 8, A3=3 X 8, A4=3 X 8	A1=Black tea, A2=Black tea, A3=Black tea, A4=Black tea
Enicostemma axillare; Shilajit								
Kumar 2014	<i>Enicostemma axillare</i> (whole plant extract)	Shilajit (<i>Asphaltum punjabianum</i>)	OAD			A1=Capsule, BD, A2=Capsule, BD	A1=1 X 13, A2=1 X 13	A1=Water, A2=Water
Enicostemma axillare+Emblica officinalis+Tinospora cordifolia								
Sharma 2019	<i>Enicostemma axillare</i> (whole plant)+ <i>Emblica officinalis</i> (fruit)+ <i>Tinospora cordifolia</i> (stem)	No additional medicine				A1=Capsule, BD+Powder, BD+Powder, BD	A1=2+6+6 X 26	A1=Lukewarm water
Linum usitatissimum; Plantago ovata								
Ricklefs-Johnson 2017	<i>Linum usitatissimum</i> (seed)	<i>Plantago ovata</i> (seed husk)				A1=Powder, Unclear, A2=Fiber, Unclear	A1=28 X 8, A2=9 X 8	
Syzygium cumini+Withania coagulans								
Siddiqui 2017	<i>Syzygium cumini</i> (seed?)+ <i>Withania coagulans</i> (fruit)	OAD				A1=Powder, BD+Infusion, BD	A1=12+Unclear (10 pieces) X 13	A1=Water (infused in)
Trigonella foenum-graecum; Aegle marmelos; Trigonella foenum-graecum+Aegle marmelos								
Yaheya 2009	<i>Trigonella foenum-graecum</i> (seed)	<i>Aegle marmelos</i> (leaf)	<i>Trigonella foenum-graecum</i> + <i>Aegle marmelos</i>	No additional medicine		A1=Powder, OD, A2=Decoction, OD, A3=Powder,	A1=20 X 16, A2=5 X 16, A3=20+5 X 16	

Author and year	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Form and timing of administration of Ayurvedic medicine	Dose (g/day or otherwise mentioned) X duration (weeks) of Ayurvedic medicine	Anupan of Ayurvedic medicine
						OD+Decoction, OD		
Ayurvedic medicine- combination of plant- and/or mineral-origin ingredients§								
AYUBES								
Godatwar 2019	AYUBES (<i>Gymnema sylvestre</i> , <i>Momordica charantia</i> , <i>Pterocarpus marsupium</i> , <i>Andrographis paniculata</i> , <i>Aegle marmelos</i> , <i>Syzygium cumini</i> , <i>Enicostemma axillare</i> , <i>Picrorhiza kurroa</i> , <i>Azadirachta indica</i> , <i>Cyperus rotundus</i>)	Placebo				A1=Capsule, BD	A1=Unclear (4 capsules) X 13	A1=Lukewarm water
BGR-34								
Gupta 2018	BGR-34 (<i>Berberis aristata</i> [stem], <i>Pterocarpus marsupium</i> [heartwood], <i>Gymnema sylvestre</i> [leaf], <i>Rubia cordifolia</i> [root], <i>Trigonella foenum-graecum</i> [seed], <i>Tinospora cordifolia</i> [stem])	Placebo (Triphala)				A1=Tablet, BD	A1=1.24 X 16	
Bilvadi Churna; Kiratadi Churna								
Kumari 2016	Bilvadi Churna (<i>Aegle marmelos</i> [root], <i>Bacopa monnieri</i> [whole plant], <i>Tinospora cordifolia</i> [stem], <i>Withania somnifera</i> [root], <i>Piper longum</i> [fruit])	Kiratadi Churna (<i>Swertia chirayita</i> [whole plant], <i>Picrorhiza kurroa</i> [rhizome], <i>Trigonella foenum-graecum</i> [seed], <i>Tribulus terrestris</i> [fruit], <i>Azadirachta indica</i> [bark])	Placebo (barley)			A1=Powder, TDS, A2=Powder, TDS	A1=15 X 9, A2=15 X 9	A1=Lukewarm water, A2=Lukewarm water
CardiPro								
Fatima 2012	CardiPro (<i>Terminalia arjuna</i> , <i>Emblica officinalis</i> [fruit], <i>Withania somnifera</i> , <i>Boerhavia diffusa</i> , <i>Ocimum tenuiflorum</i>)	Placebo				A1=Capsule, TDS	A1=1.2 X 12	
Cogent db								
Shekhar 2002	Cogent db (<i>Azadirachta indica</i> , <i>Emblica officinalis</i> [fruit], <i>Curcuma longa</i> [rhizome], <i>Trigonella foenum-graecum</i> , <i>Syzygium cumini</i> , <i>Tribulus terrestris</i> , <i>Terminalia bellirica</i> [fruit], <i>Terminalia chebula</i> [fruit], <i>Rotula aquatica</i>)	No additional medicine				A1=Tablet, TDS	A1=60 X 13	
DCBT 2345								
Mohan 2001	DCBT 2345 (extracts of <i>Gymnema sylvestre</i> , <i>Syzygium cumini</i> , <i>Coccinia grandis</i>)	Placebo				A1=Tablet, TDS	A1=Unclear (6 tablets) X 26	
Diabetea tea								

Author and year	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Form and timing of administration of Ayurvedic medicine	Dose (g/day or otherwise mentioned) X duration (weeks) of Ayurvedic medicine	Anupan of Ayurvedic medicine
Mahmoud 2016	Diabetea tea (extracts of <i>Camellia sinensis</i> [black tea; leaf], <i>Cassia tora</i> [leaf, seed], <i>Ficus racemosa</i> [bark, fruit], <i>Ficus bengalensis</i> [bark, fruit], <i>Syzygium cumini</i> [bark], <i>Terminalia arjuna</i> [bark], <i>Terminalia chebula</i> [fruit], <i>Terminalia bellirica</i> [fruit], <i>Emblica officinalis</i> [fruit], <i>Tribulus terrestris</i> [fruit], <i>Trigonella foenum-graecum</i> [seed], <i>Cardiospermum halicacabum</i> [leaf], <i>Cinnamomum verum</i> [bark], <i>Azadirachta indica</i> [leaf, seed])	Placebo (black tea)				A1=Infusion, TDS	A1=7.5 X 12	A1=Hot water (infused in)
Emblica officinalis; Withania somnifera; Emblica officinalis, Withania somnifera								
Usharani 2014	<i>Emblica officinalis</i> (fruit extract)	<i>Withania somnifera</i> (root+leaf extract)	<i>Emblica officinalis</i> , <i>Withania somnifera</i>			A1=Capsule, BD, A2=Capsule, BD, A3=Capsule, BD	A1=1 X 12, A2=1 X 12, A3=1 X 12	
Herbal combination								
Shokoohi 2017	Herbal combination (<i>Terminalia chebula</i> [fruit extract], <i>Commiphora wightii</i> [oleo-gum resin], <i>Commiphora myrrha</i> [oleo-gum resin])	Placebo				A1=Capsule, TDS	A1=1.8 X 13	
Hyponidd								
Poongothai 2002	Hyponidd (Shilajit [<i>Asphaltum punjabianum</i>], Yashad Bhasma [zinc preparation], <i>Momordica charantia</i> [fruit], <i>Curcuma longa</i> [rhizome extract], <i>Cassia auriculata</i> [seed extract], <i>Emblica officinalis</i> [fruit extract], <i>Syzygium cumini</i> [seed extract], <i>Gymnema sylvestre</i> [leaf extract], <i>Enicostemma axillare</i> [whole plant extract], <i>Azadirachta indica</i> [leaf extract], <i>Pterocarpus marsupium</i> [bark extract], <i>Tinospora cordifolia</i> [stem extract], <i>Swertia chirayita</i> [whole plant extract])	Placebo				A1=Tablet, TDS	A1=8.262 ? X 12	
Inolter								
Agrawal 2002	Inolter (<i>Momordica charantia</i> [fruit+seed+leaf extract], <i>Trigonella foenum-graecum</i> [seed+pod+leaf extract], Shilajit [<i>Asphaltum punjabianum</i>], <i>Gymnema sylvestre</i> [root, leaf], <i>Syzygium cumini</i> [seed, fruit, leaf, bark])	Placebo				A1=Capsule, OD?	A1=0.5? X 13	
Kalpit								
Agarwal 2013	Kalpit (<i>Holoptelea integrifolia</i> [bark], <i>Berberis aristata</i> [rhizome], <i>Mangifera indica</i> [seed], <i>Syzygium cumini</i> [seed], <i>Momordica charantia</i> [fruit], <i>Azadirachta indica</i> , <i>Aegle marmelos</i> [leaf], <i>Gymnema sylvestre</i> [leaf],	Kalpit+OAD	OAD			A1=Powder, BD, A2=Powder, BD	A1=10 X 9, A2=10 X 9	A1=Lukewarm water, A2=Lukewarm water

Author and year	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Form and timing of administration of Ayurvedic medicine	Dose (g/day or otherwise mentioned) X duration (weeks) of Ayurvedic medicine	Anupan of Ayurvedic medicine
	<i>Curcuma longa</i> [rhizome], <i>Trigonella foenum-graecum</i> [seed], <i>Emblica officinalis</i> [fruit], <i>Terminalia bellirica</i> [fruit], <i>Terminalia chebula</i> [fruit])							
Khadira-Kramuka Kashaya Ghanavati; Nishamalaki, Shilajit; Khadira-Kramuka Kashaya Ghanavati+Nishamalaki, Shilajit								
Paliwal 2018	Khadira-Kramuka Kashaya Ghanavati (<i>Acacia catechu</i> [extract], <i>Areca catechu</i> [fruit])	Nishamalaki (<i>Curcuma longa</i> [rhizome], <i>Emblica officinalis</i> [fruit]), Shilajit (<i>Asphaltum punjabianum</i>)	Khadira-Kramuka Kashaya Ghanavati +Nishamalaki, Shilajit			A1=Tablet, BD, A2=Powder, BD, A3=Tablet, BD+Powder, BD	A1=1 X 13, A2=13 X 13, A3=1+13 X 13	
Lodhradi Kashaya Ghana Vati								
Bramhankar 2017	Lodhradi Kashaya Ghana Vati (extracts of <i>Symplocos racemosa</i> , <i>Terminalia chebula</i> [fruit], <i>Cyperus rotundus</i> , <i>Myrica esculenta</i>)	Lodhradi Kashaya Ghana Vati+OAD	OAD			A1=Tablet?, TDS, A2=Tablet?, TDS	A1=1.5 X 13, A2=1.5 X 13	A1=Warm water, A2=Warm water
Madhumeha Nashini Gutika; Darvyadi Kwatha; Madhumeha Nashini Gutika+Darvyadi Kwatha								
Bhawana 2015	Madhumeha Nashini Gutika (Trivanga Bhasma [tin, lead, zinc preparation], <i>Gymnema sylvestre</i> [leaf], <i>Azadirachta indica</i> [leaf], Shilajit [<i>Asphaltum punjabianum</i>])	Darvyadi Kwatha (<i>Berberis aristata</i> , <i>Cedrus deodara</i> , <i>Terminalia chebula</i> [fruit], <i>Terminalia bellirica</i> [fruit], <i>Emblica officinalis</i> [fruit], <i>Cyperus rotundus</i>)	Madhumeha Nashini Gutika+Darvyadi Kwatha			A1=Tablet, TDS, A2=Decoction, BD, A3=Tablet, TDS+Decoction, BD	A1=1.5 X 13, A2=40(ml) X 13, A3=1.5+40(ml) X 13	A1=Lukewarm water, A3=Lukewarm water (for Madhumeha Nashini Gutika)
Mamajjaka Ghana Vati; Tejashiladi Vati								
Bhagat 2017	Mamajjaka Ghana Vati (<i>Enicostemma axillare</i> [leaf], <i>Aconitum heterophyllum</i> [root], <i>Picrorhiza kurroa</i> [rhizome], <i>Piper longum</i> [fruit])	Tejashiladi Vati (<i>Cinnamomum tamala</i> [leaf], Shilajit [<i>Asphaltum punjabianum</i>], Yashad Bhasma [zinc preparation])				A1=Tablet, BD, A2=Tablet, BD	A1=1 X 8, A2=1 X 8	A1=Lukewarm water, A2=Lukewarm water
Mamajjaka Ghana Vati; Trikatu Gutika								
Kataria 2017	Mamajjaka Ghana Vati (<i>Enicostemma axillare</i> [leaf], <i>Aconitum heterophyllum</i> [root], <i>Picrorhiza kurroa</i> [rhizome], <i>Piper longum</i> [fruit])	Trikatu Gutika (<i>Piper longum</i> [fruit], <i>Zingiber officinale</i> [rhizome], <i>Piper nigrum</i> [fruit], <i>Terminalia chebula</i> [fruit], <i>Terminalia bellirica</i> [fruit], <i>Emblica officinalis</i> [fruit], <i>Commiphora wightii</i>)				A1=Tablet, TDS, A2=Tablet, TDS	A1=6 X 8, A2=6 X 8	A1=Lukewarm water, A2=Lukewarm water

Author and year	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Form and timing of administration of Ayurvedic medicine	Dose (g/day or otherwise mentioned) X duration (weeks) of Ayurvedic medicine	Anupan of Ayurvedic medicine
		[oleo-gum resin], <i>Tribulus terrestris</i> [root]]						
Mehagni								
Gopalakrishna 2017	Mehagni (<i>Curcuma longa</i> [rhizome], <i>Emblica officinalis</i> [fruit], <i>Gymnema sylvestre</i> , <i>Salacia reticulata</i>)	No additional medicine				A1=Tablet, BD	A1=2 X 12	
Mustadi Kwatha Ghana Vati								
Kushwaha 2017	Mustadi Kwatha Ghana Vati (<i>Cyperus rotundus</i> [tuber], <i>Terminalia bellirica</i> [fruit rind], <i>Citrullus colocynthis</i> [root], <i>Marsdenia tenacissima</i> [root bark], <i>Cedrus deodara</i> [inner wood, oil], <i>Terminalia chebula</i> [fruit], <i>Curcuma longa</i> [rhizome], <i>Symplocos racemosa</i> [stem bark], <i>Emblica officinalis</i> [fruit])	Placebo (Godanti Bhasma)				A1=Tablet, BD	A1=1 X 9	A1=Lukewarm water
Naga Bhasma, Nishamalaki, Nishamalaki, Hordeum vulgare								
Desale 2018	Naga Bhasma (lead preparation), Nishamalaki (<i>Curcuma longa</i> [rhizome], <i>Emblica officinalis</i> [fruit])	Nishamalaki (<i>Curcuma longa</i> [rhizome], <i>Emblica officinalis</i> [fruit]), <i>Hordeum vulgare</i> (seed)				A1=Capsule, OD, A2=Capsule, OD	A1=0.375 X 13, A2=0.5 X 13	A1=Honey, A2=Honey
Nigella sativa, Trigonella foenum-graecum								
Memon 2010a, Memon 2010b, Memon 2012	<i>Nigella sativa</i> (seed), <i>Trigonella foenum-graecum</i> (seed)	No additional medicine				A1=Capsule, BD?	A1=1 to 2 X 13	
Nisha Katakadi Kashaya; Yashad Bhasma; Nisha Katakadi Kashaya+Yashad Bhasma								
Srinivas 2018	Nisha Katakadi Kashaya (<i>Curcuma longa</i> [rhizome], <i>Strychnos potatorum</i> , <i>Acacia catechu</i> , <i>Emblica officinalis</i> [fruit], <i>Salacia chinensis</i> , <i>Berberis aristata</i> , <i>Mimosa pudica</i> , <i>Salix caprea</i> , <i>Cissampelos pareira</i> , <i>Mangifera indica</i> , <i>Terminalia chebula</i> [fruit], <i>Cyperus rotundus</i>)	Yashad Bhasma (zinc preparation)	Nisha Katakadi Kashaya+Yashad Bhasma			A1=Decoction, BD, A2=Capsule, TDS, A3=Decoction, BD+Capsule, TDS	A1=30(ml) X 12, A2=0.375 X 12, A3=30(ml) +0.375 X 12	A1=Lukewarm water (diluted with), A2=Lukewarm water, A3=Lukewarm water (diluted with)+Lukewarm water
Pancreas tonic								

Author and year	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Form and timing of administration of Ayurvedic medicine	Dose (g/day or otherwise mentioned) X duration (weeks) of Ayurvedic medicine	Anupan of Ayurvedic medicine
Hsia 2004	Pancreas tonic (extracts of <i>Aegle marmelos</i> [leaf], <i>Pterocarpus marsupium</i> [heartwood], <i>Syzygium cumini</i> [fruit], <i>Momordica charantia</i> [seed], <i>Gymnema sylvestre</i> [leaf], <i>Trigonella foenum-graecum</i> [seed], <i>Azadirachta indica</i> [seed], <i>Ficus racemosa</i> , <i>Tinospora cordifolia</i> [stem], <i>Cinnamomum tamala</i> [leaf])	Placebo				A1=Capsule, TDS	A1=Unclear (6 capsules) X 12	
Polyherbal formulation								
Awasthi 2015	Polyherbal formulation (extracts of <i>Berberis aristata</i> , <i>Cyperus rotundus</i> , <i>Cedrus deodara</i> , <i>Embolia officinalis</i> [fruit], <i>Terminalia chebula</i> [fruit], <i>Terminalia bellirica</i> [fruit])	OAD				A1=Capsule, Unclear	A1=0.5 to 3 X 24	
Salasaradi Kashaya+Shilajit+Trivanga Bhasma+Tinospora cordifolia, Azadirachta indica; Hyponidd								
Bhat 2012	Salasaradi Kashaya (<i>Shorea robusta</i> [bark], <i>Acacia catechu</i> [bark extract?], <i>Acacia polyacantha</i> [bark], <i>Areca catechu</i> [fruit], <i>Betula utilis</i> [bark], <i>Gymnema sylvestre</i> [leaf], <i>Ougeinia oojeinensis</i> [bark+stem extract?], <i>Santalum album</i> [stem extract], <i>Pterocarpus santalinus</i> [stem extract], <i>Dalbergia sissoo</i> [bark extract?], <i>Albizia lebbek</i> [bark, seed], <i>Pterocarpus marsupium</i> [stem extract], <i>Anogeissus latifolia</i> [bark], <i>Terminalia arjuna</i> [bark], <i>Borassus flabellifer</i> [fruit, root], <i>Tectona grandis</i> [stem extract?], <i>Pongamia pinnata</i> [bark, leaf], <i>Holoptelea integrifolia</i> [bark], <i>Dipterocarpus turbinatus</i> [bark], <i>Aquilaria malaccensis</i> [stem extract]) + Shilajit (<i>Asphaltum punjabianum</i>) + Trivanga Bhasma (tin, lead, zinc preparation) + <i>Tinospora cordifolia</i> , <i>Azadirachta indica</i> (bark)	Hyponidd (Shilajit [<i>Asphaltum punjabianum</i>], Yashad Bhasma [zinc preparation], <i>Momordica charantia</i> [fruit], <i>Curcuma longa</i> [rhizome extract], <i>Cassia auriculata</i> [seed extract], <i>Embolia officinalis</i> [fruit extract], <i>Syzygium cumini</i> [seed extract], <i>Gymnema sylvestre</i> [leaf extract], <i>Enicostemma axillare</i> [whole plant extract], <i>Azadirachta indica</i> [leaf extract], <i>Pterocarpus marsupium</i> [bark extract], <i>Tinospora cordifolia</i> [stem extract], <i>Swertia chirayita</i> [whole plant extract])				A1=Decoction, TDS+Capsule, BD+Powder?, OD+Powder, TDS, A2=Tablet, BD	A1=60(ml) +1+0.125+12 X 13, A2=5.508 ? X 13	A1=Water+Water+Water+Lukewarm water, A2=Water
Shilajit; Asanadi Ghana Vati								
Gupta 2016	Shilajit (<i>Asphaltum punjabianum</i>)	Asanadi Ghana Vati (extracts of <i>Pterocarpus marsupium</i> , <i>Ougeinia oojeinensis</i> , <i>Betula utilis</i> , <i>Terminalia arjuna</i> , <i>Holoptelea integrifolia</i> , <i>Acacia catechu</i> , <i>Acacia</i>				A1=Capsule, BD, A2=Tablet, BD	A1=1 X 13, A2=2 X 13	

Author and year	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Form and timing of administration of Ayurvedic medicine	Dose (g/day or otherwise mentioned) X duration (weeks) of Ayurvedic medicine	Anupan of Ayurvedic medicine
		<i>polyacantha, Albizia lebbeck, Dalbergia sissoo, Gymnema sylvestre, Santalum album, Pterocarpus santalinus, Berberis aristata, Borassus flabellifer, Butea monosperma, Aquilaria malaccensis, Tectona grandis, Shorea robusta, Anogeissus latifolia, Areca catechu, Holarrhena pubescens, Vateria indica, Dipterocarpus alatus</i>						
Swarnamakshika Bhasma								
Taviad 2016	Swarnamakshika Bhasma (chalcopryrite preparation)	Placebo				A1=Capsule, BD	A1=1 X 8	A1=Honey
Talapotaka Churna								
Nille 2018	Talapotaka Churna (<i>Cassia auriculata</i> , <i>Emblica officinalis</i> [fruit], <i>Curcuma longa</i> [rhizome], <i>Berberis aristata</i>)	Talapotaka Churna+OAD	OAD			A1=Powder, TDS, A2=Powder, TDS	A1=12 X 9, A2=12 X 9	A1=Takra (butter milk) or warm water, A2=Warm water
Trigonella foenum-graecum, Ocimum tenuiflorum								
Mitra 2006	<i>Trigonella foenum-graecum</i> (seed), <i>Ocimum tenuiflorum</i> (leaf)	No medicine				A1=Powder, BD	A1=27.5, 52.5, 77.5, 102.5 X 9	A1=Water
Triticum aestivum; Nishamalaki; Triticum aestivum+Nishamalaki								
Samagandi 2012	<i>Triticum aestivum</i> (grass)	Nishamalaki (<i>Curcuma longa</i> [rhizome], <i>Emblica officinalis</i> [fruit])	<i>Triticum aestivum</i> +Nishamalaki			A1=Juice, BD, A2=Tablet, BD, A3=Juice, BD+Tablet, BD	A1=100(m l) X 9, A2=2 X 9, A3=100(m l)+2 X 9	
Vidangadi Yoga								
Deshpande 2018	Vidangadi Yoga (extracts of <i>Embelia ribes</i> [fruit], <i>Shorea robusta</i> [bark], <i>Terminalia arjuna</i> [bark], <i>Myrica esculenta</i> [bark], <i>Neolamarckia cadamba</i> [bark], <i>Symplocos</i>	OAD				A1=Tablet, TDS	A1=1.5 X 12	A1=Water

Author and year	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Form and timing of administration of Ayurvedic medicine	Dose (g/day or otherwise mentioned) X duration (weeks) of Ayurvedic medicine	Anupan of Ayurvedic medicine
	<i>racemosa</i> [bark], <i>Pterocarpus marsupium</i> [bark], <i>Holarrhena pubescens</i> [bark])							
Vijaysaradi Ghana Vati; Madhumehari Vati								
Sharma 2018	Vijaysaradi Ghana Vati (<i>Pterocarpus marsupium</i> [heartwood], <i>Terminalia chebula</i> [fruit], <i>Emblica officinalis</i> [fruit], <i>Terminalia bellirica</i> [fruit], <i>Swertia chirayita</i> [whole plant], <i>Trichosanthes dioica</i> [leaf], <i>Picrorhiza kurroa</i> [rhizome], <i>Tribulus terrestris</i> [fruit], <i>Cyperus rotundus</i> [root], <i>Santalum album</i> [heartwood], <i>Berberis aristata</i> [stem, root], <i>Vetiveria zizanioides</i> [root])	Madhumehari Vati (<i>Enicostemma axillare</i> [whole plant], <i>Gymnema sylvestre</i> [leaf], <i>Caesalpinia bonduc</i> [nut], <i>Picrorhiza kurroa</i> [rhizome], <i>Piper longum</i> [fruit], <i>Capsicum frutescens</i> [fruit], <i>Citrullus colocynthis</i> [fruit])				A1=Tablet, TDS, A2=Tablet, TDS	A1=3 X 8, A2=3 X 8	A1=Water, A2=Water

A1, A2, A3, A4, A5=Eligible study arms (Ayurvedic detoxifying and purifying therapies [e.g., Panchakarma] are not mentioned but only Ayurvedic medicines [and their active ingredients] are mentioned), BD=Twice a day, OAD=Oral antidiabetic drug, OD=Once a day, QDS=Four times a day, TDS=Thrice a day

⊕ Two or more study arms were pooled together.

¶ Voucher specimen number/other reference number provided for Ayurvedic medicines.

§ Some of the Ayurvedic medicines contain single plant- or mineral-origin ingredient.

Appendix S6: Assessment of methodological quality of included studies.

Author and year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	% of Y
Ayurvedic medicine- single plant- or mineral-origin ingredient														
<i>Abelmoschus esculentus</i>														
Moradi 2020	Y	U	N	U	U	U	U	N	U	Y	U	N	Y	23
<i>Acacia Senegal</i>														
Babiker 2017, Babiker 2018	U	U	N	U	Y	U	Y	N	N	Y	U	N	Y	31
<i>Aegle marmelos</i>														
Sankhla 2009	U	U	N	U	U	U	U	N	N	Y	U	N	Y	15
Sharma 2013	U	U	Y	Y	U	Y	Y	Y	Y	Y	U	N	Y	62
Nigam 2019	U	U	N	U	U	U	U	N	N	Y	U	N	Y	15
<i>Allium sativum</i>														
Ashraf 2005	U	U	Y	Y	U	U	U	N	N	Y	U	N	Y	31
Ashraf 2011a	U	U	Y	U	U	U	U	N	N	Y	U	N	Y	23
Ashraf 2011b	U	U	N	U	U	U	Y	N	N	U	U	N	Y	15

Author and year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	% of Y
Kumar 2013	U	U	U	N	N	N	Y	U	U	Y	U	N	Y	23
<i>Aloe vera</i>														
Arora 2009	U	U	N	U	U	U	Y	N	N	U	U	N	Y	15
Huseini 2012a, Huseini 2012b	U	U	N	Y	U	U	Y	N	N	Y	U	N	Y	31
Zarrintan 2015	Y	Y	N	Y	Y	Y	Y	N	N	Y	U	N	Y	62
<i>Anethum graveolens</i>														
Mobasser 2014	Y	U	N	Y	U	U	Y	N	N	Y	U	N	Y	38
Haidari 2020	Y	U	N	Y	U	U	Y	N	N	Y	U	N	Y	38
<i>Azadirachta indica</i>														
Usharani 2020	Y	U	N	Y	Y	U	Y	N	N	U	U	N	Y	38
<i>Berberis aristata</i>														
Sharma 2017	U	U	N	N	N	N	Y	N	N	Y	U	N	Y	23
<i>Boswellia serrata</i>														
Azadmehr 2014	U	U	Y	Y	U	U	Y	Y	Y	Y	U	N	Y	54
Mehrzadi 2018	Y	U	N	Y	Y	U	Y	N	Y	Y	U	N	Y	54
<i>Camellia sinensis</i>														
MacKenzie 2007	Y	U	N	U	Y	U	Y	N	N	U	U	N	Y	31
Mirzaei 2009	U	U	N	U	U	U	U	U	Y	Y	U	N	Y	23
Hsu 2011	Y	U	Y	Y	Y	U	Y	N	N	Y	U	N	Y	54
Lasait 2014	U	U	Y	U	U	U	U	N	N	Y	U	N	Y	23
Liu 2014	Y	Y	N	Y	Y	U	Y	N	N	Y	U	N	Y	54
Quezada-Fernandez 2019	U	U	N	Y	U	U	Y	N	N	Y	U	N	Y	31
<i>Capparis spinosa</i>														
Huseini 2013	U	U	N	Y	U	Y	Y	N	N	Y	U	N	Y	38
<i>Cichorium intybus</i>														
Chandra 2020	U	U	Y	Y	U	Y	Y	N	N	Y	U	N	Y	46
<i>Cinnamomum aromaticum</i>														
Mang 2006	U	U	N	Y	U	U	U	N	N	Y	U	N	Y	23
Suppapitiporn 2006	U	U	N	U	U	U	Y	Y	Y	U	U	N	Y	31
Blevins 2007	U	U	N	U	U	U	U	N	N	U	U	N	Y	8
Crawford 2009	Y	U	Y	N	U	Y	Y	N	Y	Y	U	N	Y	54
Akilen 2010	Y	Y	Y	Y	Y	U	U	N	Y	Y	U	N	Y	62
Wainstein 2011	U	U	N	Y	U	U	U	U	Y	U	U	N	Y	23
Lu 2012	U	U	N	Y	Y	U	Y	N	N	Y	U	N	Y	38
Sharma 2012	U	U	N	Y	U	Y	Y	U	Y	U	U	N	Y	38
Hasanzade 2013	U	U	N	Y	U	U	Y	U	Y	Y	U	N	Y	38
Tangvarasittichai 2015, Sengsuk 2016	Y	Y	N	Y	U	U	Y	N	N	Y	U	N	Y	46
<i>Cinnamomum verum</i>														
Vafa 2012	U	U	N	Y	U	U	Y	N	N	Y	U	N	Y	31
Zahmatkesh 2012	U	U	N	U	U	U	U	N	N	U	U	N	Y	8
Talaei 2017	U	U	Y	Y	U	U	Y	N	N	Y	U	N	Y	38
Zare 2019	Y	Y	N	Y	Y	U	U	N	N	Y	U	N	Y	46
Mirmiranpour 2020	Y	U	Y	U	U	U	U	N	N	Y	U	N	Y	31
<i>Citrullus colocynthis</i>														
Huseini 2009	Y	Y	N	Y	U	Y	Y	Y	Y	Y	U	N	Y	69

Author and year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	% of Y
Barghamdi 2016	U	U	N	Y	U	U	Y	Y	Y	U	U	N	Y	38
<i>Coccinia grandis</i>														
Kuriyan 2008, Kurpad 2008	U	U	N	U	U	U	Y	N	N	Y	U	N	Y	23
Quamri 2017	Y	U	Y	U	U	U	U	U	U	U	U	N	Y	23
Wasana 2021	Y	U	N	Y	U	U	Y	N	Y	Y	U	N	Y	46
<i>Convolvulus prostratus</i>														
Patel 2012	U	U	N	U	U	U	U	N	N	U	U	N	Y	8
<i>Crocus sativus</i>														
Milajerdi 2018	Y	N	N	Y	U	U	Y	N	N	Y	U	N	Y	38
Aleali 2019	U	U	N	Y	U	U	Y	N	N	Y	U	N	Y	31
Ebrahimi 2019	Y	U	N	Y	U	U	Y	N	N	Y	U	N	Y	38
Mobasseri 2020	Y	U	N	U	U	U	U	N	N	Y	U	N	Y	23
<i>Cuminum cyminum</i>														
Jafari 2017	U	U	N	Y	U	U	Y	N	N	Y	U	N	Y	31
Hendre 2020	U	U	U	U	U	U	Y	U	U	U	U	U	Y	15
<i>Curcuma longa</i>														
Usharani 2008	U	U	Y	U	U	U	U	N	N	U	U	N	Y	15
Na 2013	Y	U	Y	Y	U	Y	Y	N	N	Y	U	N	Y	54
Chuengsamarn 2014	Y	Y	Y	Y	U	U	Y	N	N	U	U	Y	Y	54
Panahi 2017, Panahi 2018	U	U	N	Y	U	U	Y	N	N	U	U	N	Y	23
Adab 2019	U	U	N	Y	U	U	Y	N	N	Y	U	N	Y	31
Adibian 2019	U	U	N	Y	U	U	Y	N	N	U	U	N	Y	23
Srinivasan 2019	Y	U	N	Y	U	U	Y	N	N	Y	U	N	Y	38
de Sousa 2020	U	U	N	U	U	U	U	N	N	U	U	N	Y	8
<i>Cyamopsis tetragonoloba</i>														
Uusitupa 1984	U	U	N	U	U	U	Y	N	N	Y	U	N	Y	23
Uusitupa 1989	U	U	N	U	U	U	Y	Y	Y	Y	U	N	Y	38
<i>Eclipta prostrata</i>														
Sazia 2015a, Sazia 2015b	Y	U	U	U	U	U	Y	N	N	Y	U	N	Y	31
<i>Elettaria cardamomum</i>														
Aghasi 2019	U	U	N	Y	U	U	Y	N	Y	Y	U	N	Y	38
<i>Emblica officinalis</i>														
Usharani 2013	U	U	N	Y	U	U	U	U	U	U	U	N	Y	15
<i>Enicostemma axillare</i>														
Shankarrao 2017	U	U	U	N	N	N	Y	U	U	U	U	N	Y	15
<i>Gynostemma pentaphyllum</i>														
Huyen 2010	U	U	N	U	U	U	Y	Y	N	Y	U	N	Y	31
Huyen 2012	U	U	N	U	U	U	Y	Y	Y	Y	U	N	Y	38
<i>Hibiscus sabdariffa</i>														
Sarbini 2019	Y	U	N	Y	U	Y	Y	N	N	Y	U	N	Y	46
<i>Ipomoea batatas</i>														
Ludvik 2004	U	U	N	U	U	U	Y	U	U	U	U	N	Y	15
Ludvik 2008	U	U	N	U	U	U	Y	N	N	Y	U	N	Y	23
<i>Juglans regia</i>														
Hosseini 2014a	U	U	Y	Y	U	Y	Y	N	N	Y	U	N	Y	46

Author and year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	% of Y
Hosseini 2014b	U	U	N	Y	U	U	Y	Y	Y	Y	U	N	Y	46
Abdoli 2017	Y	U	N	Y	U	U	Y	N	N	Y	U	N	Y	38
Zibaeenezhad 2016, Zibaeenezhad 2017	Y	U	N	U	U	Y	Y	N	N	Y	U	N	Y	38
Rabiei 2018	U	U	N	U	U	U	Y	N	N	U	U	N	Y	15
<i>Linum usitatissimum</i>														
Barre 2008	U	U	N	U	U	U	U	N	N	Y	U	N	Y	15
Hashemzadeh 2017	Y	U	Y	Y	U	U	U	Y	Y	Y	U	N	Y	54
<i>Momordica charantia</i>														
Dans 2007	Y	U	Y	Y	U	U	Y	N	Y	U	U	N	Y	46
Zänker 2012	U	U	Y	Y	U	U	Y	N	N	U	U	N	Y	31
Trakoon-osot 2013	U	U	Y	U	U	U	Y	Y	Y	Y	U	N	Y	46
Rahman 2015	U	U	N	U	U	U	Y	N	N	Y	U	N	Y	23
Suthar 2016a	U	U	N	N	N	N	U	N	N	U	U	N	Y	8
Suthar 2016b	U	U	N	N	N	N	Y	N	N	U	U	N	Y	15
Cortez-Navarrete 2018	U	U	N	Y	U	U	Y	N	N	Y	U	N	Y	31
Kumari 2018	Y	U	N	U	U	U	Y	Y	Y	Y	U	N	Y	46
Amini 2020	U	U	Y	Y	U	U	U	N	N	Y	U	N	Y	31
Kim 2020	U	U	N	U	U	U	U	N	N	U	U	N	Y	8
<i>Nigella sativa</i>														
Najmi 2012	U	U	N	N	N	N	Y	U	Y	U	U	N	Y	23
Hosseini 2013	U	U	Y	U	U	U	Y	Y	Y	Y	U	N	Y	46
Hadi 2015	U	U	N	U	U	U	Y	N	N	U	U	N	Y	15
Heshmati 2015	Y	U	N	Y	U	U	U	N	Y	Y	U	N	Y	38
Kaatabi 2015	Y	U	N	Y	U	U	Y	N	N	Y	U	N	Y	38
Moustafa 2019	Y	U	N	N	N	N	Y	N	N	U	U	N	Y	23
Kooshki 2020	U	U	N	Y	U	U	Y	U	U	U	U	N	Y	23
Jangjo-Borazjani 2021	U	U	N	Y	U	U	U	U	Y	Y	U	N	Y	31
<i>Plantago ovata</i>														
Ziai 2005	U	U	N	U	U	U	Y	N	N	Y	U	N	Y	23
Feinglos 2013	U	U	N	U	U	U	Y	N	U	U	U	N	Y	15
Abutair 2016	U	U	N	U	U	U	U	N	N	Y	U	N	Y	15
<i>Portulaca oleracea</i>														
El-Sayed 2011	U	U	N	U	U	U	U	U	U	Y	U	N	Y	15
Farzanegi 2014	U	U	N	U	U	U	U	U	U	Y	U	N	U	8
Dehghan 2016	U	U	N	U	U	U	U	U	U	Y	U	N	Y	15
Wainstein 2016	Y	U	N	Y	U	U	U	N	Y	Y	U	N	Y	38
<i>Pterocarpus marsupium</i>														
Hariharan 2005	U	U	Y	Y	Y	U	Y	N	N	Y	U	U	Y	46
<i>Punica granatum</i>														
Faghihimani 2016	U	U	N	U	U	U	Y	N	N	Y	U	N	Y	23
Babaeian 2013	U	U	Y	U	U	U	Y	N	N	Y	U	N	Y	31
Sohrab 2014, Sohrab 2015	U	U	N	U	U	U	Y	N	N	Y	U	N	Y	23
Khajebishak 2019a, Khajebishak 2019b	U	U	N	Y	U	U	U	N	N	Y	U	N	Y	23
Grabež 2020	U	U	N	Y	U	U	Y	Y	Y	Y	U	N	Y	46
Hashemi 2020	Y	U	N	U	Y	U	Y	N	N	U	U	N	Y	31

Author and year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	% of Y
<i>Sesamum indicum</i>														
Shahi 2017	U	U	N	U	U	U	U	N	N	Y	U	N	Y	15
Aslam 2018	U	U	N	U	U	U	Y	N	N	Y	U	N	Y	23
<i>Shilajit</i>														
Narasimha Raju 2016	U	U	N	U	U	U	U	N	N	U	U	N	Y	8
Niranjan 2016	U	U	Y	U	U	U	U	Y	Y	U	U	N	Y	31
<i>Syzygium cumini</i>														
Sahana 2010	Y	U	N	N	N	N	Y	N	U	U	U	N	Y	23
Sidana 2016, Sidana 2017	U	U	N	U	U	U	Y	N	N	U	U	N	Y	15
<i>Terminalia chebula</i>														
Usharani 2020	Y	U	N	Y	Y	U	U	Y	Y	U	U	N	Y	46
<i>Tinospora cordifolia</i>														
Mishra 2015	U	U	N	U	U	U	Y	U	U	Y	U	N	Y	23
Roy 2015	U	U	N	N	N	N	Y	U	U	U	U	N	Y	15
<i>Tribulus terrestris</i>														
Samani 2016	U	U	N	Y	Y	U	Y	N	N	Y	U	N	Y	38
<i>Trigonella foenum-graecum</i>														
Gupta 2001	U	U	N	U	U	U	U	U	Y	U	U	N	Y	15
Lu 2008	Y	U	N	Y	U	U	Y	Y	Y	Y	U	N	Y	54
Ansari 2011	Y	U	U	U	U	U	U	N	N	U	U	U	Y	15
Rafrat 2014	Y	U	N	U	U	U	Y	N	N	Y	U	N	Y	31
Suchitra 2015	U	U	Y	U	U	U	U	Y	Y	U	U	N	Y	31
Kaur 2016	Y	U	U	N	N	N	Y	Y	Y	U	U	N	Y	38
Singh 2016	U	U	N	N	N	N	U	Y	Y	Y	U	N	Y	31
Verma 2016	Y	U	U	U	U	U	Y	U	U	Y	U	N	Y	31
Ranade 2017	Y	U	Y	N	U	U	Y	U	U	U	U	N	Y	31
Gholaman 2018	U	U	N	U	U	U	Y	Y	Y	U	U	N	U	23
Kandhare 2018	Y	U	N	Y	U	U	Y	N	N	U	U	N	Y	31
Hassani 2019	U	U	N	U	U	U	Y	N	N	Y	U	N	Y	23
Hota 2019	U	U	Y	N	N	N	Y	U	U	U	U	U	Y	23
Najdi 2019	Y	Y	N	N	N	N	Y	N	N	U	U	N	Y	31
Rashid 2019	U	U	N	U	U	U	Y	Y	Y	U	U	N	Y	31
Hadi 2020	U	U	N	U	U	Y	Y	N	N	Y	U	N	Y	31
<i>Urtica dioica</i>														
Namazi 2011, Esfanjani 2012a, Esfanjani 2012b	U	U	N	U	U	U	Y	N	N	Y	U	N	Y	23
Kianbakht 2013	Y	Y	N	Y	Y	N	Y	N	N	Y	U	N	Y	54
Khajeh-Mehrizi 2014	U	U	N	U	U	U	Y	N	N	Y	U	N	Y	23
Dabagh 2016	U	U	Y	U	U	U	U	U	U	Y	U	N	U	15
Hassani 2016	U	U	N	U	U	U	U	N	N	Y	U	N	Y	15
Dadvar 2017	U	U	N	U	U	U	U	U	U	Y	U	N	U	8
Ghalavand 2017	U	U	Y	U	U	U	U	U	U	Y	U	N	U	15
Korani 2017	U	U	N	U	U	U	U	N	N	Y	U	N	Y	15
Mohammadnia 2017	U	U	U	U	U	U	U	N	N	Y	U	N	U	8
<i>Vernonia cinerea</i>														
Sayeed 2013	Y	U	N	Y	U	U	Y	U	U	Y	U	N	Y	38

Author and year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	% of Y
Withania coagulans														
Hemalatha 2018	U	U	U	U	U	U	Y	U	U	Y	U	N	Y	23
Withania somnifera														
Usharani 2014	U	U	N	Y	U	U	U	N	N	U	U	N	Y	15
Zingiber officinale														
Mahluji 2013	U	U	N	Y	U	U	Y	N	N	Y	U	N	Y	31
Arablou 2014a, Arablou 2014b	U	U	N	Y	U	U	Y	N	N	Y	U	N	Y	31
Mozaffari-Khosravi 2014, Talaei 2017, Talaei 2018	Y	U	N	Y	U	U	Y	N	N	U	U	N	Y	31
Shidfar 2015	U	U	N	Y	U	U	Y	N	N	Y	U	N	Y	31
Arzati 2017, Zarezadeh 2018	U	U	N	Y	U	U	Y	N	N	Y	U	N	Y	31
Mohammadi 2017, Mohammadi 2019	U	U	N	U	U	U	U	U	Y	Y	U	N	U	15
Carvalho 2020	Y	U	N	Y	U	U	Y	N	N	Y	U	N	Y	38
Gholinezhad 2020	U	U	N	Y	U	U	U	N	N	Y	U	N	Y	23
Ziziphus mauritiana														
Yazdanpanah 2017	Y	U	N	U	U	Y	Y	N	N	Y	U	N	Y	38
Acalypha indica/Allium cepa/Allium sativum/Azadirachta indica/Mangifera indica/Murraya koenigii/Musa sapientum/Ocimum tenuiflorum/Phyllanthus amarus/Tinospora cordifolia														
Balasubramaniam 2010	Y	U	U	U	U	U	Y	Y	Y	Y	U	N	Y	46
Allium sativum; Cuminum cyminum														
Mansouri 2018	U	U	N	U	U	U	U	U	U	U	U	N	Y	8
Aloe vera; Pterocarpus marsupium; Aloe vera+Pterocarpus marsupium														
Maurya 2017	N	U	N	U	N	N	Y	N	N	U	U	N	N	8
Cinnamomum verum; Crocus sativus; Elettaria cardamomum; Zingiber officinale														
Azimi 2014, Azimi 2016	U	U	N	U	U	U	U	N	N	Y	U	N	Y	15
Enicostemma axillare; Shilajit														
Kumar 2014	U	U	N	U	U	U	U	N	N	U	U	N	U	0
Enicostemma axillare+Emblica officinalis+Tinospora cordifolia														
Sharma 2019	U	U	N	N	N	N	Y	N	N	U	U	N	Y	15
Linum usitatissimum; Plantago ovata														
Ricklefs-Johnson 2017	Y	U	N	U	U	U	Y	N	N	Y	U	N	Y	31
Syzygium cumini+Withania coagulans														
Siddiqui 2017	Y	U	Y	N	N	N	U	N	N	U	U	N	Y	23
Trigonella foenum-graecum; Aegle marmelos; Trigonella foenum-graecum+Aegle marmelos														
Yaheya 2009	U	U	U	U	U	U	U	Y	Y	Y	U	N	Y	31
Ayurvedic medicine- combination of plant- and/or mineral-origin ingredients§														
AYUBES														
Godatwar 2019	Y	U	N	Y	U	U	N	U	N	U	U	N	Y	23
BGR-34														
Gupta 2018	U	U	N	U	U	U	U	N	N	U	U	N	Y	8
Bilvadi Churna; Kiratadi Churna														
Kumari 2016	U	U	N	U	U	U	U	U	U	U	U	N	Y	8
CardiPro														
Fatima 2012	U	U	N	Y	U	U	U	N	N	U	U	N	Y	15
Cogent db														
Shekhar 2002	U	U	N	U	U	U	Y	N	N	U	U	N	U	8
DCBT 2345														

Author and year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	% of Y
Mohan 2001	U	U	N	Y	U	U	Y	N	N	Y	U	N	Y	31
Diabetea tea														
Mahmoud 2016	U	U	N	U	U	U	Y	N	N	Y	U	N	Y	23
Emblica officinalis; Withania somnifera; Emblica officinalis, Withania somnifera														
Usharani 2014	U	U	Y	U	U	U	U	N	N	U	U	N	Y	15
Herbal combination														
Shokoohi 2017	U	U	N	Y	Y	U	Y	N	Y	Y	U	N	Y	46
Hyponidd														
Poongothai 2002	U	U	N	Y	U	U	Y	N	N	Y	U	N	Y	31
Inolter														
Agrawal 2002	U	U	Y	Y	U	U	Y	Y	Y	Y	U	N	Y	54
Kalpita														
Agarwal 2013	U	U	N	U	U	U	U	U	Y	U	U	N	Y	15
Khadira-Kramuka Kashaya Ghanavati; Nishamalaki, Shilajit; Khadira-Kramuka Kashaya Ghanavati+Nishamalaki, Shilajit														
Paliwal 2018	U	N	N	U	U	U	U	U	U	U	U	N	Y	8
Lodhradi Kashaya Ghana Vati														
Bramhankar 2017	U	U	N	U	U	U	Y	N	N	U	U	N	Y	15
Madhumeha Nashini Gutika; Darvyadi Kwatha; Madhumeha Nashini Gutika+Darvyadi Kwatha														
Bhawana 2015	U	U	N	U	U	U	U	U	U	U	U	N	Y	8
Mamajjaka Ghana Vati; Tejashiladi Vati														
Bhagat 2017	Y	U	N	N	N	N	Y	N	N	U	U	N	Y	23
Mamajjaka Ghana Vati; Trikatu Gutika														
Kataria 2017	U	U	N	U	U	U	Y	Y	Y	U	U	N	Y	31
Mehagni														
Gopalakrishna 2017	U	U	N	N	N	N	N	Y	Y	Y	U	N	Y	31
Mustadi Kwatha Ghana Vati														
Kushwaha 2017	U	U	N	N	N	N	U	U	U	Y	U	N	Y	15
Naga Bhasma, Nishamalaki; Nishamalaki, Hordeum vulgare														
Desale 2018	Y	U	N	U	U	U	Y	N	N	U	U	N	Y	23
Nigella sativa, Trigonella foenum-graecum														
Memon 2010a, Memon 2010b, Memon 2012	U	U	N	N	N	N	Y	Y	Y	Y	U	N	Y	38
Nisha Katakadi Kashaya; Yashad Bhasma; Nisha Katakadi Kashaya+Yashad Bhasma														
Srinivas 2018	Y	U	Y	N	N	N	U	N	N	U	U	N	Y	23
Pancreas tonic														
Hsia 2004	U	U	N	Y	U	U	Y	N	N	Y	U	N	Y	31
Polyherbal formulation														
Awasthi 2015	Y	U	N	N	N	N	Y	N	N	Y	U	N	Y	31
Salasaradi Kashaya+Shilajit+Trivanga Bhasma+Tinospora cordifolia, Azadirachta indica; Hyponidd														
Bhat 2012	U	U	N	U	U	U	Y	N	N	U	U	N	Y	15
Shilajit; Asanadi Ghana Vati														
Gupta 2016 [^]	U	U	U	U	U	U	U	N	N	U	U	N	Y	8
Swarnamakshika Bhasma														
Taviad 2016	Y	U	N	U	U	U	U	N	N	U	U	N	Y	15
Talapotaka Churna														
Nille 2018	U	U	N	U	U	U	U	N	N	U	U	N	Y	8

Author and year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	% of Y
<i>Trigonella foenum-graecum, Ocimum tenuiflorum</i>														
Mitra 2006	U	U	U	U	U	U	Y	U	U	Y	U	N	Y	23
<i>Triticum aestivum; Nishamalaki, Triticum aestivum+Nishamalaki</i>														
Samagandi 2012	U	U	N	U	U	U	U	Y	Y	U	U	N	Y	23
<i>Vidangadi Yoga</i>														
Deshpande 2018	Y	Y	N	N	N	N	U	N	N	U	U	N	Y	23
<i>Vijaysaradi Ghana Vati; Madhumehari Vati</i>														
Sharma 2018	Y	U	N	N	N	N	U	N	N	U	U	N	Y	15

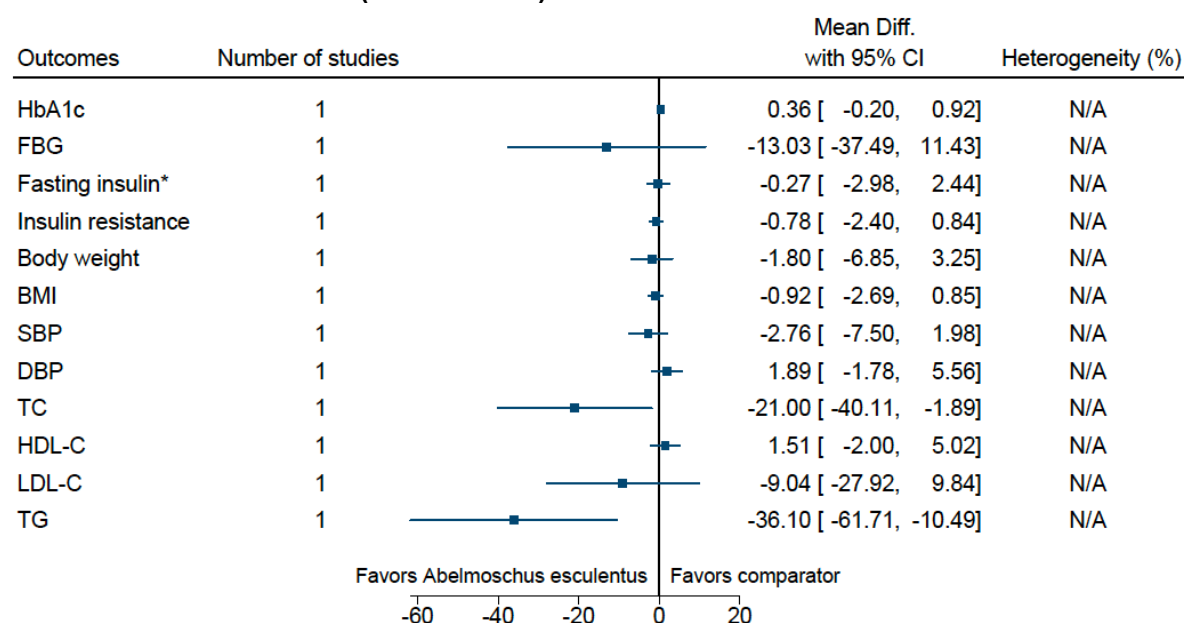
Y=Yes, N=No, U=Unclear; JBI critical appraisal checklist for RCTs: 1. Was true randomization used for assignment of participants to treatment groups? 2. Was allocation to treatment groups concealed? 3. Were treatment groups similar at the baseline? 4. Were participants blind to treatment assignment? 5. Were those delivering treatment blind to treatment assignment? 6. Were outcomes assessors blind to treatment assignment? 7. Were treatment groups treated identically other than the intervention of interest? 8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed? 9. Were participants analyzed in the groups to which they were randomized? 10. Were outcomes measured in the same way for treatment groups? 11. Were outcomes measured in a reliable way? 12. Was appropriate statistical analysis used? 13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

§Some of the Ayurvedic medicines contain single plant- or mineral-origin ingredient.

^Extracted only adverse event data.

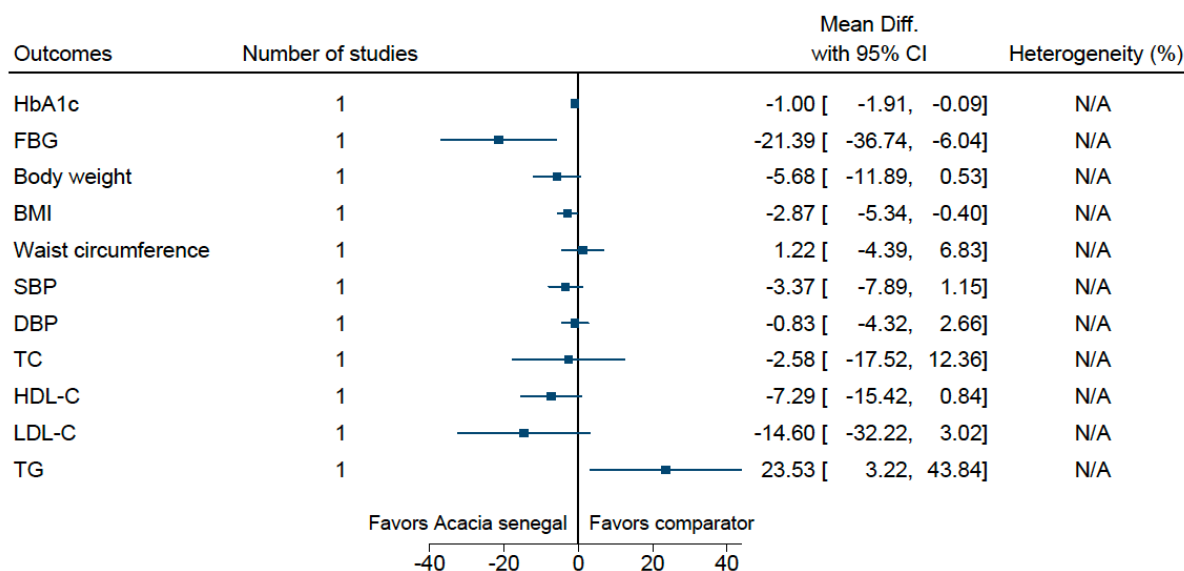
Appendix S7: 89 comparisons of Ayurvedic medicines which could not be included in meta-analyses.

***Abelmoschus esculentus* (Moradi 2020)**

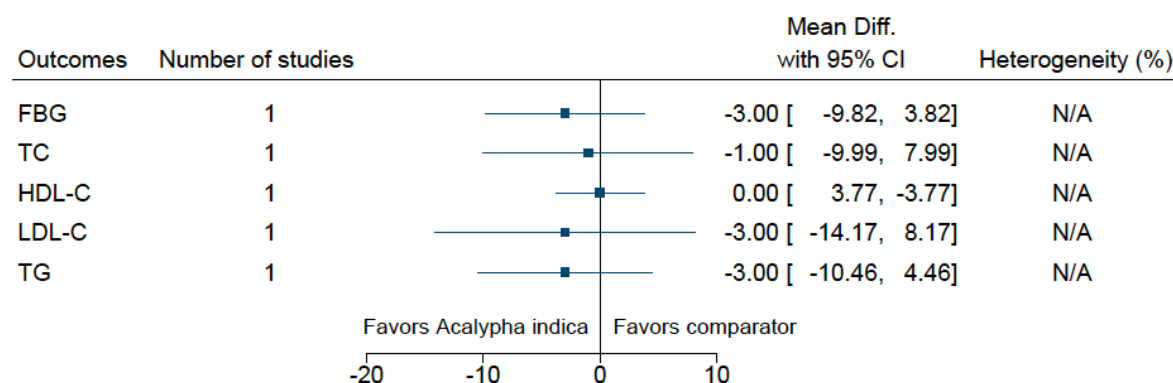


*Favors intervention/comparator as insulin sensitizer

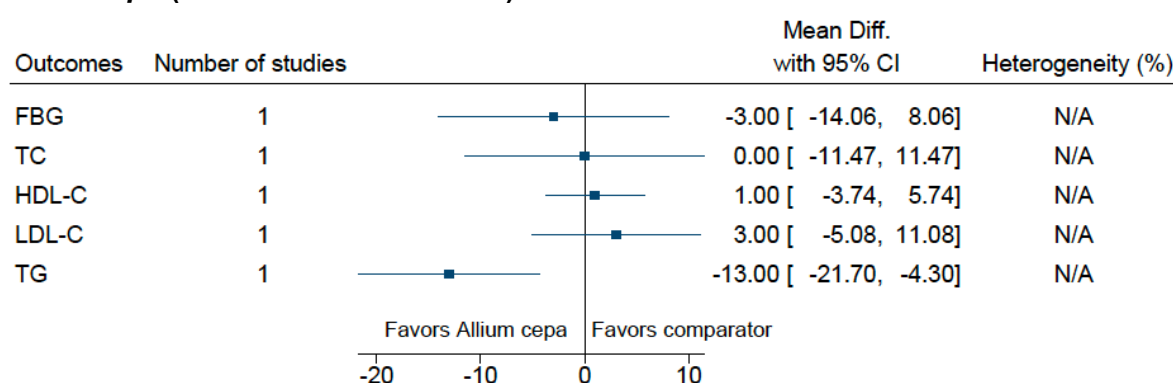
***Acacia senegal* (Babiker 2017, Babiker 2018)**



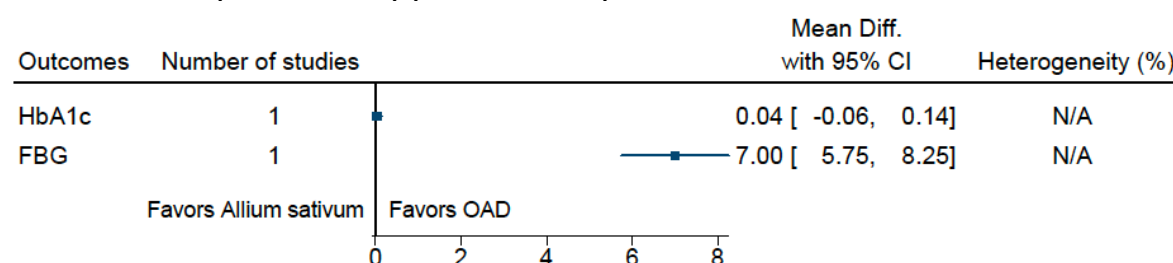
***Acalypha indica* (Balasubramaniam 2010)**



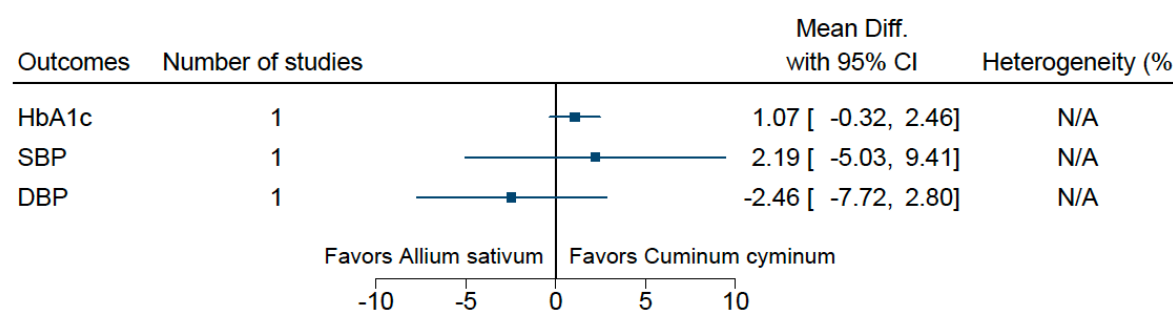
***Allium cepa* (Balasubramaniam 2010)**



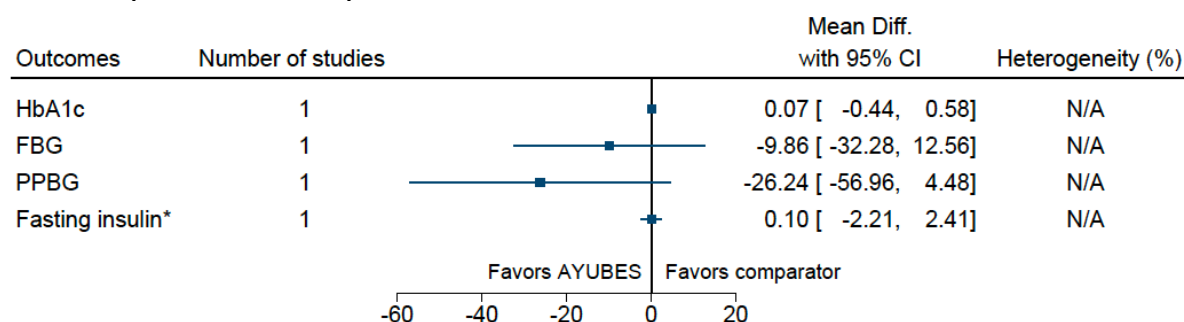
***Allium sativum* (versus OAD) (Ashraf 2011a)**



***Allium sativum* versus *Cuminum cyminum* (Mansouri 2018)**

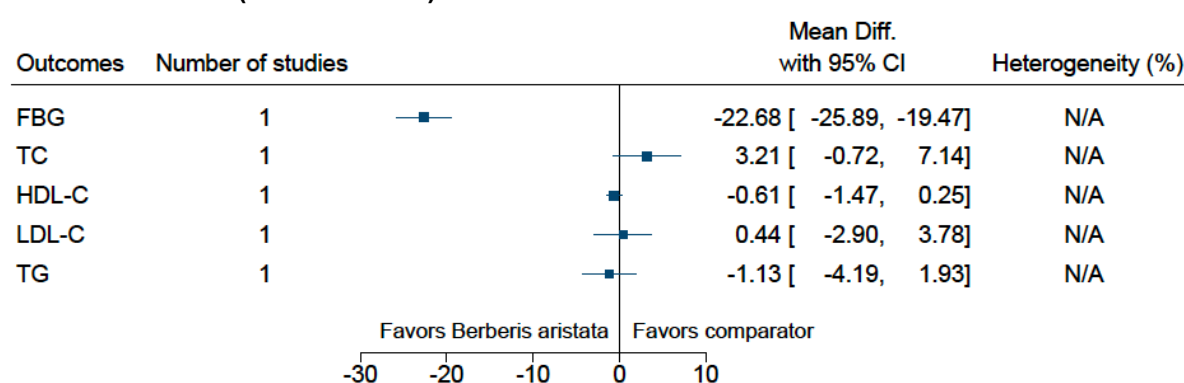


AYUBES (Godatwar 2019)

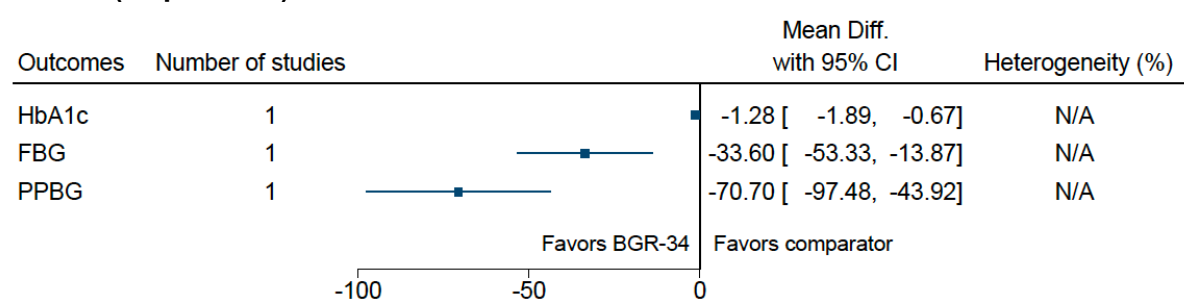


*Favors intervention/comparator as insulin sensitizer

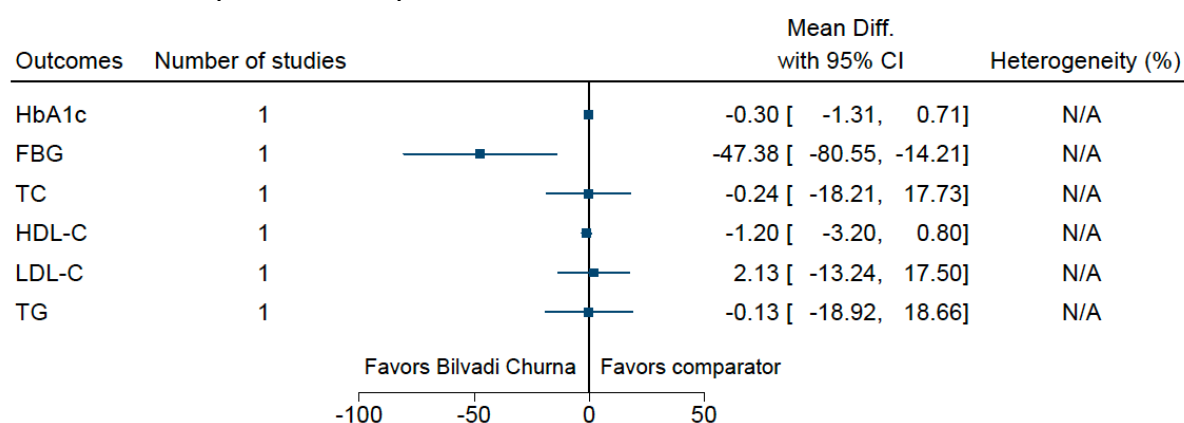
Berberis aristata (Sharma 2017)



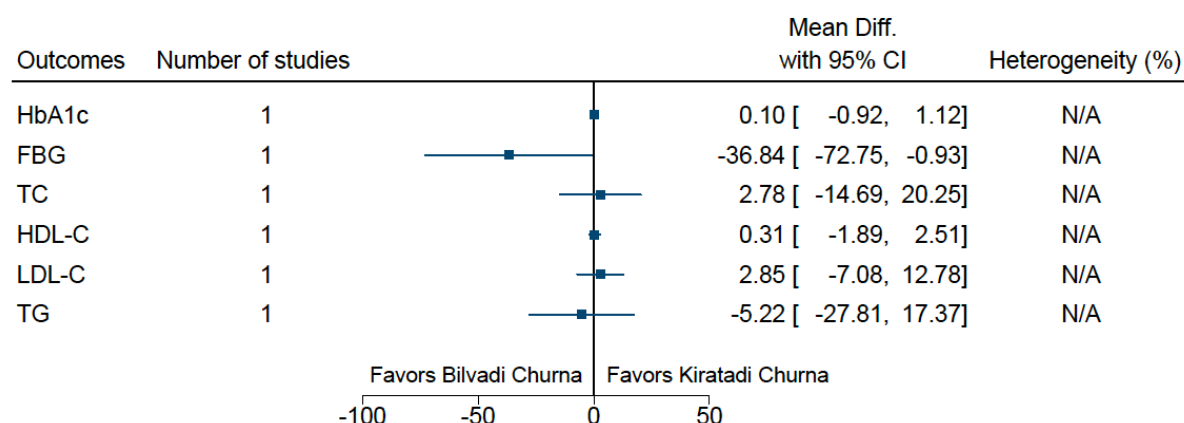
BGR-34 (Gupta 2018)



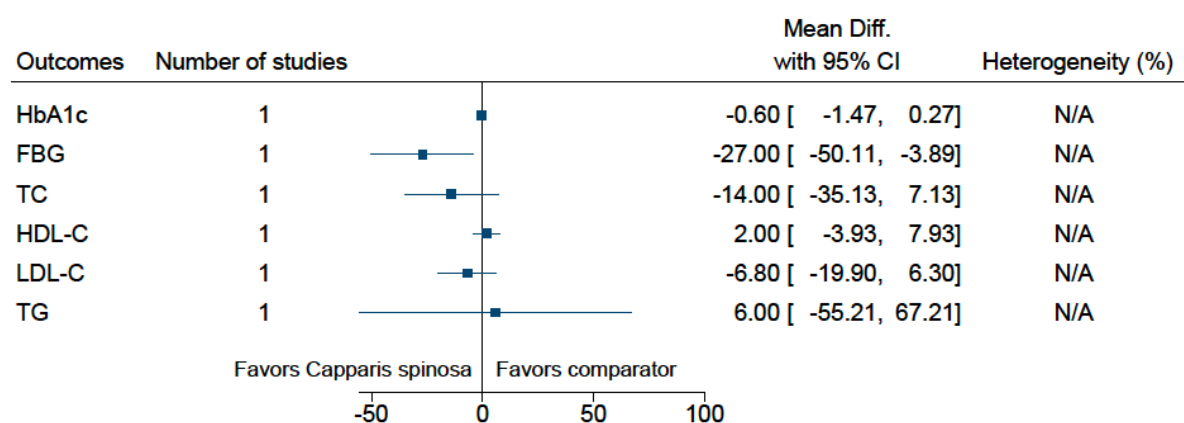
Bilvadi Churna (Kumari 2016)



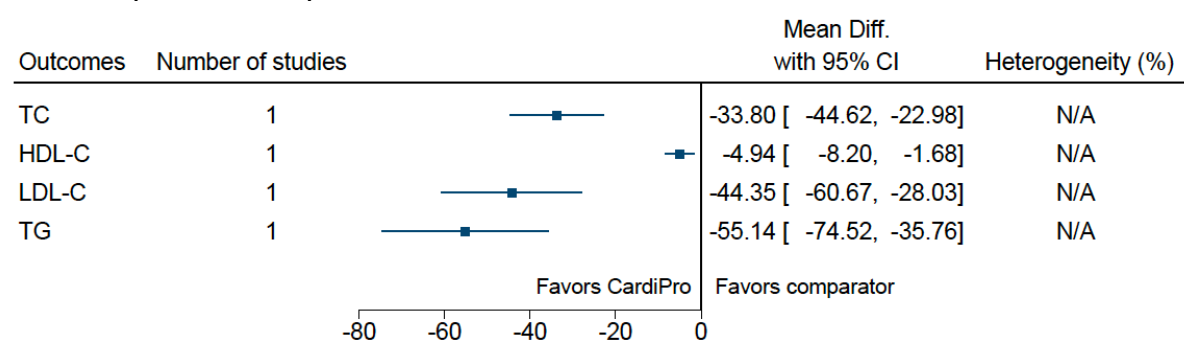
Bilvadi Churna versus Kiratadi Churna (Kumari 2016)



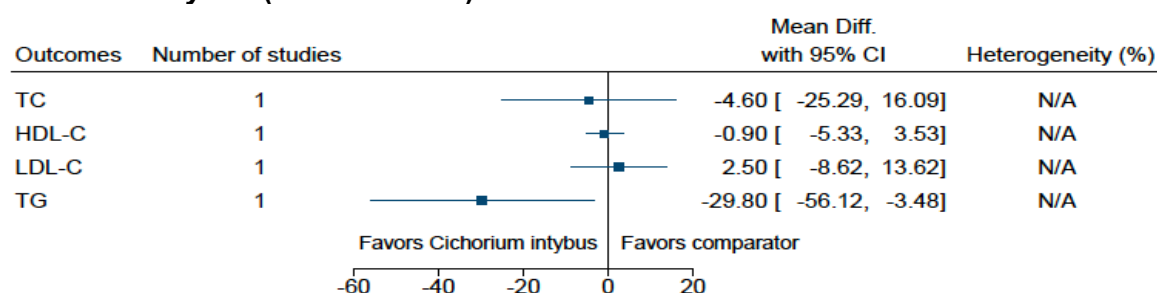
Capparis spinosa (Huseini 2013)



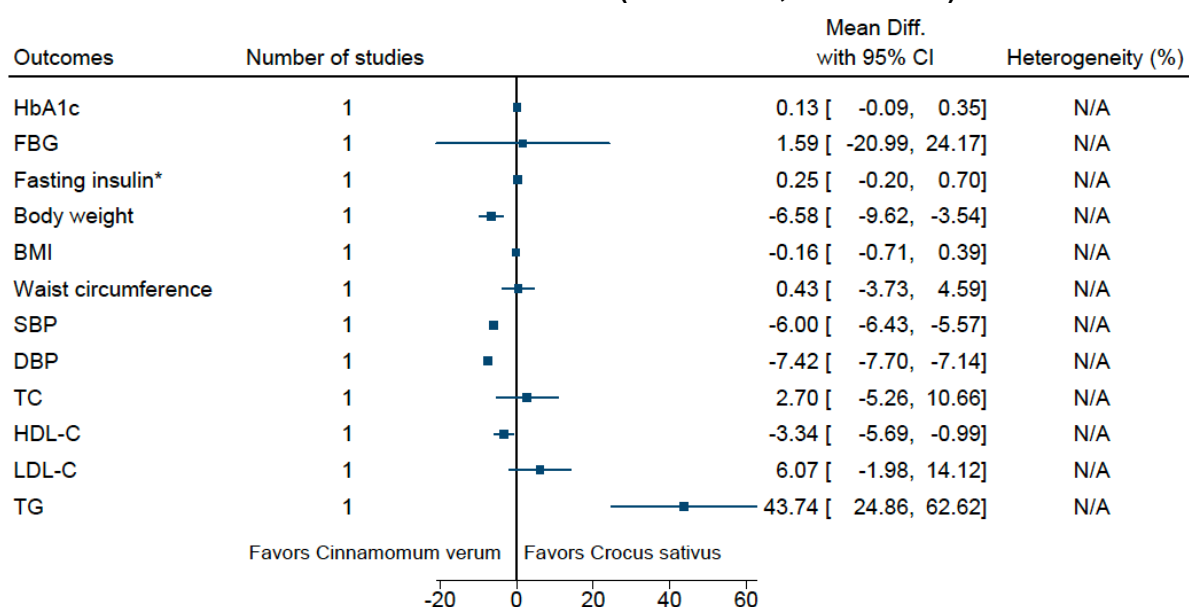
CardiPro (Fatima 2012)



***Cichorium intybus* (Chandra 2020)**

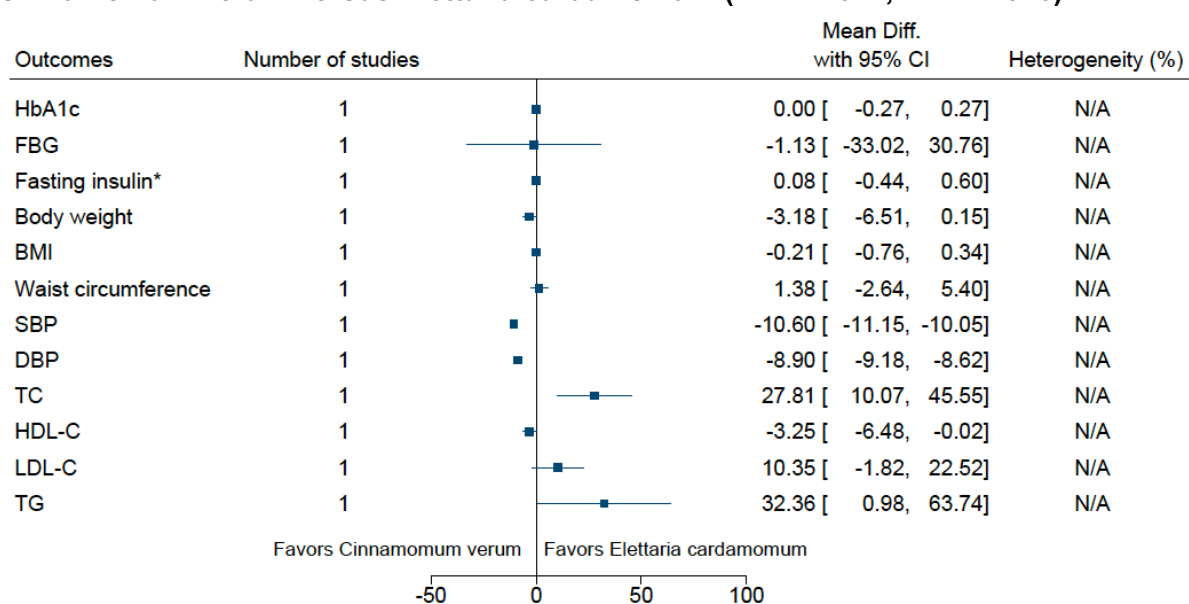


***Cinnamomum verum* versus *Crocus sativus* (Azimi 2014, Azimi 2016)**



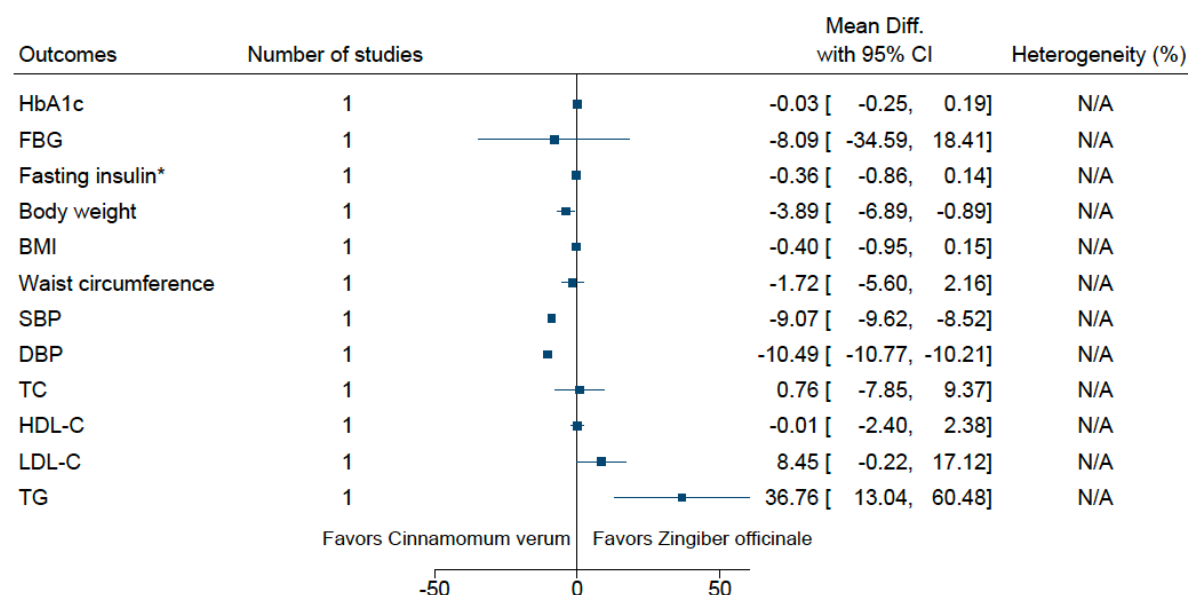
*Favors intervention/comparator as insulin sensitizer

***Cinnamomum verum* versus *Elettaria cardamomum* (Azimi 2014, Azimi 2016)**



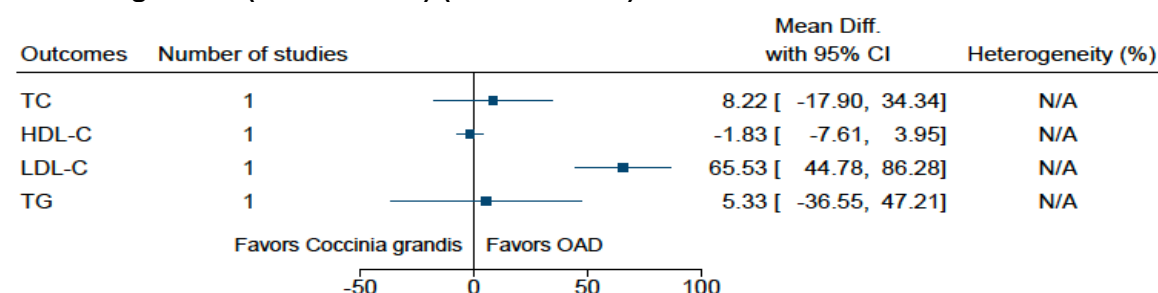
*Favors intervention/comparator as insulin sensitizer

***Cinnamomum verum* versus *Zingiber officinale* (Azimi 2014, Azimi 2016)**

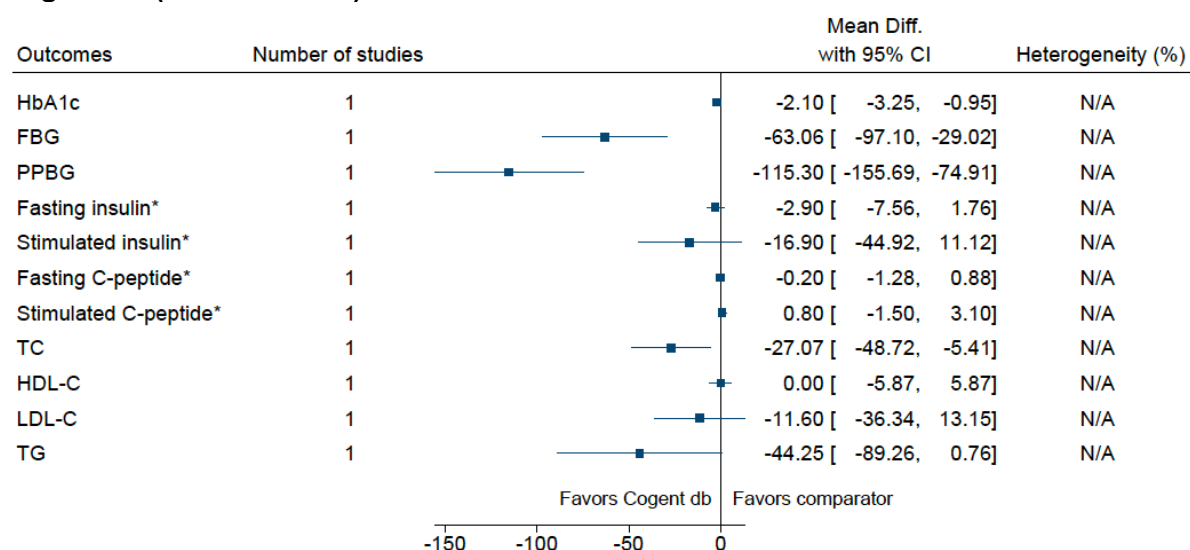


*Favors intervention/comparator as insulin sensitizer

***Coccinia grandis* (versus OAD) (Quamri 2017)**

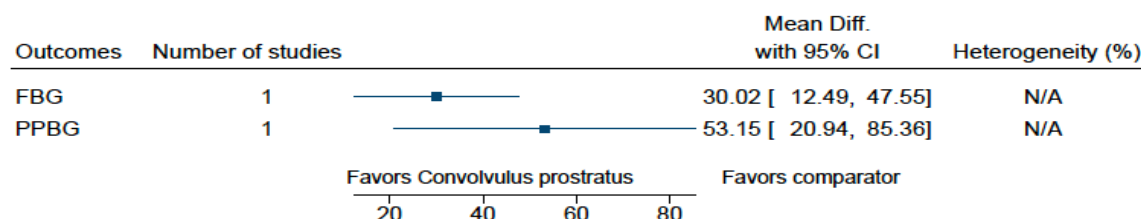


Cogent db (Shekhar 2002)

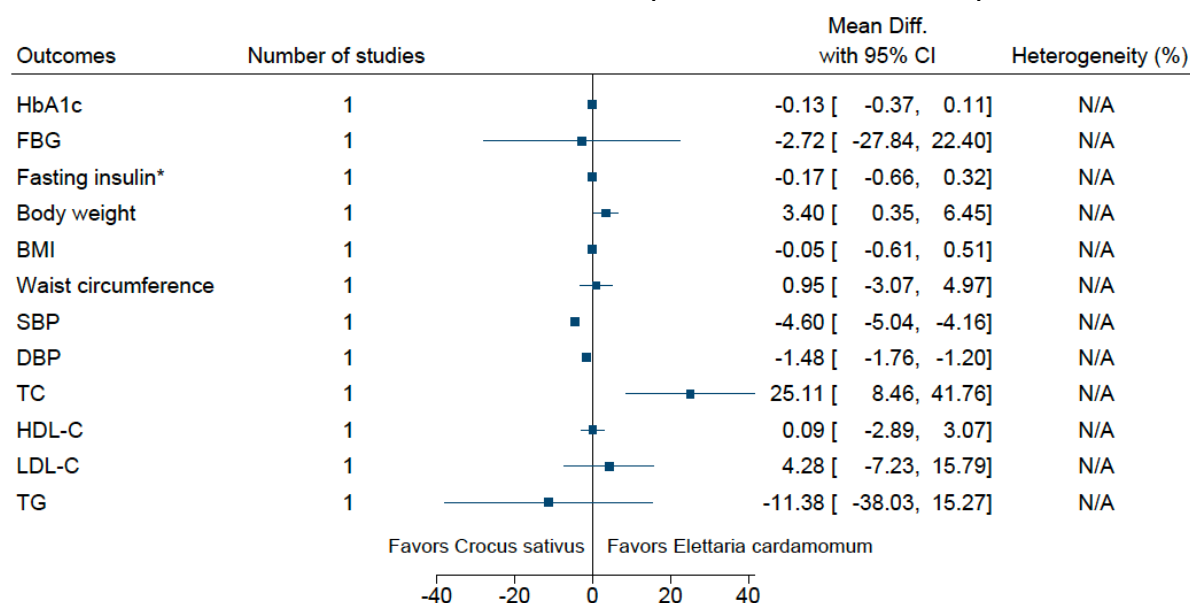


*Favors intervention/comparator as insulin sensitizer

***Convolvulus prostratus* (Patel 2012)**

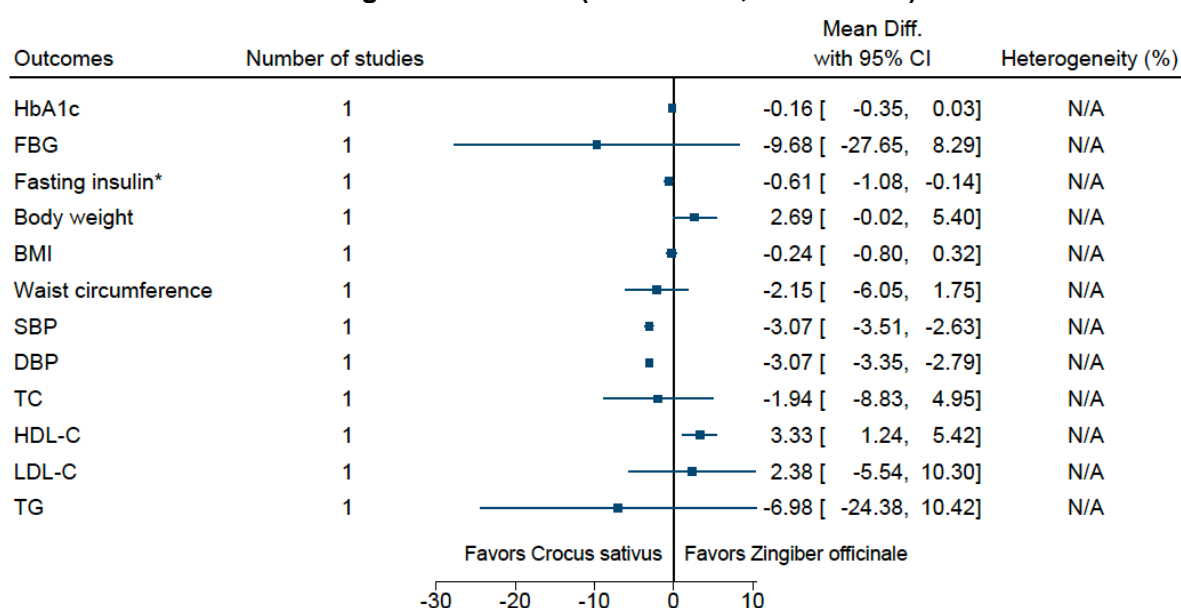


***Crocus sativus* versus *Elettaria cardamomum* (Azimi 2014, Azimi 2016)**



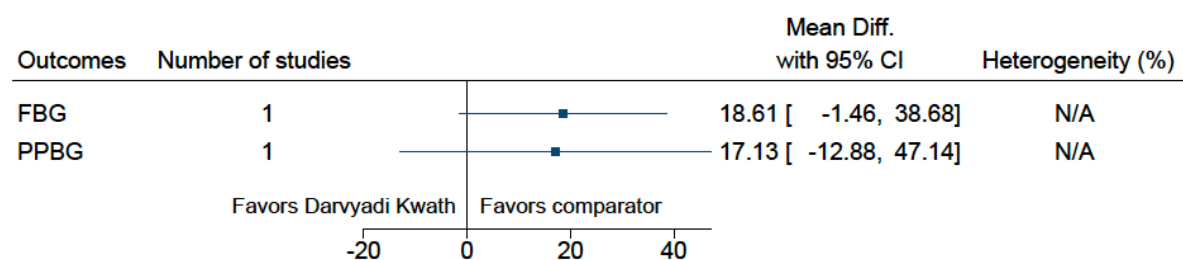
*Favors intervention/comparator as insulin sensitizer

***Crocus sativus* versus *Zingiber officinale* (Azimi 2014, Azimi 2016)**

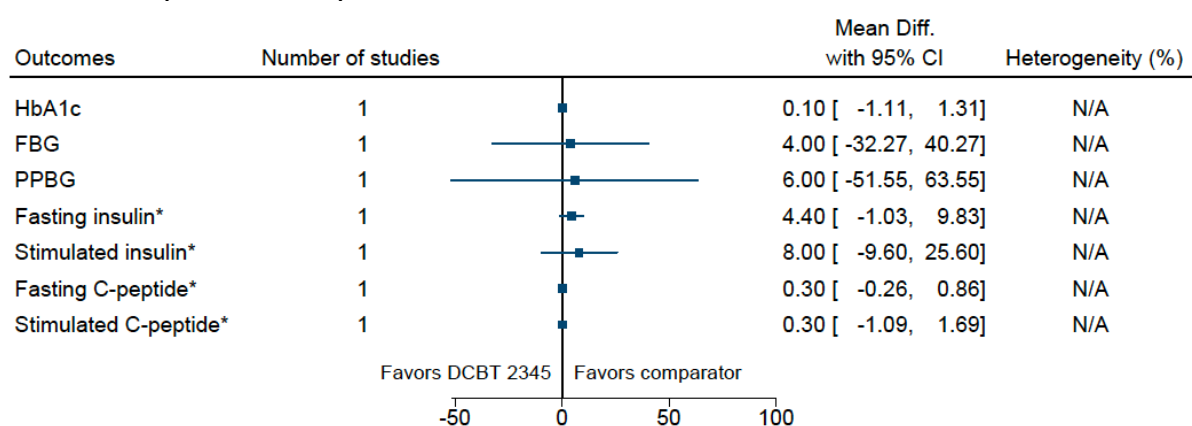


*Favors intervention/comparator as insulin sensitizer

Darvyadi Kwatha (Bhawana 2015)

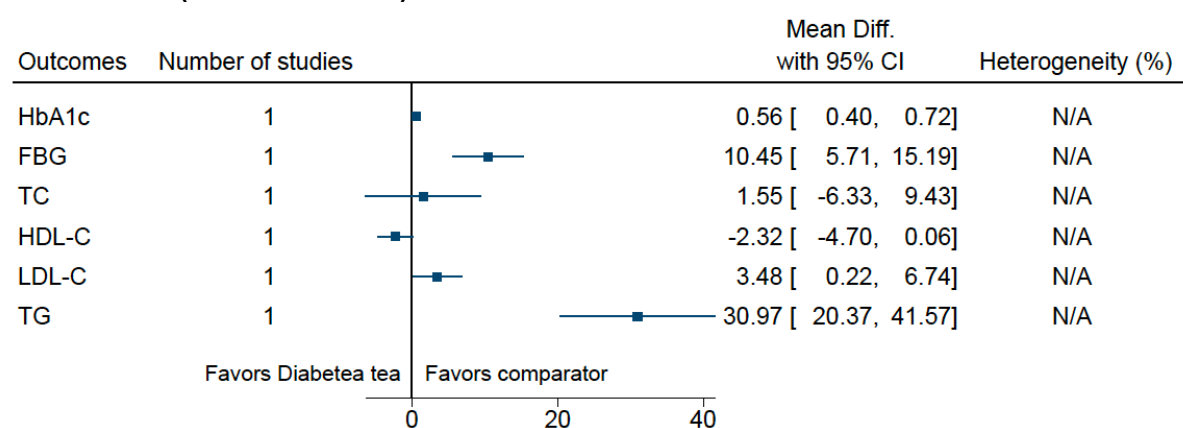


DCBT 2345 (Mohan 2001)

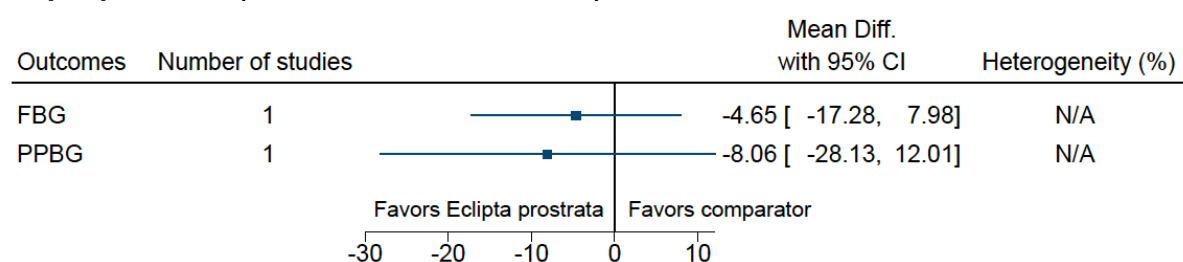


*Favors intervention/comparator as insulin sensitizer

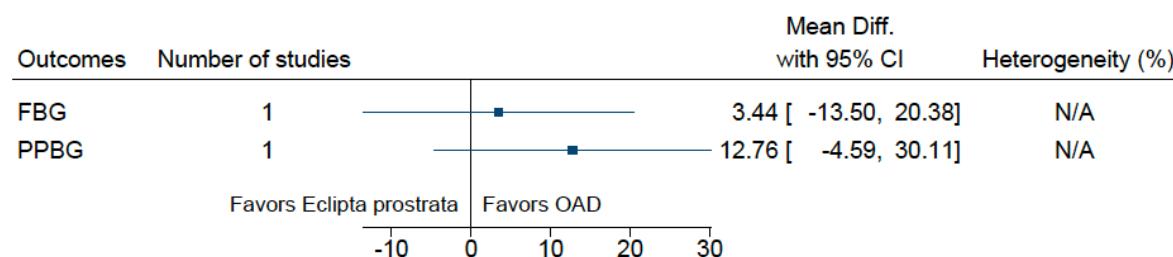
Diabetea tea (Mahmoud 2016)



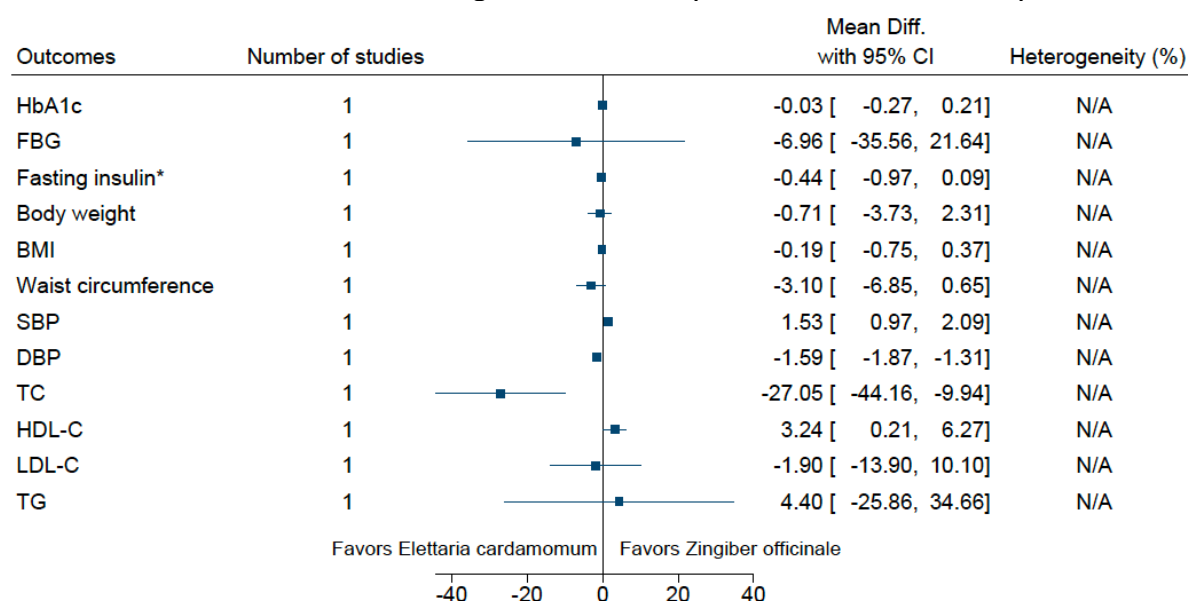
Eclipta prostrata (Sazia 2015a, Sazia 2015b)



***Eclipta prostrata* (versus OAD) (Sazia 2015a, Sazia 2015b)**

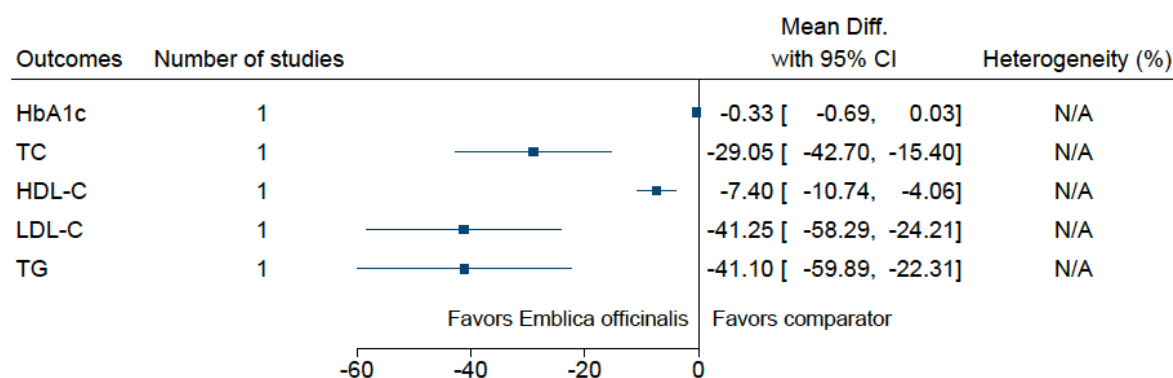


***Elettaria cardamomum* versus *Zingiber officinale* (Azimi 2014, Azimi 2016)**

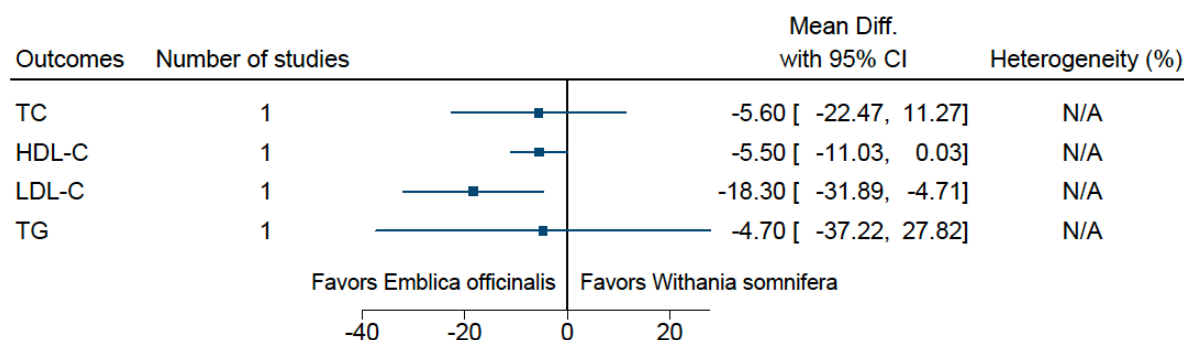


*Favors intervention/comparator as insulin sensitizer

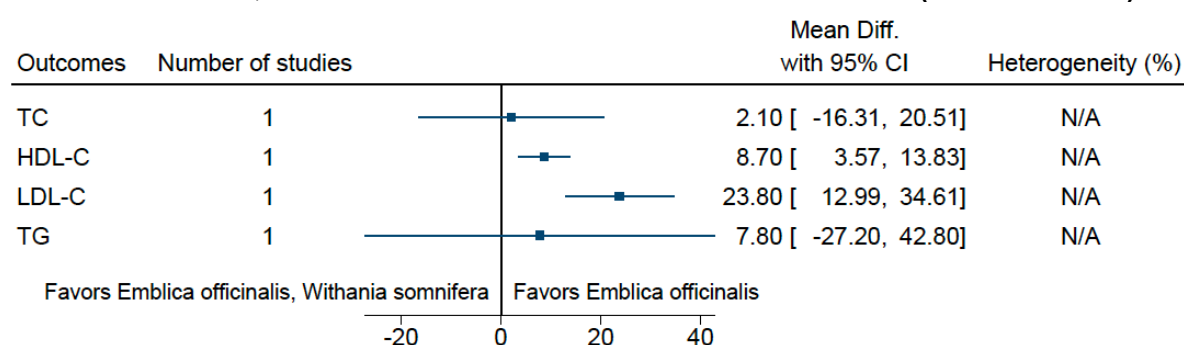
***Emblica officinalis* (Usharani 2013)**



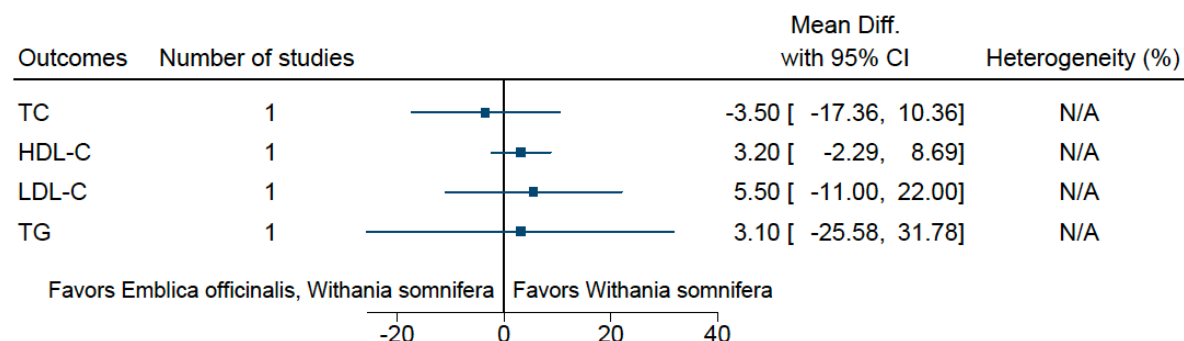
***Emblica officinalis* versus *Withania somnifera* (Usharani 2014)**



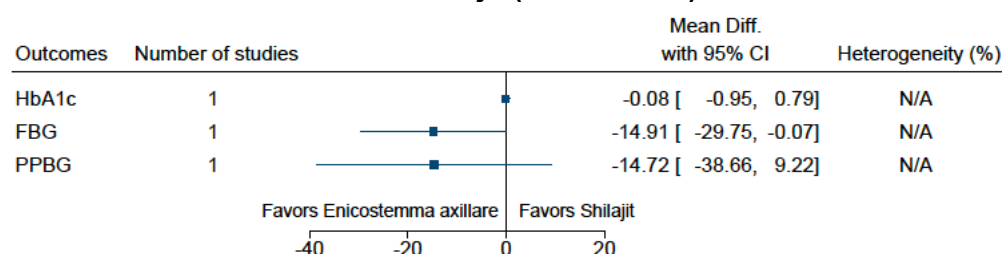
***Emblica officinalis*, *Withania somnifera* versus *Emblica officinalis* (Usharani 2014)**



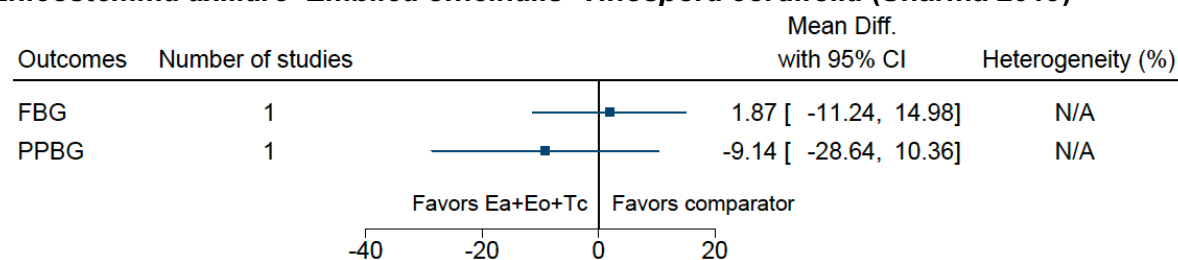
***Emblica officinalis*, *Withania somnifera* versus *Withania somnifera* (Usharani 2014)**



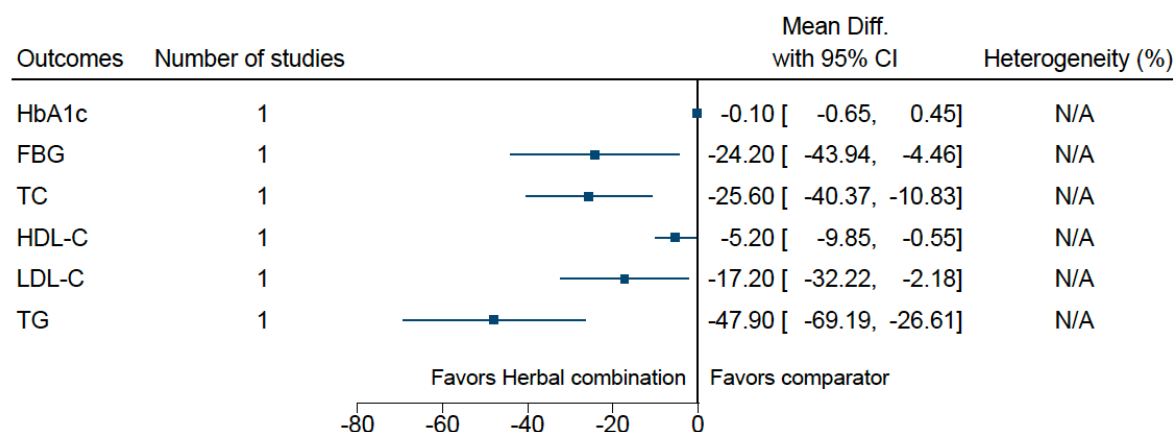
***Enicostemma axillare* versus Shilajit (Kumar 2014)**



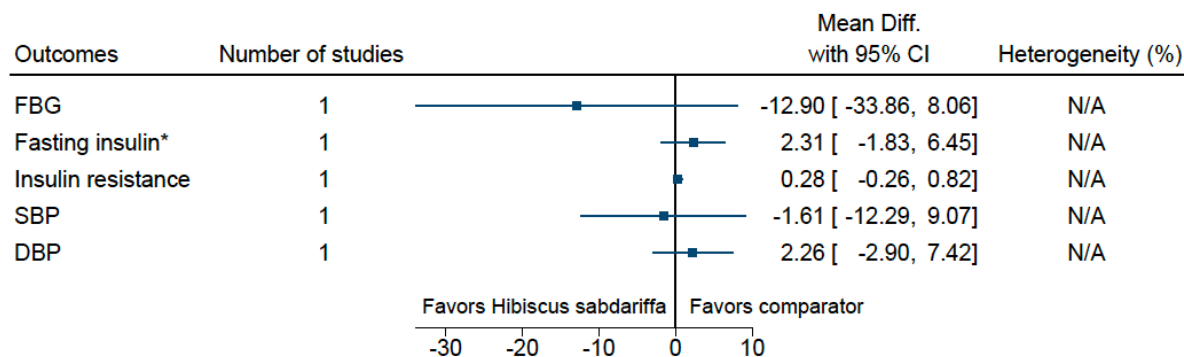
***Enicostemma axillare*+*Emblica officinalis*+*Tinospora cordifolia* (Sharma 2019)**



Herbal combination (Shokoohi 2017)

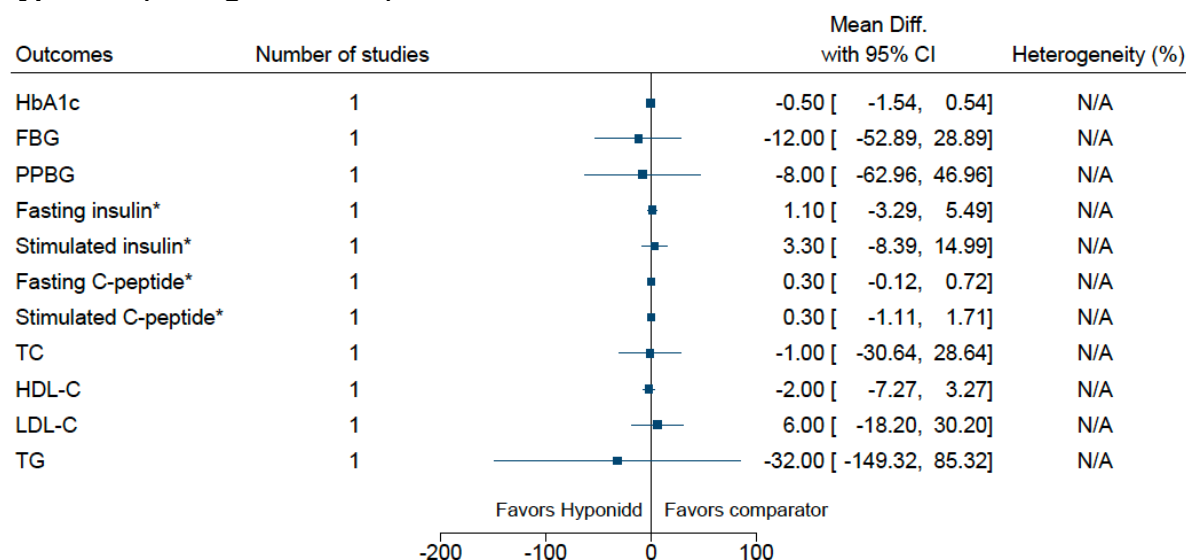


***Hibiscus sabdariffa* (Sarhini 2019)**



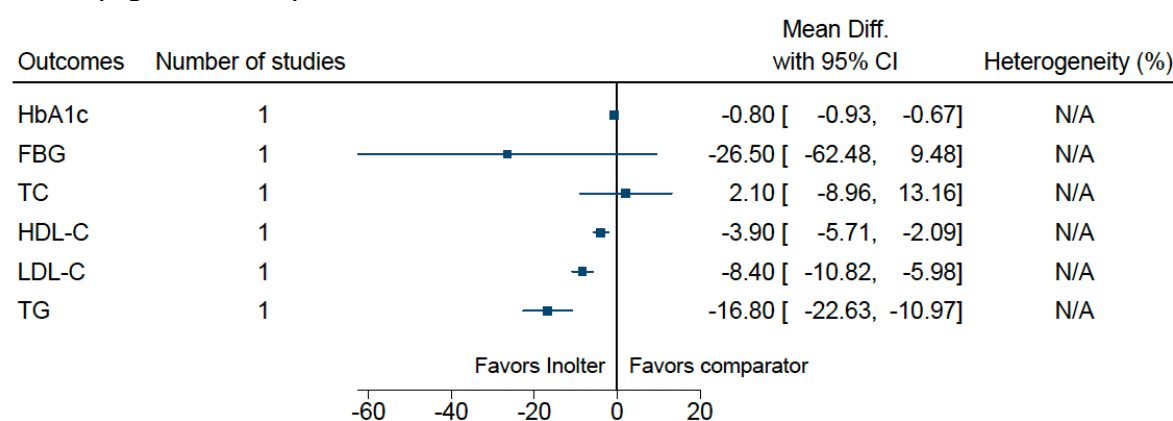
*Favors Intervention/comparator as insulin sensitizer

Hyponidd (Poongothai 2002)

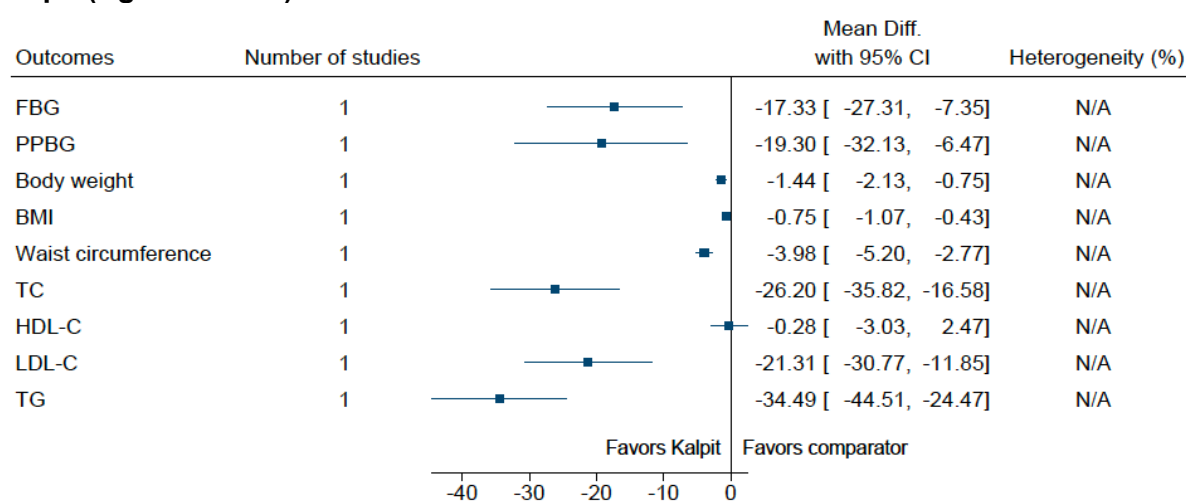


*Favors intervention/comparator as insulin sensitizer

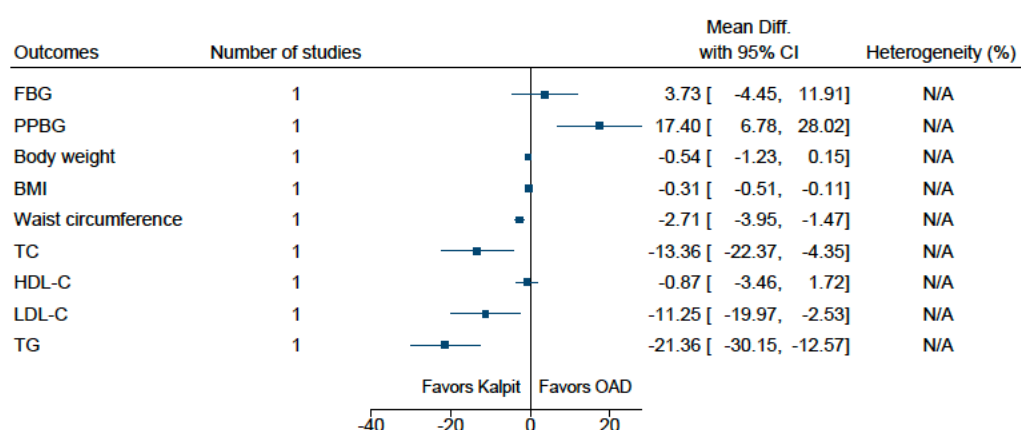
Inolter (Agrawal 2002)



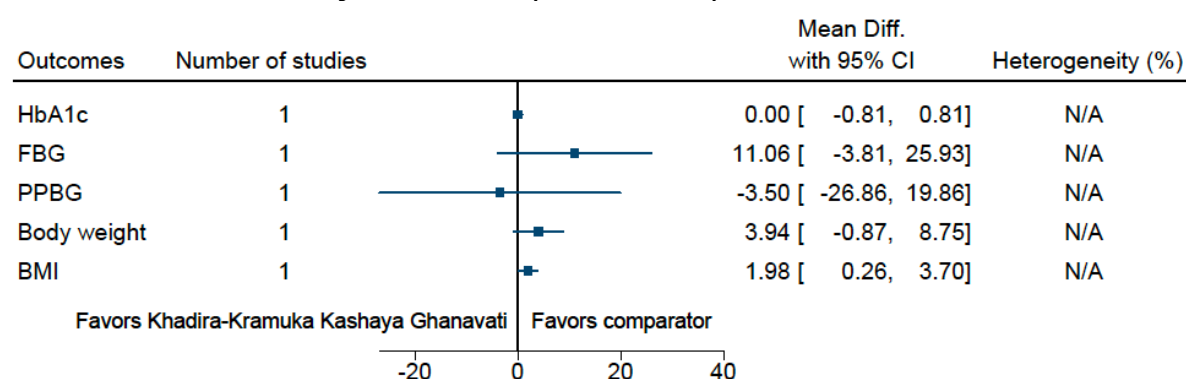
Kalpit (Agarwal 2013)



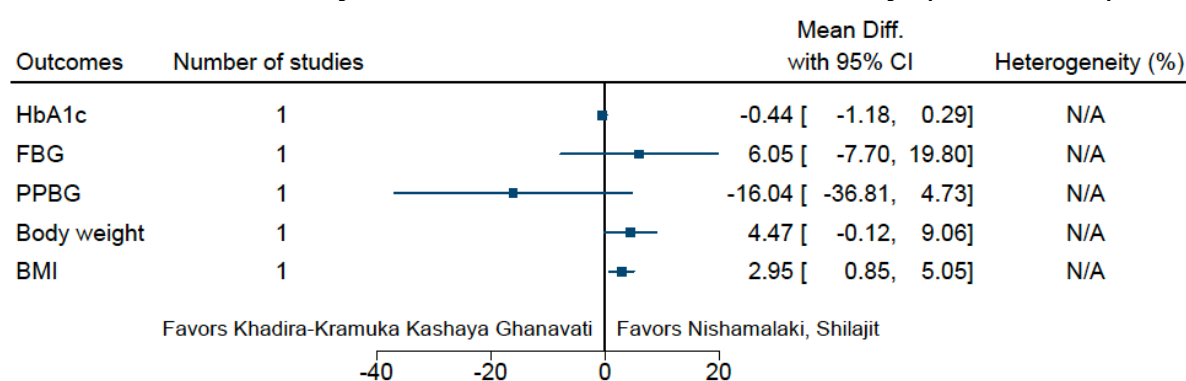
Kalpita (versus OAD) (Agarwal 2013)



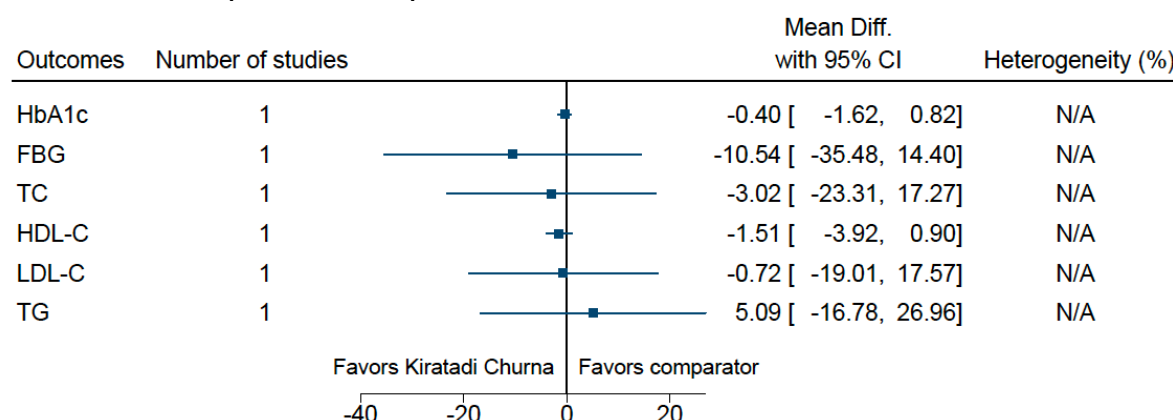
Khadira-Kramuka Kashaya Ghanavati (Paliwal 2018)



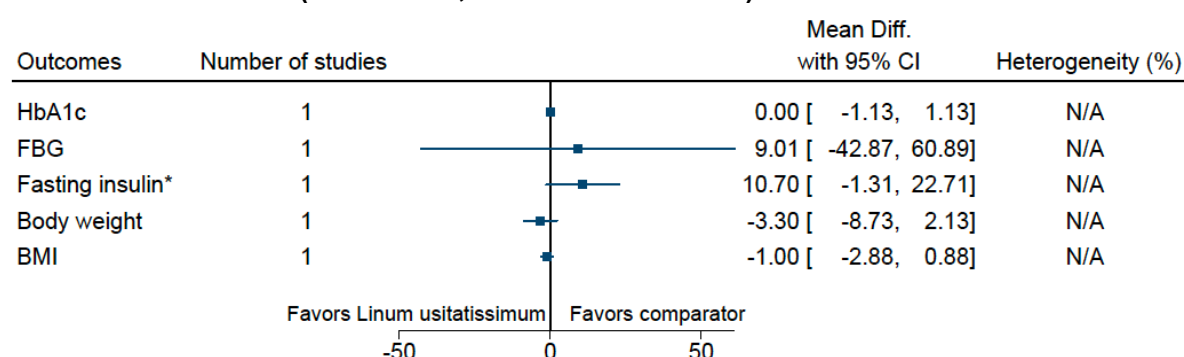
Khadira-Kramuka Kashaya Ghanavati versus Nishamalaki, Shilajit (Paliwal 2018)



Kiratadi Churna (Kumari 2016)

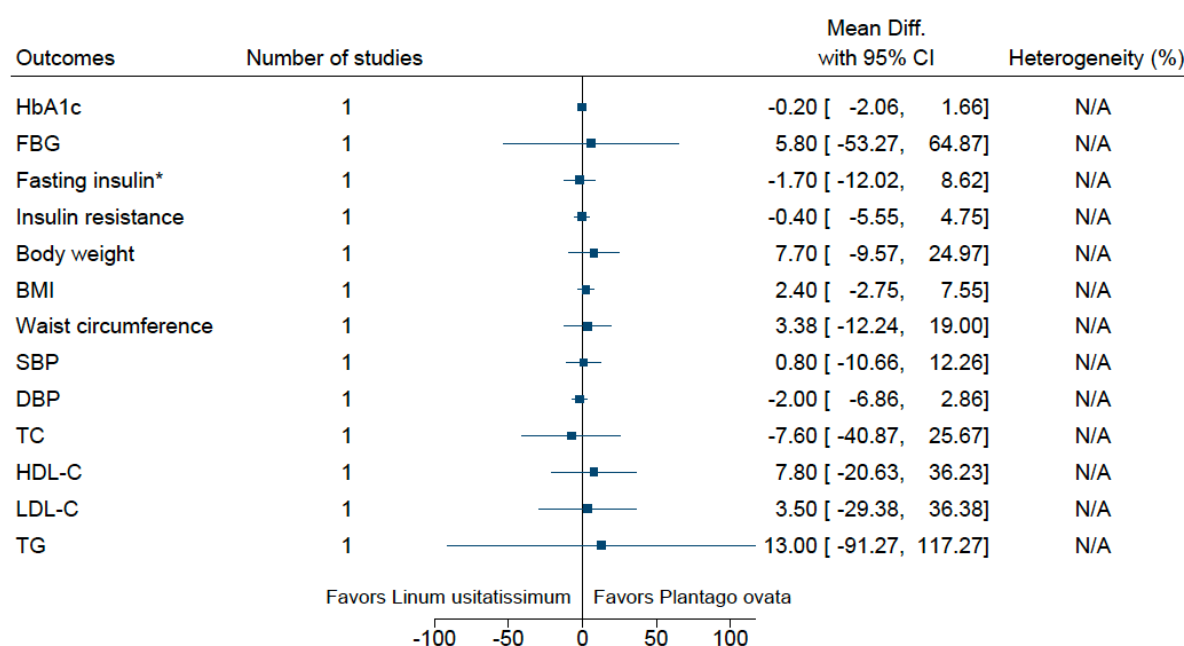


Linum usitatissimum (Barre 2008, Hashemzadeh 2017)



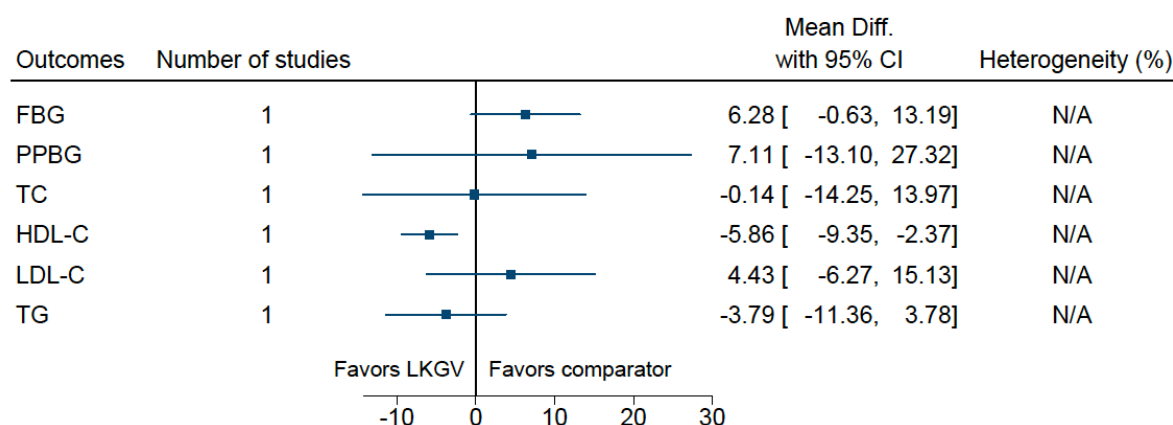
*Favors intervention/comparator as insulin sensitizer

Linum usitatissimum versus Plantago ovata (Ricklefs-Johnson 2017)

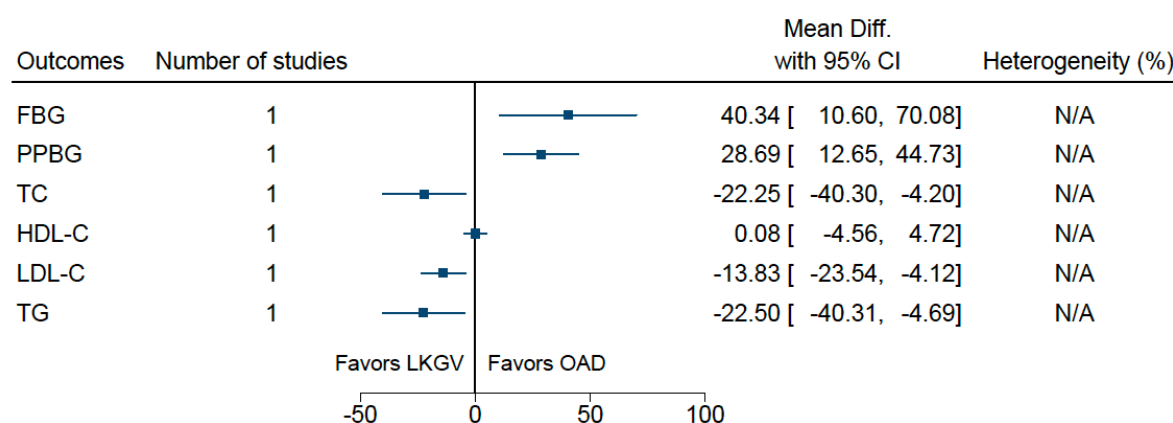


*Favors intervention/comparator as insulin sensitizer

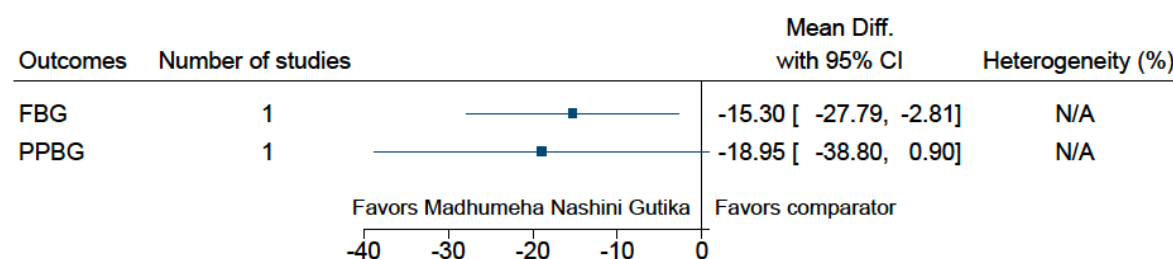
Lodhradi Kashaya Ghana Vati (Bramhankar 2017)



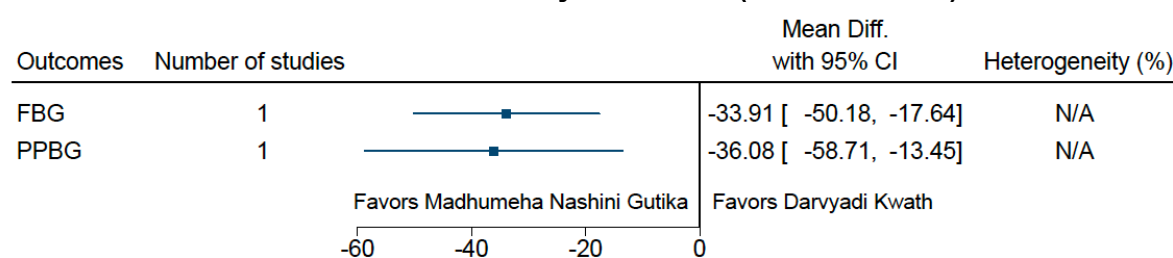
Lodhradi Kashaya Ghana Vati (versus OAD) (Bramhankar 2017)



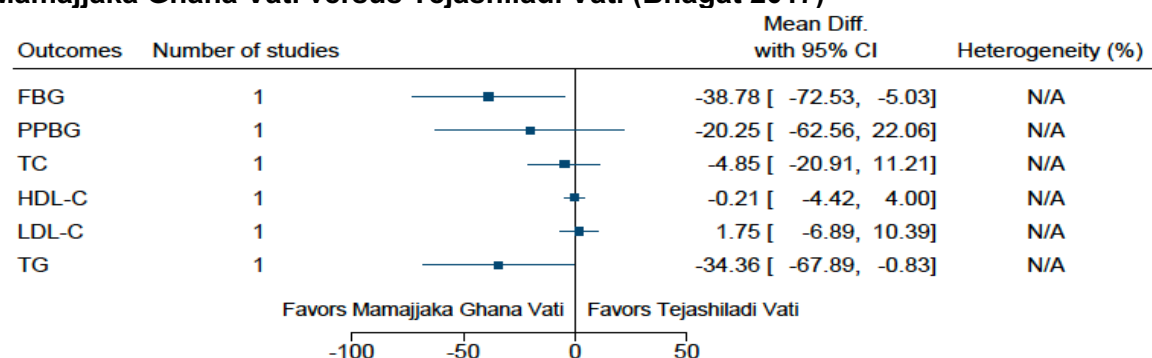
Madhumeha Nashini Gutika (Bhawana 2015)



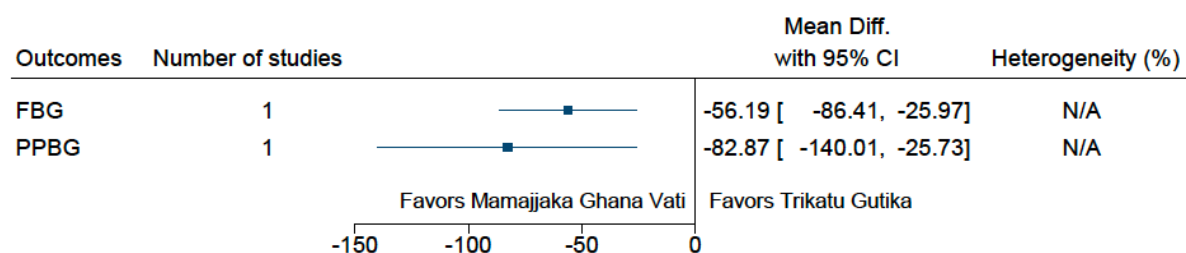
Madhumeha Nashini Gutika versus Darvyadi Kwatha (Bhawana 2015)



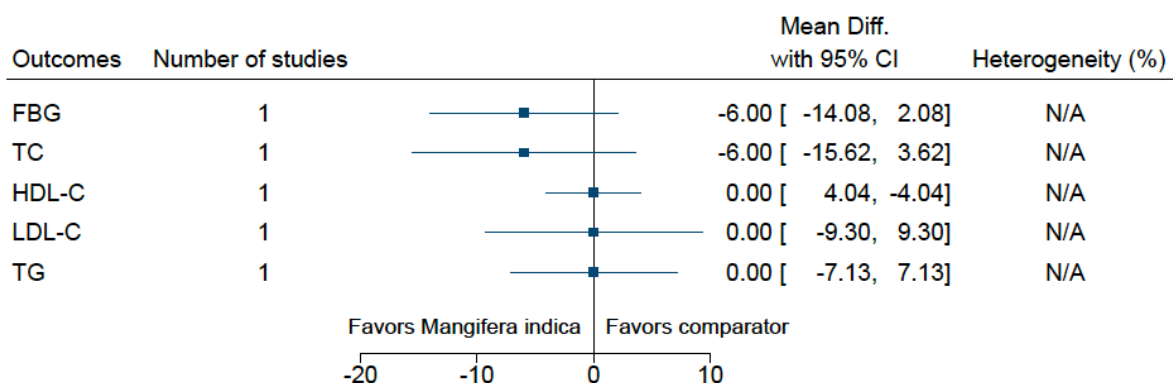
Mamajjaka Ghana Vati versus Tejashiladi Vati (Bhagat 2017)



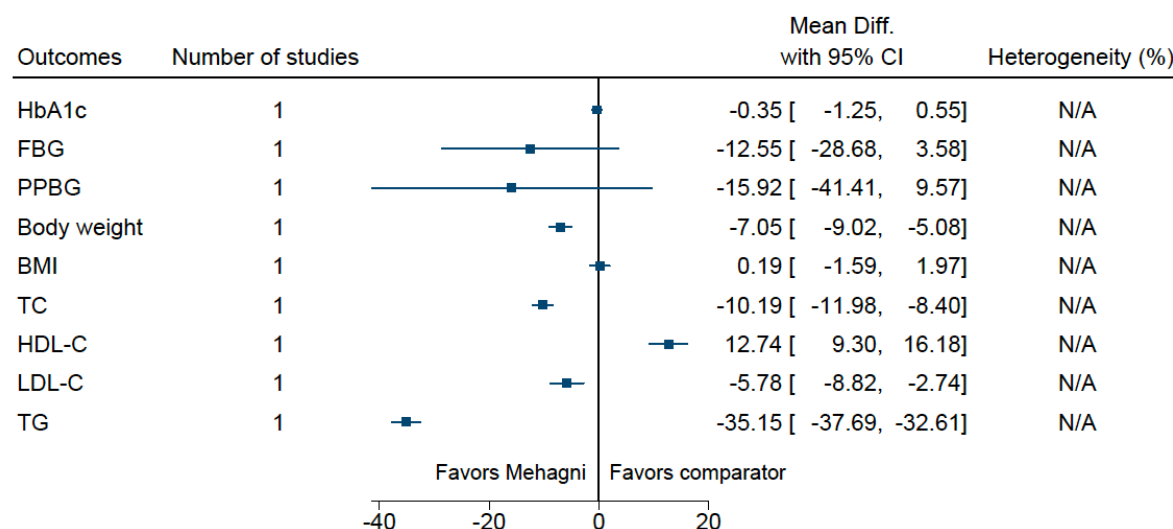
Mamajjaka Ghana Vati versus Trikatu Gutika (Kataria 2017)



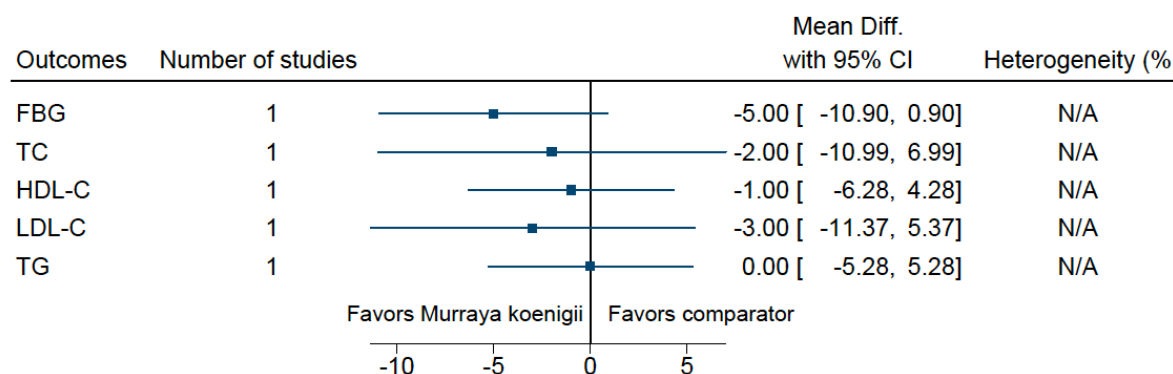
Mangifera indica (Balasubramaniam 2010)



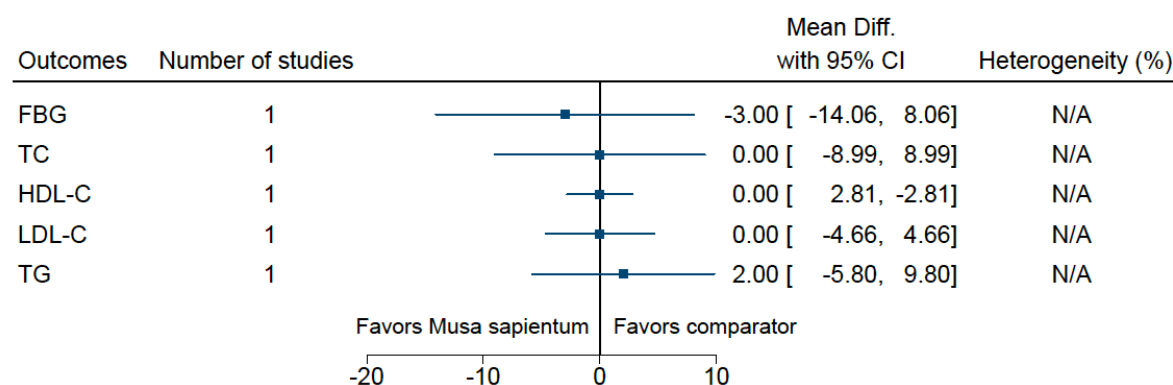
Mehagni (Gopalakrishna 2017)



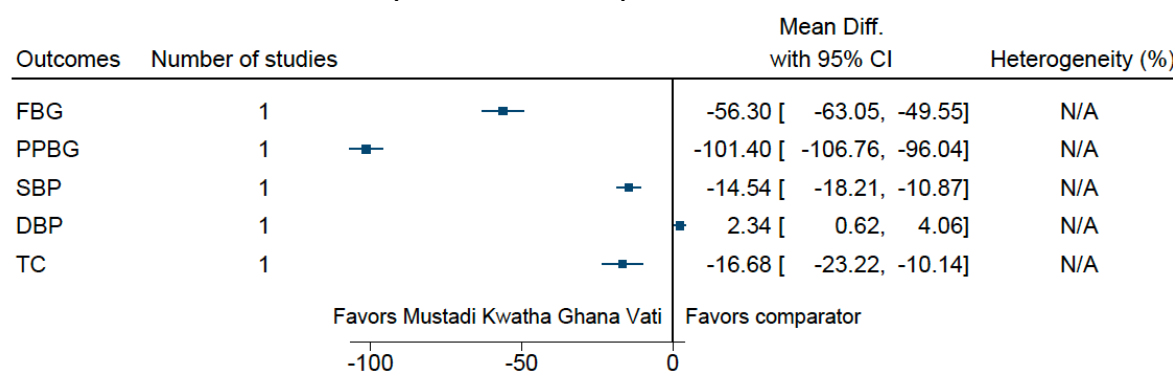
Murraya koenigii (Balasubramaniam 2010)



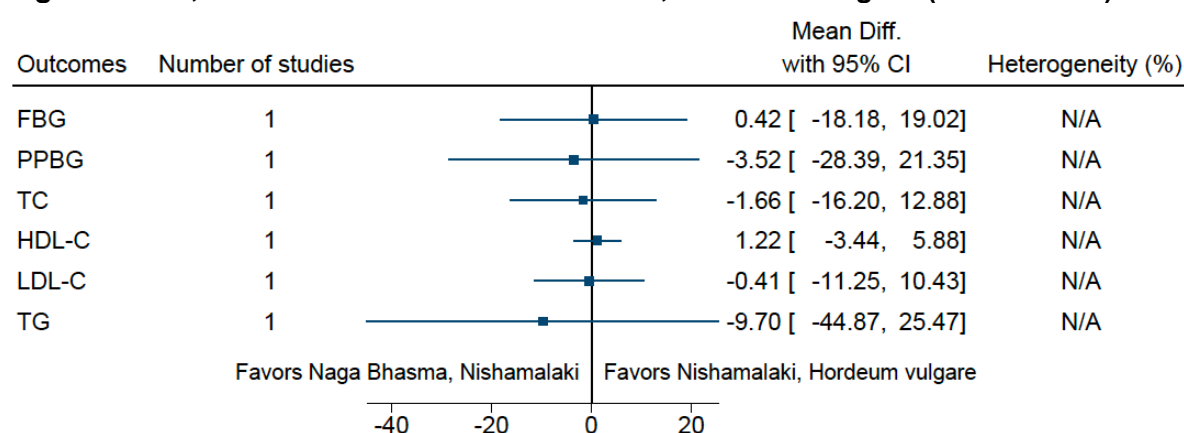
Musa sapientum (Balasubramaniam 2010)



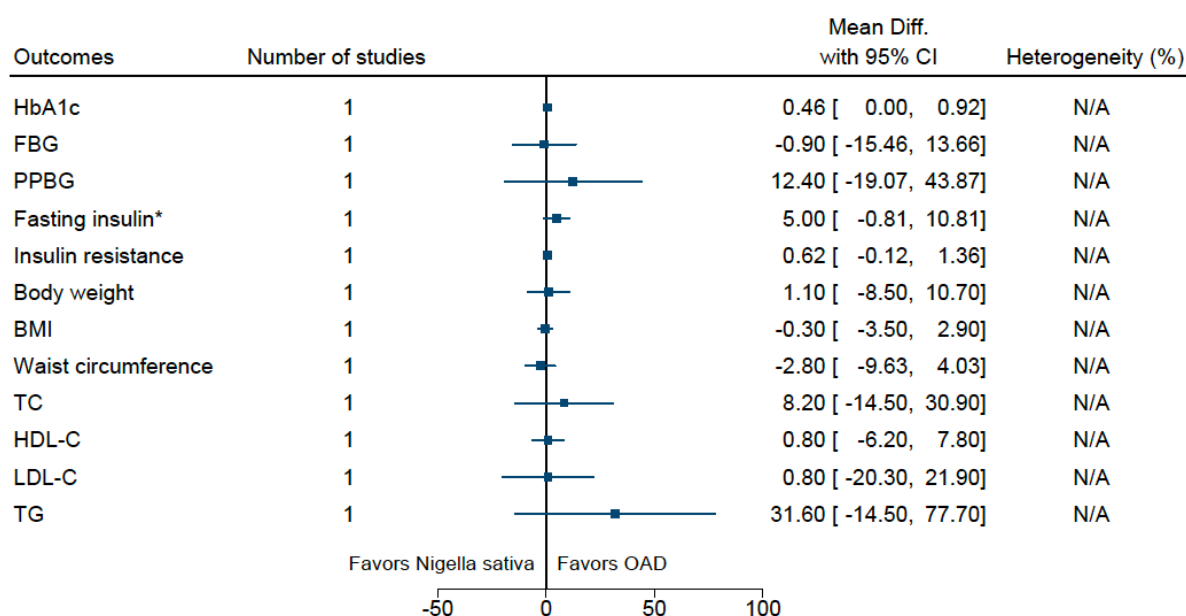
Mustadi Kwatha Ghana Vati (Kushwaha 2017)



Naga Bhasma, Nishamalaki versus Nishamalaki, *Hordeum vulgare* (Desale 2018)

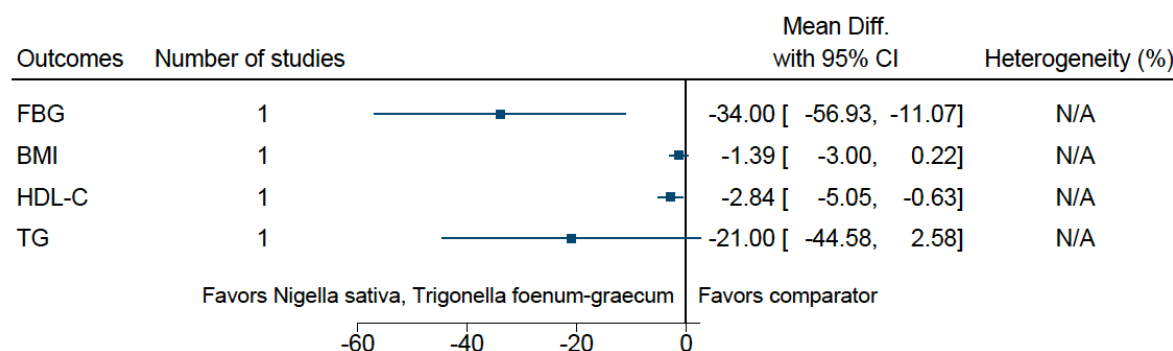


Nigella sativa (versus OAD) (Moustafa 2019)

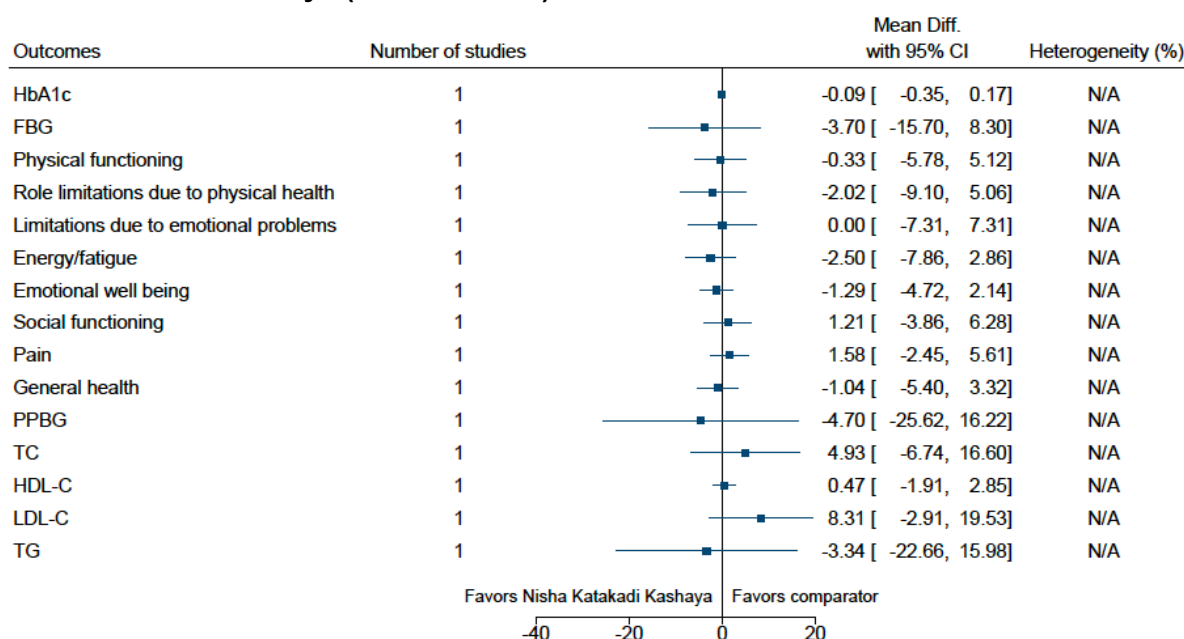


*Favors intervention/comparator as insulin sensitizer

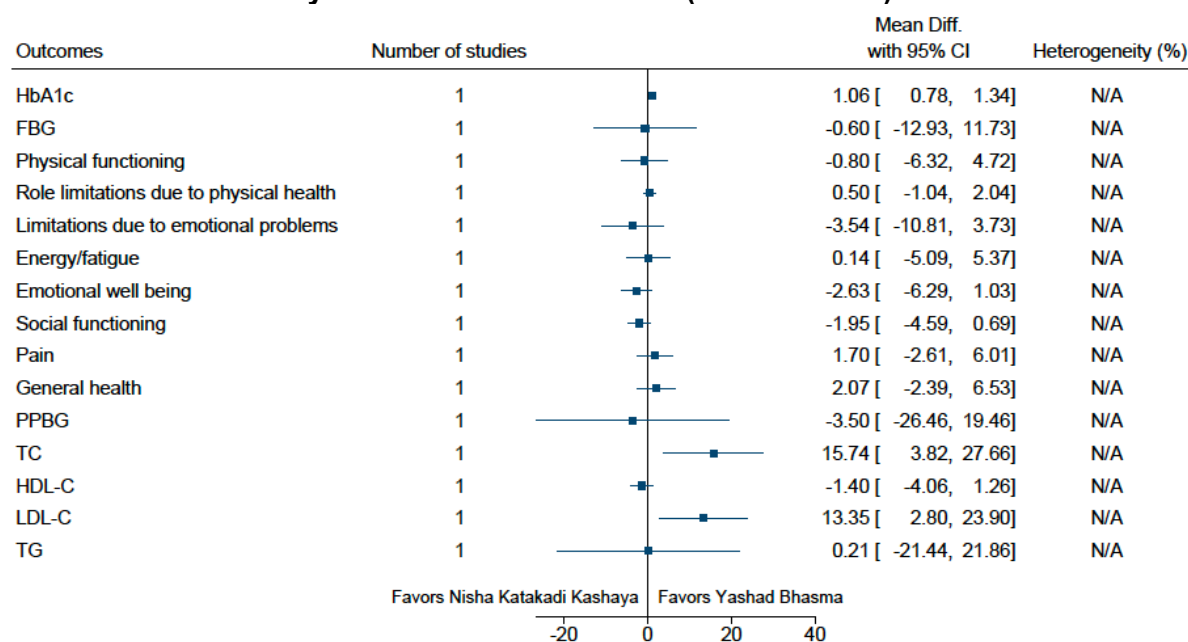
***Nigella sativa*, *Trigonella foenum-graecum* (Memon 2010a, Memon 2010b, Memon 2012)**



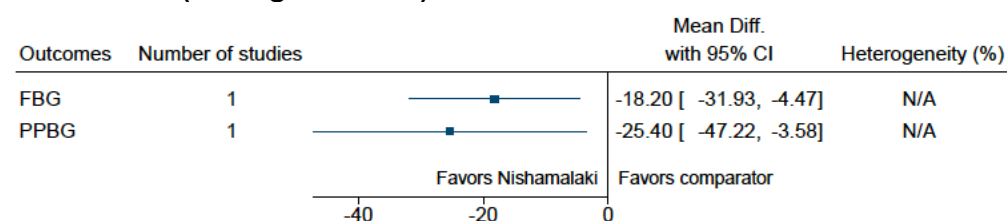
Nisha Katakadi Kashaya (Srinivas 2018)



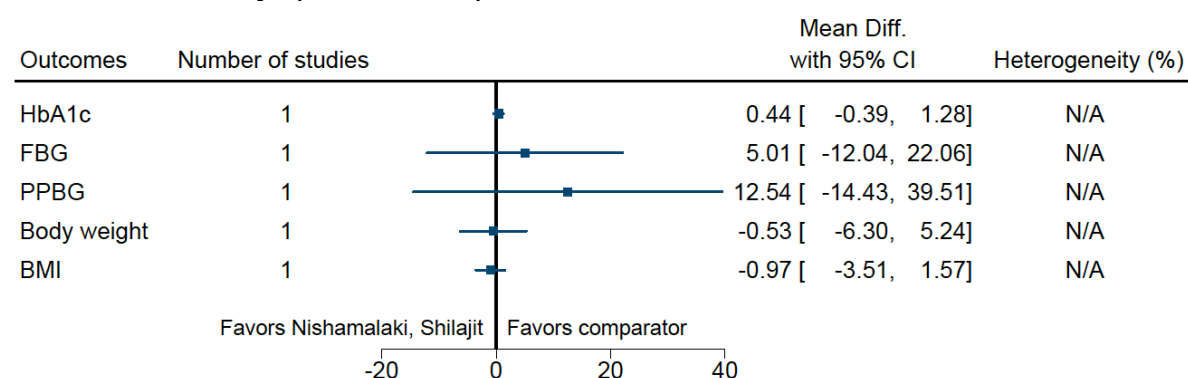
Nisha Katakadi Kashaya versus Yashad Bhasma (Srinivas 2018)



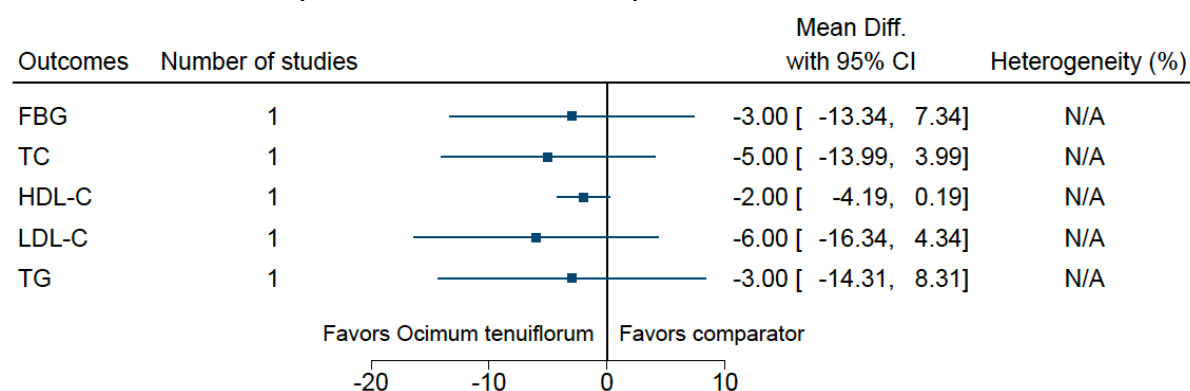
Nishamalaki (Samagandi 2012)



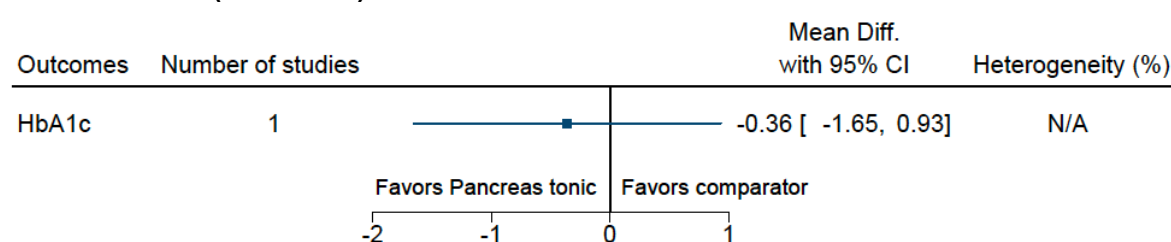
Nishamalaki, Shilajit (Paliwal 2018)



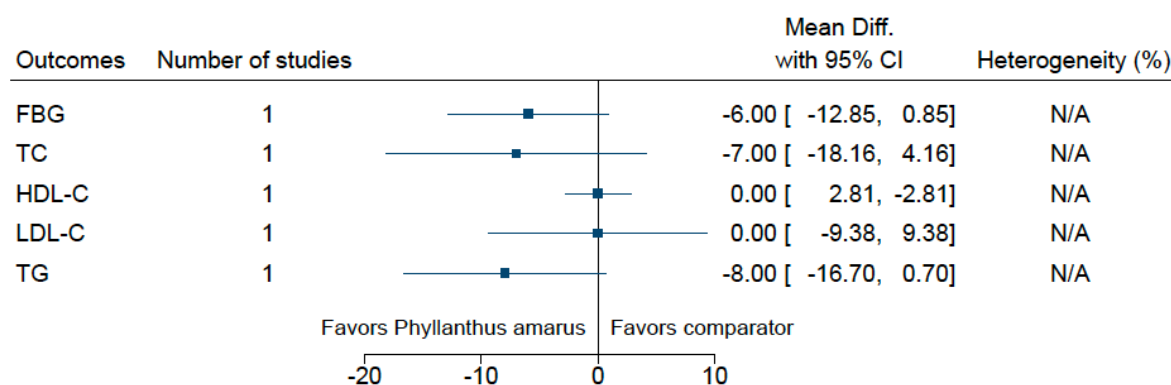
***Ocimum tenuiflorum* (Balasubramaniam 2010)**



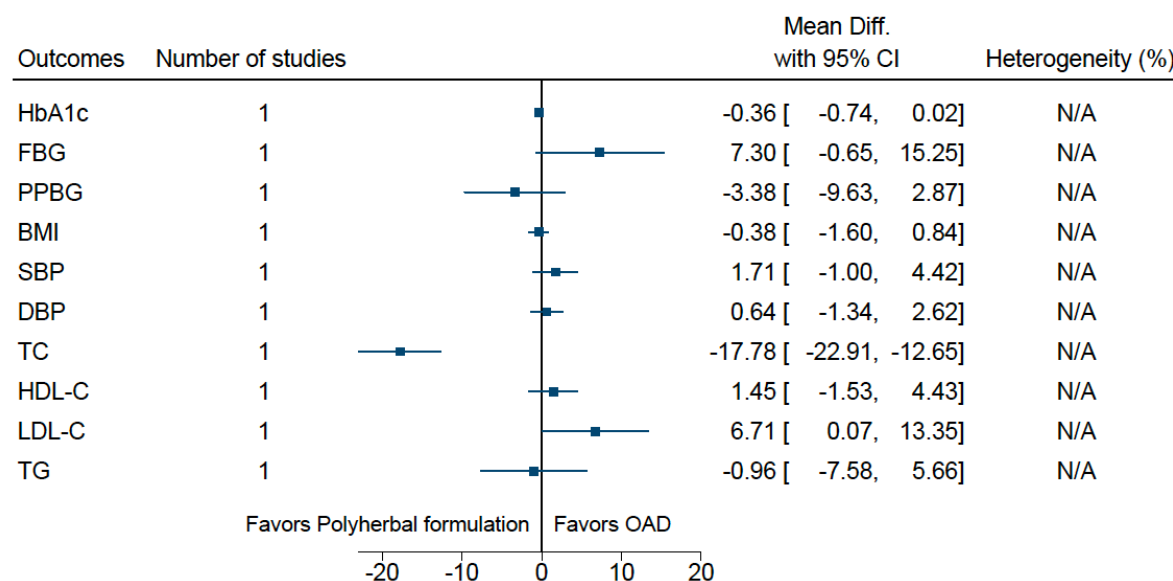
Pancreas tonic (Hsia 2004)



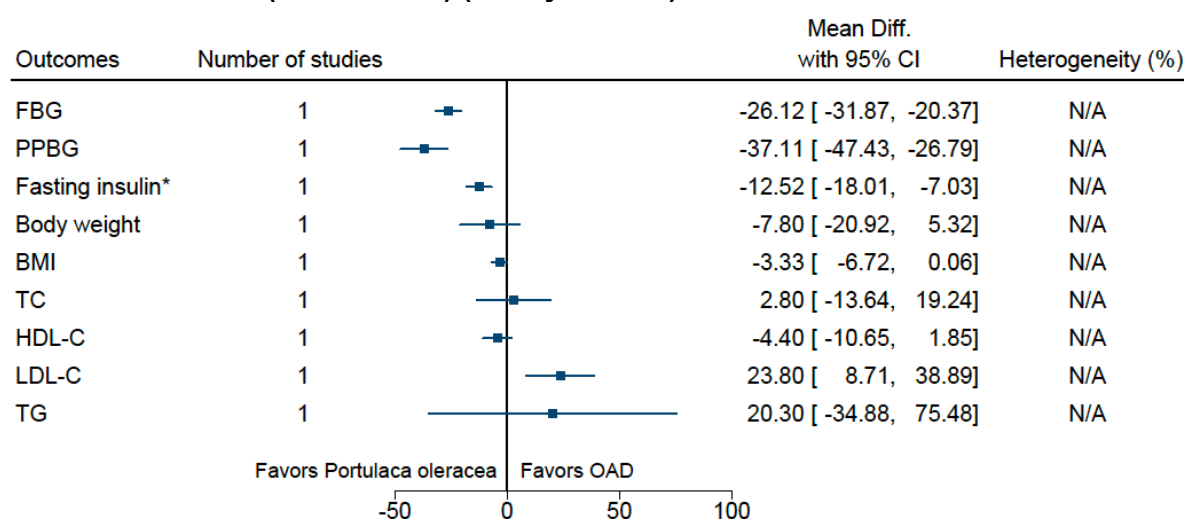
***Phyllanthus amarus* (Balasubramaniam 2010)**



Polyherbal formulation (Awasthi 2015)

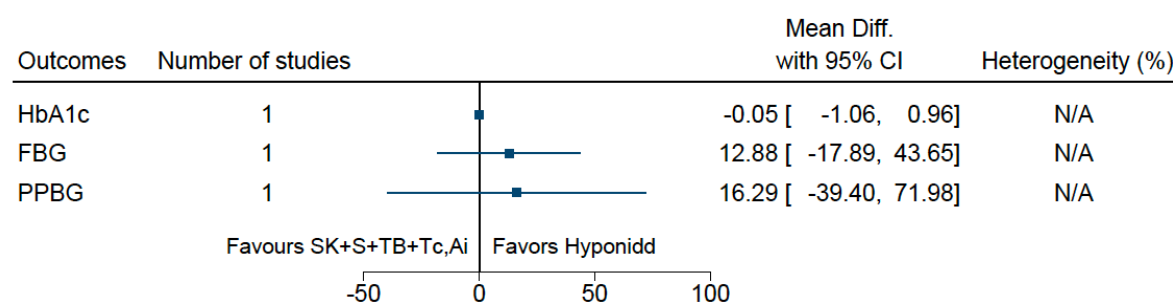


Portulaca oleracea (versus OAD) (El-Sayed 2011)

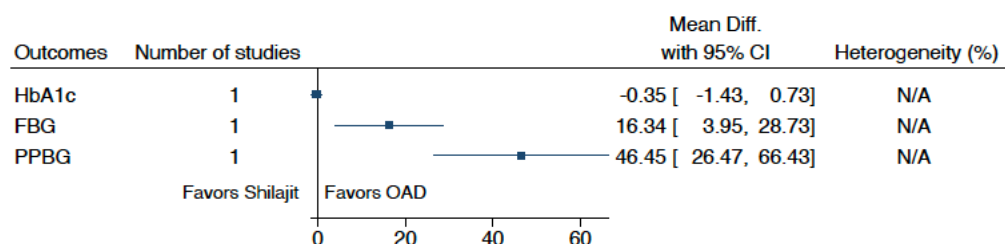


*Favors intervention/comparator as insulin sensitizer

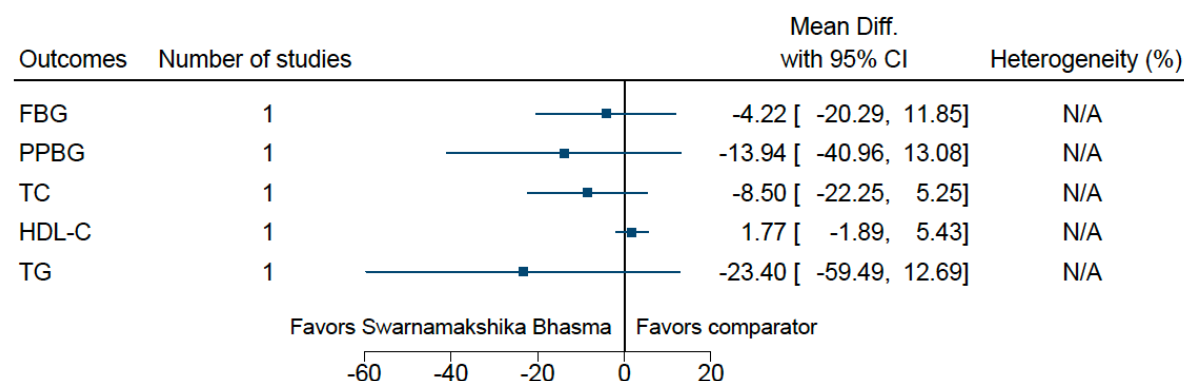
Salasaradi Kashaya+Shilajit+Trivanga Bhasma+Tinospora cordifolia, Azadirachta indica versus Hyponidd (Bhat 2012)



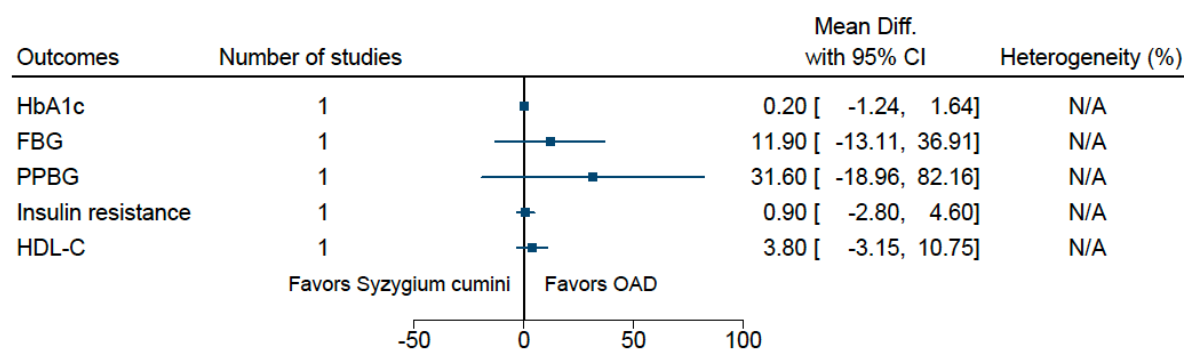
Shilajit (versus OAD) (Kumar 2014)



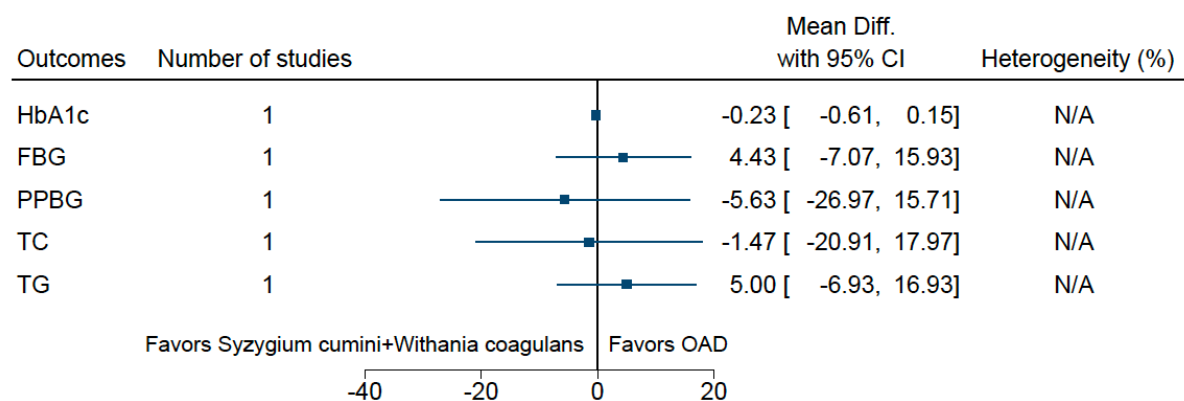
Swarnamakshika Bhasma (Taviad 2016)



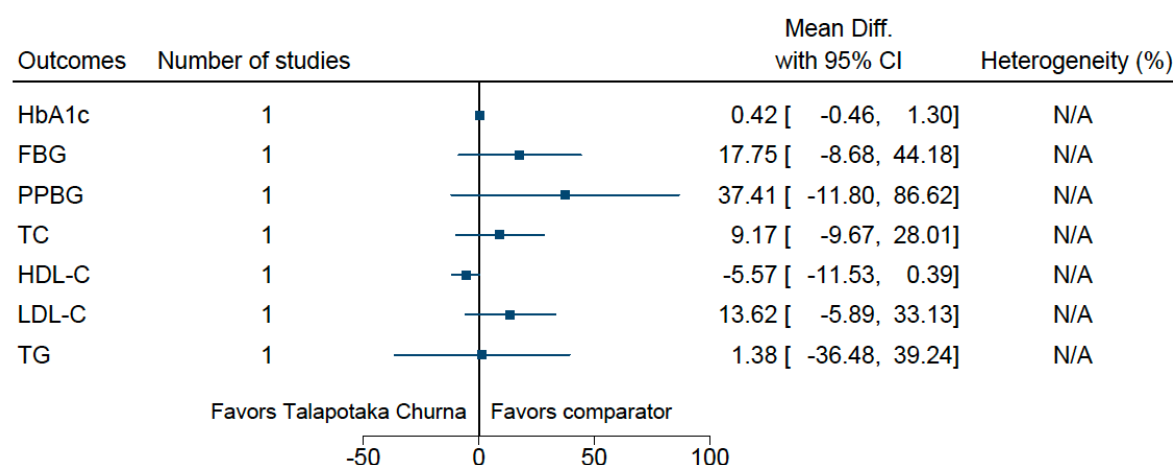
Syzygium cumini (versus OAD) (Sahana 2010)



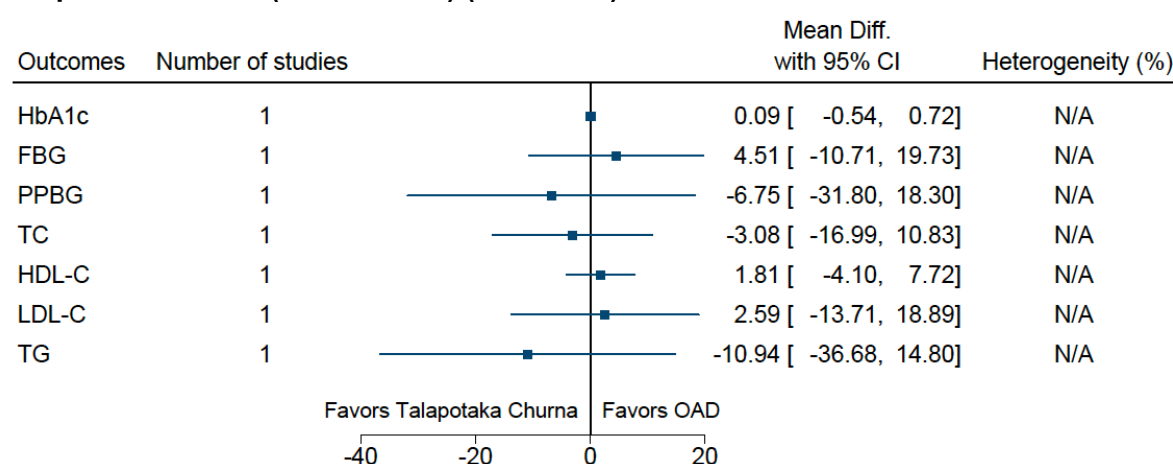
Syzygium cumini+Withania coagulans (Siddiqui 2017)



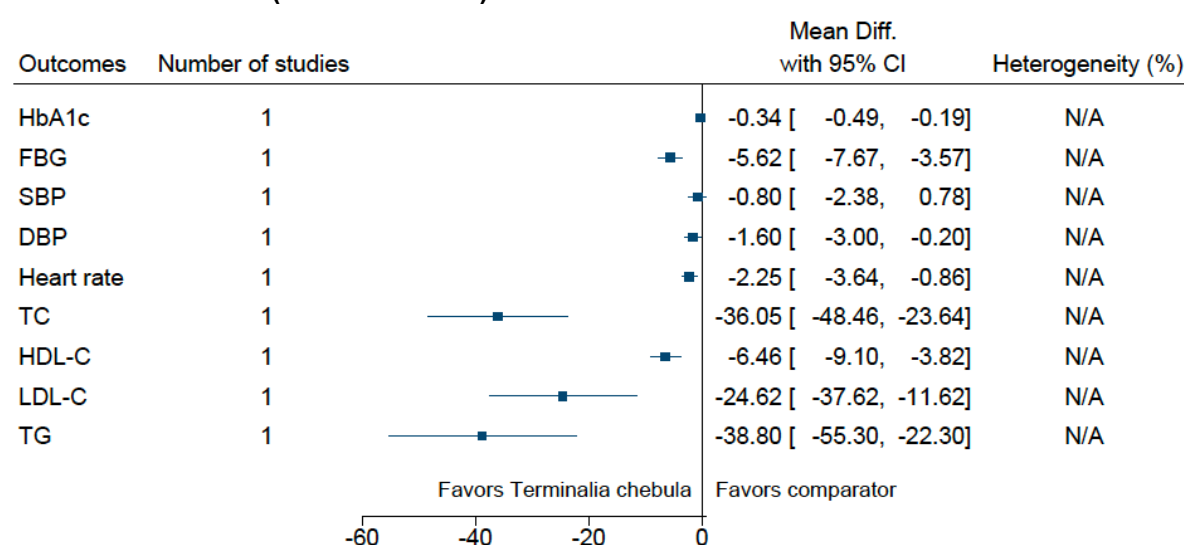
Talapotaka Churna (Nille 2018)



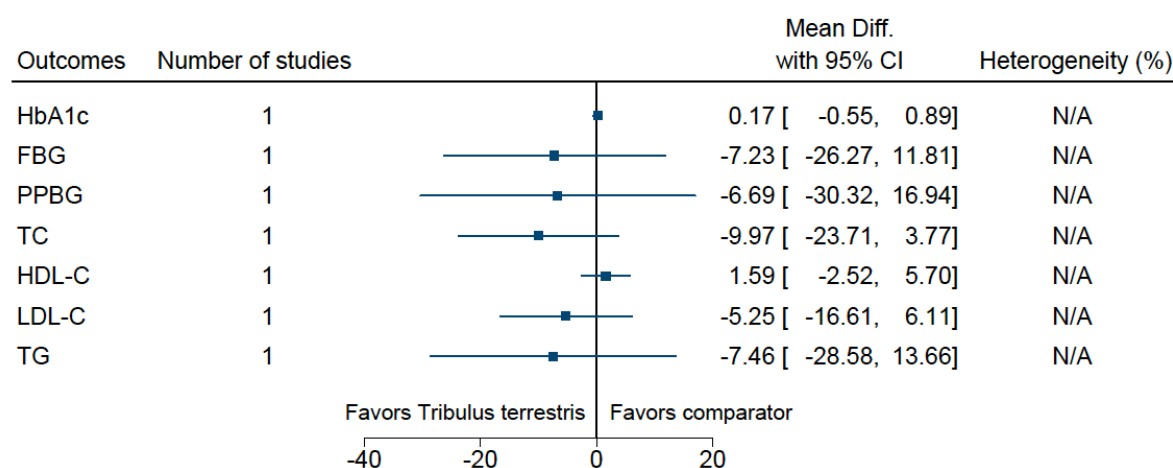
Talapotaka Churna (versus OAD) (Nille 2018)



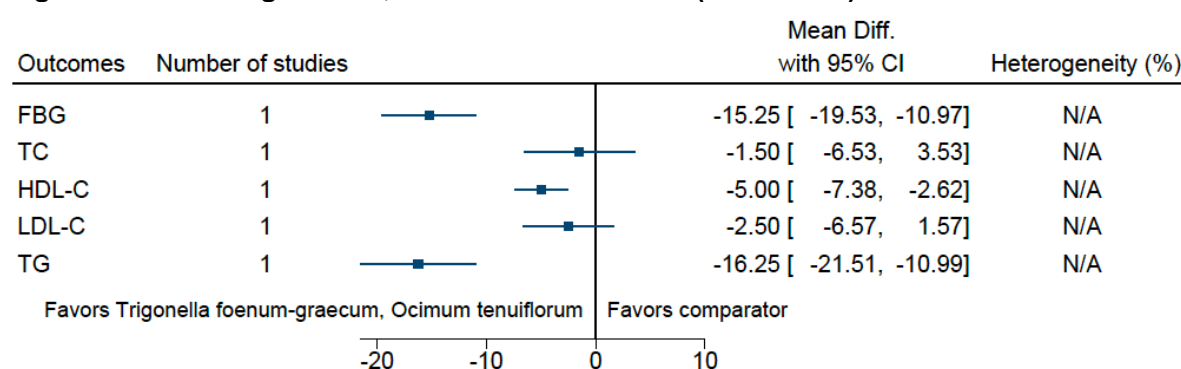
Terminalia chebula (Usharani 2020)



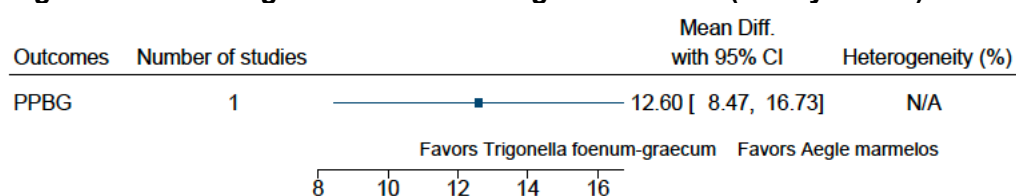
***Tribulus terrestris* (Samani 2016)**



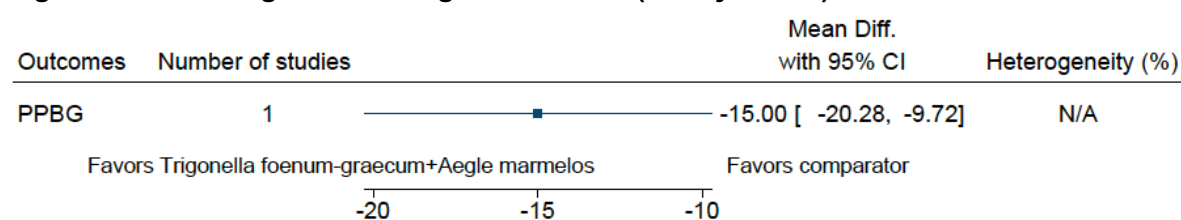
***Trigonella foenum-graecum, Ocimum tenuiflorum* (Mitra 2006)**



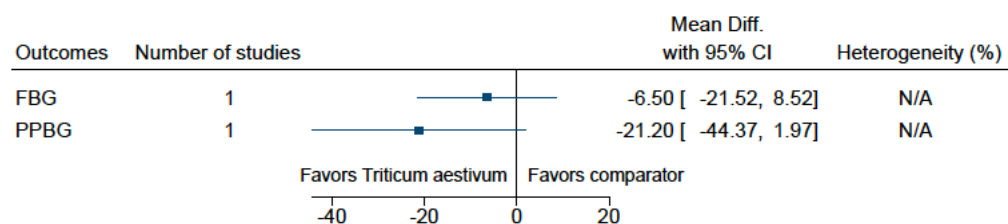
***Trigonella foenum-graecum* versus *Aegle marmelos* (Yaheya 2009)**



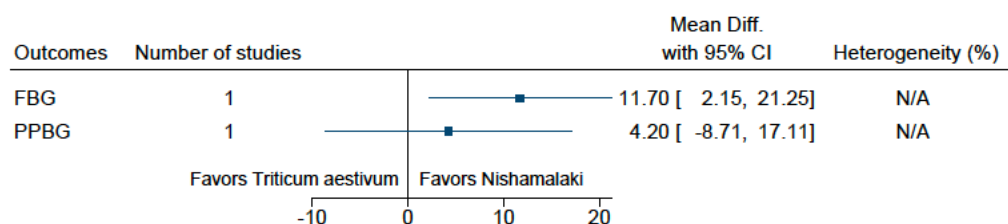
***Trigonella foenum-graecum*+*Aegle marmelos* (Yaheya 2009)**



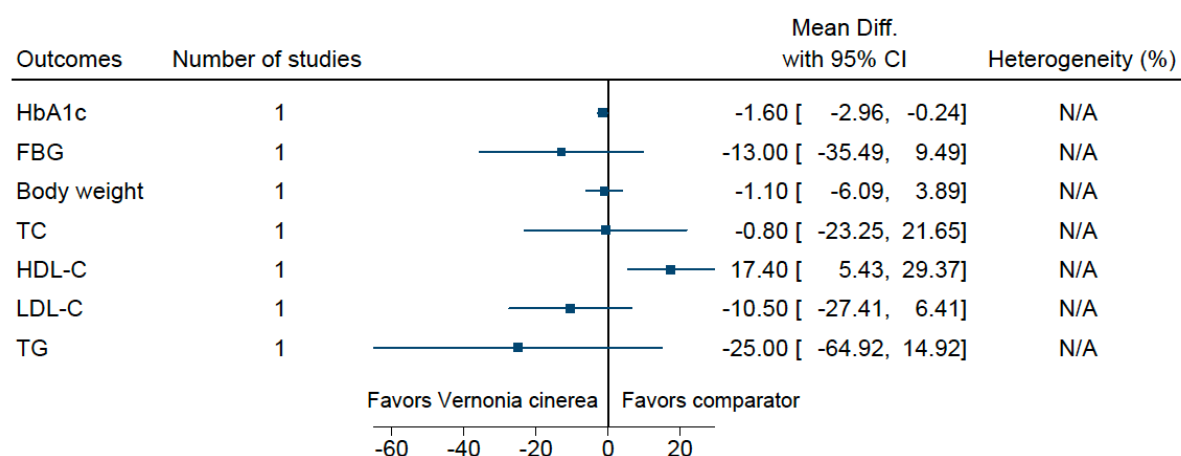
***Triticum aestivum* (Samagandi 2012)**



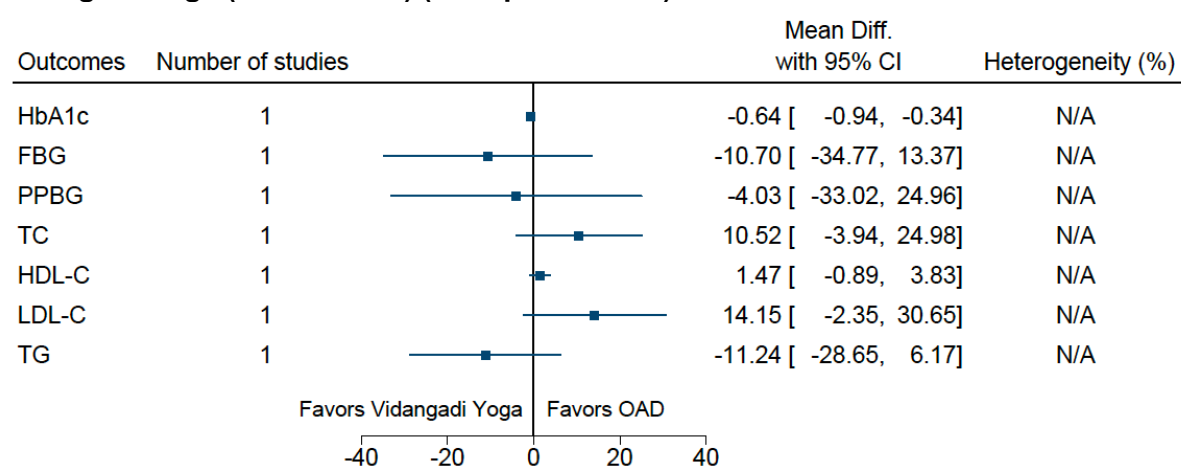
***Triticum aestivum* versus Nishamalaki (Samagandi 2012)**



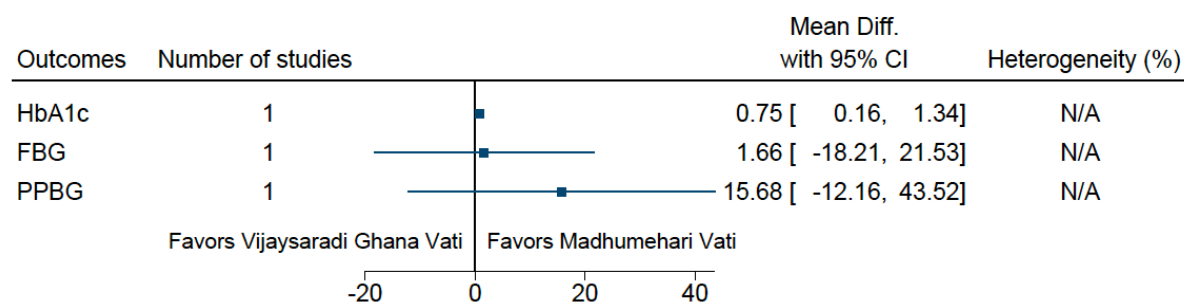
***Vernonia cinerea* (Sayeed 2013)**



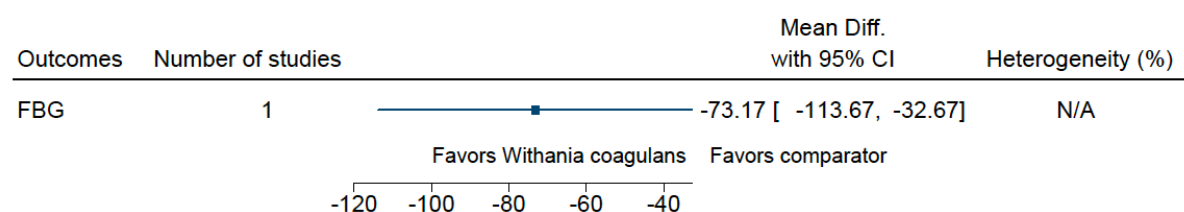
Vidangadi Yoga (versus OAD) (Deshpande 2018)



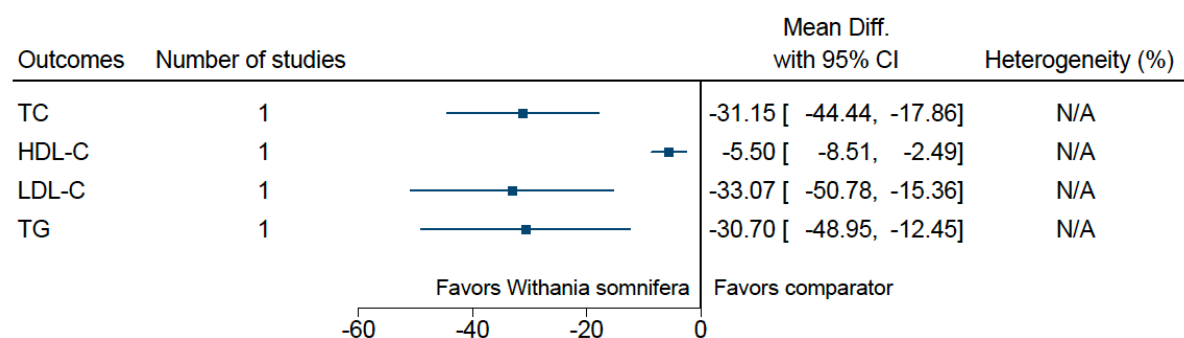
Vijaysaradi Ghana Vati versus Madhumehari Vati (Sharma 2018)



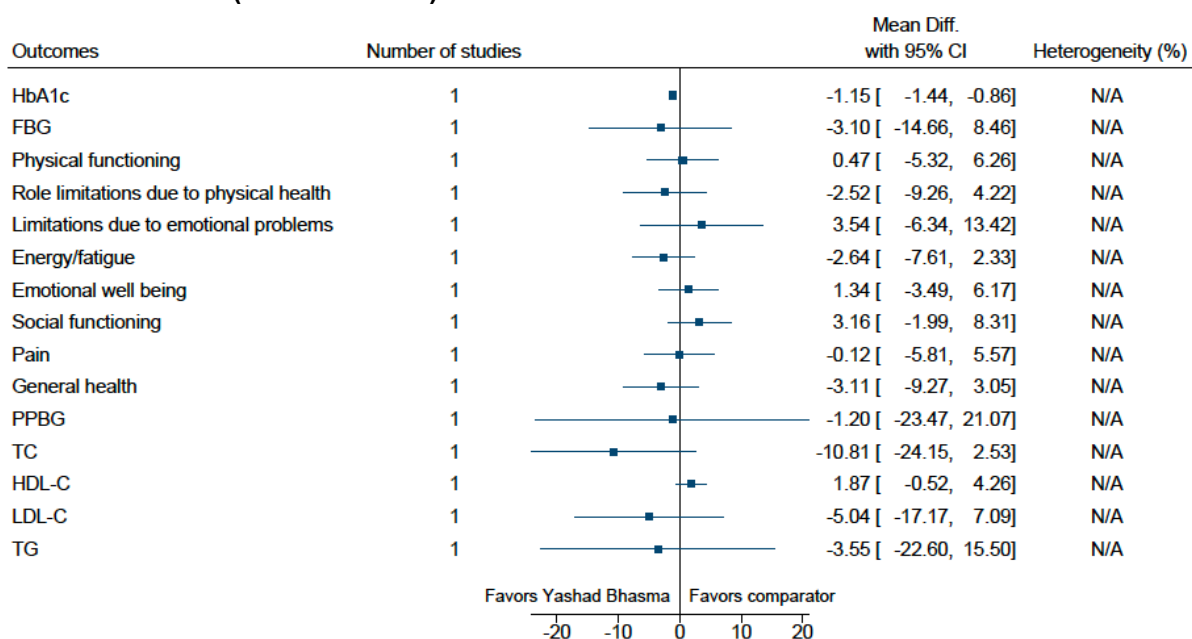
Withania coagulans (Hemalatha 2018)



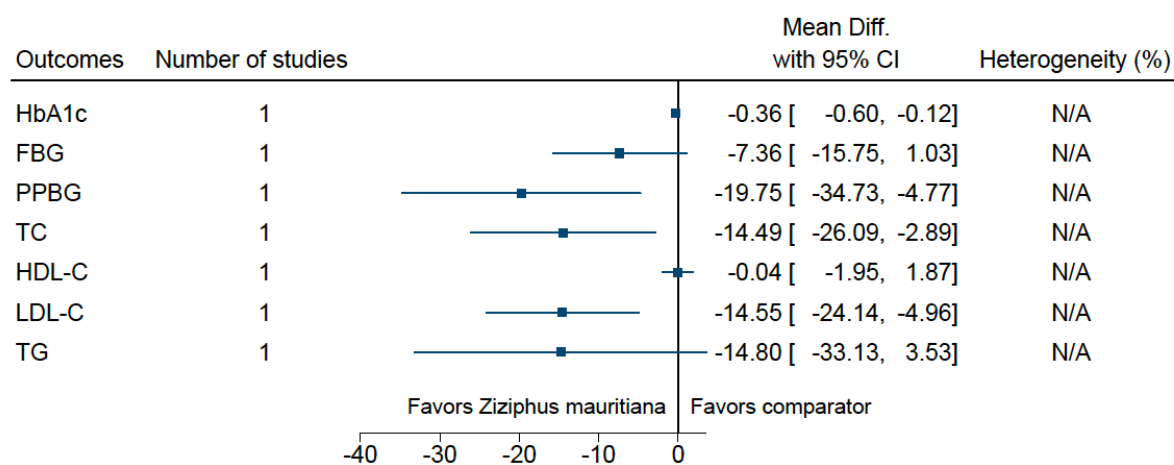
Withania somnifera (Usharani 2014)



Yashad Bhasma (Srinivas 2018)



***Ziziphus mauritiana* (Yazdanpanah 2017)**



Appendix S8: Adverse events and dropouts/withdrawals/discontinued interventions due to adverse events in the included studies.

Author and year	Study arms	Adverse events (including serious adverse events)	Dropouts/withdrawals/discontinued interventions due to adverse events (if mentioned)
Ayurvedic medicine- single plant- or mineral-origin ingredient			
<i>Abelmoschus esculentus</i>			
Moradi 2020	A1= <i>Abelmoschus esculentus</i>	0	
	A2=Placebo		
<i>Acacia Senegal</i>			
Babiker 2017, Babiker 2018	A1= <i>Acacia senegal</i>	Abdominal boating-6, Diarrhea-11, Discomfort with viscous sensation-32, Nausea-8	
	A2=Placebo		
<i>Aegle marmelos</i>			
Sankhla 2009	A1= <i>Aegle marmelos</i>		
	A2=Placebo		
Sharma 2013	A1= <i>Aegle marmelos</i>	0	
	A2=Placebo	0	
Nigam 2019	A1= <i>Aegle marmelos</i>	Exact names and numbers not provided	
	A2=No additional medicine?		
<i>Allium sativum</i>			
Ashraf 2005	A1= <i>Allium sativum</i>		Heart burn-1
	A2=Placebo		
Ashraf 2011a	A1= <i>Allium sativum</i>	Gastric discomfort-1	Heart burn-3
	A2=OAD		Vague abdominal discomfort-2, Weight loss-1
	A3=Placebo		
Ashraf 2011b	A1= <i>Allium sativum</i>	Gastric discomfort-1	Heart burn-1
	A2=Placebo		
Kumar 2013	A1= <i>Allium sativum</i>		
	A2=No additional medicine		
<i>Aloe vera</i>			
Arora 2009	A1= <i>Aloe vera</i>		Diarrhea-1, Vomiting-1
	A2=No additional medicine		
Huseini 2012a, Huseini 2012b	A1= <i>Aloe vera</i>	0	
	A2=Placebo	0	
Zarrintan 2015	A1= <i>Aloe vera</i>		
	A2=Placebo		
<i>Anethum graveolens</i>			
Mobasser 2014	A1= <i>Anethum graveolens</i>		
	A2=Placebo		
Haidari 2020	A1= <i>Anethum graveolens</i>		
	A2=Placebo		
<i>Azadirachta indica</i>			
Usharani 2020	A1= <i>Azadirachta indica</i>	Mild gastrointestinal disturbances-2	
	A2=Placebo		

Author and year	Study arms	Adverse events (including serious adverse events)	Dropouts/withdrawals/discontinued interventions due to adverse events (if mentioned)
Ayurvedic medicine- single plant- or mineral-origin ingredient			
Berberis aristata			
Sharma 2017	A1=Berberis aristata	Nausea-2.2%, Flatulence-1.1%, Diarrhea-3.3%, Constipation- 1.1%, Rash-2.2%, Headache-4.4%, Abdominal pain-4.4%, Metallic taste-3.3%	
	A2=No additional medicine		
Boswellia serrata			
Azadmehr 2014	A1=Boswellia serrata	0	
	A2=Placebo		
Mehrzadi 2018	A1=Boswellia serrata	0	
	A2=Placebo	0	
Camellia sinensis			
MacKenzie 2007	A1=Camellia sinensis	Profuse sweating after ingestion of a single dose of the medicine-1, Systemic rash-1	Profuse sweating after ingestion of a single dose of the medicine-1, Systemic rash-1
	A2=Placebo	0	
Mirzaei 2009	A1=Camellia sinensis		
	A2=Placebo		
Hsu 2011	A1=Camellia sinensis	Hypoglycemia-1, Mild constipation-2, Abdominal discomfort-2	Hypoglycemia-1
	A2=Placebo	Mild constipation-1, Abdominal discomfort-1	
Lasaite 2014	A1=Camellia sinensis		
	A2=Placebo		
Liu 2014	A1=Camellia sinensis	Epigastric dullness-1, Mild constipation-2	
	A2=Placebo	Abdominal discomfort-1	
Quezada-Fernández 2019	A1=Camellia sinensis		Insulin therapy-1
	A2=Placebo		Insulin therapy-1
Capparis spinosa			
Huseini 2013	A1=Capparis spinosa	0	
	A2=Placebo	0	
Cichorium intybus			
Chandra 2020	A1=Cichorium intybus		
	A2=Placebo		
Cinnamomum aromaticum			
Mang 2006	A1=Cinnamomum aromaticum		Weight change ≥5%-2, Serious disease (exact names not provided)-4
	A2=Placebo		
Suppakitiporn 2006	A1=Cinnamomum aromaticum	0	
	A2=Placebo	0	
Blevins 2007	A1=Cinnamomum aromaticum		OAD or lipid-lowering drug therapy amendment-5
	A2=Placebo		
Crawford 2009	A1=Cinnamomum aromaticum	Rash-1	Rash-1
	A2=No additional medicine	0	
Akilen 2010	A1=Cinnamomum aromaticum	0	
	A2=Placebo	Mild gastric upset-1	Insulin therapy-2
Wainstein 2011	A1=Cinnamomum aromaticum		

Author and year	Study arms	Adverse events (including serious adverse events)	Dropouts/withdrawals/discontinued interventions due to adverse events (if mentioned)
Ayurvedic medicine- single plant- or mineral-origin ingredient			
Lu 2012	A2=Placebo		
	A1= <i>Cinnamomum aromaticum</i>		
	A2=Placebo		
Sharma 2012	A1= <i>Cinnamomum aromaticum</i> ?	0	
	A2=Placebo	0	
Hasanzade 2013	A1= <i>Cinnamomum aromaticum</i>		
	A2=Placebo		
Tangvarasittichai 2015, Sengsuk 2016	A1= <i>Cinnamomum aromaticum</i>	0	
	A2=Placebo		
<i>Cinnamomum verum</i>			
Vafa 2012	A1= <i>Cinnamomum verum</i>	0	
	A2=Placebo	0	
Zahmatkesh 2012	A1= <i>Cinnamomum verum</i>	0	
	A2=Placebo	0	
Talaee 2017	A1= <i>Cinnamomum verum</i> ?		
	A2=Placebo		
Zare 2019	A1= <i>Cinnamomum verum</i> ?	0	
	A2=Placebo	Some allergic reaction-1	Some allergic reaction-1
Mirmiranpour 2020	A1= <i>Cinnamomum verum</i>	0	
	A2=Placebo	0	
<i>Citrullus colocynthis</i>			
Huseini 2009	A1= <i>Citrullus colocynthis</i>	Mild diarrhea-3	
	A2=Placebo		
Barghamdi 2016	A1= <i>Citrullus colocynthis</i>	0	
	A2=Placebo		
<i>Coccinia grandis</i>			
Kuriyan 2008, Kurpad 2008	A1= <i>Coccinia grandis</i>	Gastrointestinal tract symptoms (such as abdominal distention, flatulence, constipation, gastritis)-7, Mild hypoglycemic symptoms (such as perspiration, excessive hunger, slight dizziness) once or twice postprandially (midmorning)-17	
	A2=Placebo	Gastrointestinal tract symptoms (such as abdominal distention, flatulence, constipation, gastritis)-8	
Quamri 2017	A1= <i>Coccinia grandis</i>	0	
	A2=OAD	0	
Wasana 2021	A1= <i>Coccinia grandis</i>	0	
	A2=Placebo	0	
<i>Convolvulus prostratus</i>			
Patel 2012	A1= <i>Convolvulus prostratus</i>		
	A2=No additional medicine		
<i>Crocus sativus</i>			
Milajerdi 2018	A1= <i>Crocus sativus</i>		Headache-1

Author and year	Study arms	Adverse events (including serious adverse events)	Dropouts/withdrawals/discontinued interventions due to adverse events (if mentioned)
Ayurvedic medicine- single plant- or mineral-origin ingredient			
Aleali 2019	A2=Placebo		Headache-1
	A1= <i>Crocus sativus</i>		Allergy to medicine-2
	A2=Placebo		Allergy to medicine-2, Insulin therapy-2
Ebrahimi 2019	A1= <i>Crocus sativus</i>		Stomach problem-1
	A2=Placebo		Insulin therapy-2
Mobasser 2020	A1= <i>Crocus sativus</i>		
	A2=Placebo		
<i>Cuminum cyminum</i>			
Jafari 2017	A1= <i>Cuminum cyminum</i>		Medicine amendment-1, Gastrointestinal complaint-1
	A2=Placebo		Medicine amendment-1
Hendre 2020	A1= <i>Cuminum cyminum</i>		
	A2=No additional medicine		
<i>Curcuma longa</i>			
Usharani 2008	A1= <i>Curcuma longa</i>	Mild diarrhea-2	
	A2=Placebo		
Na 2013	A1= <i>Curcuma longa</i>		
	A2=Placebo		
Chuengsamarn 2014	A1= <i>Curcuma longa</i>	Hot flash-1, Constipation-2, Nausea-1	
	A2=Placebo	Hot flash-1, Constipation-1, Vertigo-1, Iching-1	
Panahi 2017, Panahi 2018	A1= <i>Curcuma longa</i>	0	
	A2=Placebo	0	
Adab 2019	A1= <i>Curcuma longa</i>		Medicine dose amendment-1, Insulin therapy-1
	A2=Placebo	0	
Adibian 2019	A1= <i>Curcuma longa</i>		Stomach discomfort-1
	A2=Placebo		Medicine amendment-1
Srinivasan 2019	A1= <i>Curcuma longa</i>	Increased frequency of stools-1, Upper abdominal pain-1	
	A2=Placebo	Fatigue-1, Sleepiness-2	Fatigue-1
de Sousa 2020	A1= <i>Curcuma longa</i>	0	
	A2=Placebo	0	
<i>Cyamopsis tetragonoloba</i>			
Uusitupa 1984	A1= <i>Cyamopsis tetragonoloba</i>	Exact names not provided-2 (related)	Exact names not provided-2 (related)
	A2=Placebo		
Uusitupa 1989	A1= <i>Cyamopsis tetragonoloba</i>	Flatulence-7, Heartburn-1	
	A2=Placebo	Flatulence-1, Diarrhea-1	
<i>Eclipta prostrata</i>			
Sazia 2015, Sazia 2015	A1= <i>Eclipta prostrata</i>		
	A2=OAD		
	A3=No medicine		
<i>Elettaria cardamomum</i>			
Aghasi 2019	A1= <i>Elettaria cardamomum</i>	Dysuria-1, Mild skin inflammation-1	Medicine amendment-3

Author and year	Study arms	Adverse events (including serious adverse events)	Dropouts/withdrawals/discontinued interventions due to adverse events (if mentioned)
Ayurvedic medicine- single plant- or mineral-origin ingredient			
	A2=Placebo	0	Sudden increase in blood glucose level-1
Emblica officinalis			
Usharani 2013	A1=Emblica officinalis	Dyspepsia-3	
	A2=Placebo	0	
Enicostemma axillare			
Shankarrao 2017	A1=Enicostemma axillare		
	A2=OAD		
Gynostemma pentaphyllum			
Huyen 2010	A1=Gynostemma pentaphyllum	0	
	A2=Placebo	0	
Huyen 2012	A1=Gynostemma pentaphyllum	0	
	A2=Placebo	0	
Hibiscus sabdariffa			
Sarbini 2019	A1=Hibiscus sabdariffa		OAD dose/type amendment-1, Hospitalization due to illness-1?
	A2=Placebo		
Ipomoea batatas			
Ludvik 2004	A1=Ipomoea batatas	A1=Exact names not provided-16 (relation could not be excluded-6); A2=Exact names not provided-14 (relation could not be excluded-2); Most common in A1 and A2=Mild gastrointestinal issues (constipation, gastric pain, meteorism)	
	A2=Placebo		
Ludvik 2008	A1=Ipomoea batatas	A1=Exact names not provided-96; A2=Exact names not provided-120; Most common in A1 and A2=Nausea-3, Tympanites or diarrhea-3	
	A2=Placebo		
Juglans regia			
Hosseini 2014a	A1=Juglans regia	0	
	A2=Placebo	0	
Hosseini 2014b	A1=Juglans regia	Mild adverse events (such as diarrhea, vertigo, anxiety)-11	
	A2=Placebo	Mild adverse events (such as diarrhea, vertigo, anxiety)-4	
Abdoli 2017	A1=Juglans regia	0	
	A2=Placebo		
Zibaeenezhad 2016, Zibaeenezhad 2017	A1=Juglans regia	Gastrointestinal oil intolerance-2	Gastrointestinal oil intolerance-2?
	A2=Placebo?	0	
Rabiei 2018	A1=Juglans regia		OAD amendment and other reasons-5
	A2=Placebo		OAD amendment and other reasons-6
Linum usitatissimum			
Barre 2008	A1=Linum usitatissimum		
	A2=Placebo		
Hashemzadeh 2017	A1=Linum usitatissimum	0	
	A2=Placebo		

Author and year	Study arms	Adverse events (including serious adverse events)	Dropouts/withdrawals/discontinued interventions due to adverse events (if mentioned)
Ayurvedic medicine- single plant- or mineral-origin ingredient			
<i>Momordica charantia</i>			
Dans 2007	A1= <i>Momordica charantia</i>	Diarrhea and epigastric pain-1, Diarrhea-2, Hospitalization due to gastroenteritis-1, Hospitalization due to cholecystolithiasis-1 (unrelated), Chest pain-1, Urinary incontinence-1, Fever-1	Diarrhea and epigastric pain-1
	A2=Placebo	Diarrhea-1	
Zänker 2012	A1= <i>Momordica charantia</i>		OAD amendment-6, Insulin therapy-2, OAD amendment and lost body weight-1, Lipid-lowering drug therapy amendment-5
	A2=Placebo		
Trakoon-osot 2013	A1= <i>Momordica charantia</i>	Mild diarrhea-5, Flatulence-8	
	A2=Placebo	Flatulence-2	
Rahman 2015	A1= <i>Momordica charantia</i>	Hyperacidity/heart burn-8, Anorexia-10, Nausea-5, Diarrhea-3, Appetite-7, Abdominal discomfort-2, Headache-13, Dizziness-3, Skin rash-2	
	A2=OAD	Hyperacidity/heart burn-1, Anorexia-3, Nausea-1, Appetite-3, Headache-5, Dizziness-2, Skin rash-2	
Suthar 2016a	A1= <i>Momordica charantia</i>	0	
	A2=Placebo	0	
Suthar 2016b	A1= <i>Momordica charantia</i>	22 mild or moderate treatment emergent adverse events (exact names not provided)-14 (mostly unrelated) Hypotension-1 (unrelated)	Blood glucose level >270 mg/dL-2
	A2=OAD	9 mild or moderate treatment emergent adverse events (exact names not provided)-7 (mostly unrelated) Pyrexia-1 (unrelated)	
Cortez-Navarrete 2018	A1= <i>Momordica charantia</i>	Headache and dizziness-33.3%, Nausea-16.7%, Vomiting-8.3%, Constipation-8.3%	
	A2=Placebo	Headache-25%, Constipation-16.7%, Abdominal distension-16.7%, Dizziness-8.3%, Nausea-8.3%	
Kumari 2018	A1= <i>Momordica charantia</i>	Mild gastrointestinal discomfort such as transient dyspepsia and diarrhea-2	
	A1=Placebo	0	
Amini 2020	A1= <i>Momordica charantia</i>		
	A2=Placebo		
Kim 2020	A1= <i>Momordica charantia</i>	Anorexia/nausea-2, Abdominal discomfort-3, Diarrhea-1, Constipation-2, Foamy urine-1, Skin rash-1	Exact names not provided and other reasons-14
	A2=Placebo	Anorexia/nausea-1, Abdominal discomfort-2, Epigastric soreness-1, Foamy urine-1, Skin rash-1	Exact names not provided and other reasons-6
<i>Nigella sativa</i>			

Author and year	Study arms	Adverse events (including serious adverse events)	Dropouts/withdrawals/discontinued interventions due to adverse events (if mentioned)
Ayurvedic medicine- single plant- or mineral-origin ingredient			
Najmi 2012	A1= <i>Nigella sativa</i>	0	
	A2=No additional medicine	0	
Hosseini 2013	A1= <i>Nigella sativa</i>	Mild transient nausea-4	
	A2=Placebo	0	
Hadi 2015	A1= <i>Nigella sativa</i>		Insulin therapy-1?
	A2=Placebo		Insulin therapy-3?
Heshmati 2015	A1= <i>Nigella sativa</i>	Mild gastrointestinal problems-Exact numbers not provided	Medicine amendment-1, Stomach ache-1
	A2=Placebo		Stomach ache-2
Kaatabi 2015	A1= <i>Nigella sativa</i>	0	
	A2=Placebo		Uncomfortable with stool color-4, Nausea-2
Moustafa 2019	A1= <i>Nigella sativa</i>		Nausea-2
	A2=OAD		Gastrointestinal tract upset-3, OAD amendment-1
Kooshki 2020	A1= <i>Nigella sativa</i>	0	
	A2=Placebo	0	
Jangjo-Borazjani 2021	A1= <i>Nigella sativa</i>		
	A2=Placebo		
<i>Plantago ovata</i>			
Ziai 2005	A1= <i>Plantago ovata</i>	Flatulence-4, Diarrhea-1, Constipation-1, Reduced flushing-11	
	A2=Placebo	Flatulence-13, Diarrhea-1, Constipation-1	Exact names not provided-5
Feinglos 2013	A1= <i>Plantago ovata</i>	A1 and A2=Exact names not provided-Distributed approximately equally (80–88% of participants in each arm); A2=Transient symptoms consistent with episodes of hypoglycemia-2 (they were on OAD as well)	Exact names not provided-2
	A2=Placebo		
Abutair 2016	A1= <i>Plantago ovata</i>		
	A2=No additional medicine?		
<i>Portulaca oleracea</i>			
El-Sayed 2011	A1= <i>Portulaca oleracea</i>		
	A2=OAD		
Farzanegi 2014	A1= <i>Portulaca oleracea</i>		
	A2=Placebo		
Dehghan 2016	A1= <i>Portulaca oleracea</i>		
	A2=Placebo		
Wainstein 2016	A1= <i>Portulaca oleracea</i>	Acute bronchitis-1 (unrelated), Constipation-1 (probably related), electrocardiogram (ECG) changes-1 (not assessable), Uncontrolled hypertension-1 (not assessable), Vision disturbance-1 (unrelated)	Exact name not provided-1
	A2=Placebo	Elevated blood glucose level-1 (probably related), Influenza-1 (unrelated), Abnormal liver enzyme levels-1 (unrelated)	
<i>Pterocarpus marsupium</i>			

Author and year	Study arms	Adverse events (including serious adverse events)	Dropouts/withdrawals/discontinued interventions due to adverse events (if mentioned)
Ayurvedic medicine- single plant- or mineral-origin ingredient			
Hariharan 2005	A1= <i>Pterocarpus marsupium</i>	0	
	A2=OAD		Dizziness on fasting-1, Insulin therapy-1
<i>Punica granatum</i>			
Faghihimani 2016	A1= <i>Punica granatum</i>	Rash and itching-2, Gastrointestinal upset-1, Hospitalization due to upper gastrointestinal bleeding-1?	Rash and itching-2, Gastrointestinal upset-1, Hospitalization due to upper gastrointestinal bleeding-1?
	A2=Placebo	Headache-1, Mild abdominal pain-2	Headache-1, Mild abdominal pain-2
Babaeian 2013	A1= <i>Punica granatum</i>		Intolerance-2
	A2=Placebo		
Sohrab 2014, Sohrab 2015	A1= <i>Punica granatum</i>		Stomach discomfort-1
	A2=Placebo		Medicine amendment-1
Khajebishak 2019a, Khajebishak 2019b	A1= <i>Punica granatum</i>	0	
	A2=Placebo		
Grabež 2020	A1= <i>Punica granatum</i>		
	A2=Placebo		
Hashemi 2020	A1= <i>Punica granatum</i>	0	
	A2=Placebo	0	
<i>Sesamum indicum</i>			
Shahi 2017	A1= <i>Sesamum indicum</i>		Insulin therapy-2
	A2=Placebo		Medicine dose/type amendment-2
Aslam 2018	A1= <i>Sesamum indicum</i>		
	A2=Placebo		
<i>Shilajit</i>			
Narasimha Raju 2016	A1= Shilajit		
	A2=Placebo		
Niranjan 2016	A1=Shilajit	Mild headache-3	
	A2=Placebo	Dyspepsia-2	
<i>Syzygium cumini</i>			
Sahana 2010	A1= <i>Syzygium cumini</i>		Uncontrolled blood glucose level-2
	A2=OAD		
	A3=No medicine		
Sidana 2016, Sidana 2017	A1= <i>Syzygium cumini</i>		
	A2=Placebo		
<i>Terminalia chebula</i>			
Usharani 2020	A1= <i>Terminalia chebula</i>	Dyspepsia-3	
	A2=Placebo	Mild headache-3	
<i>Tinospora cordifolia</i>			
Mishra 2015	A1= <i>Tinospora cordifolia</i>	0	
	A2=No additional medicine		
Roy 2015	A1= <i>Tinospora cordifolia</i>	0	
	A2=No additional medicine	0	
<i>Tribulus terrestris</i>			

Author and year	Study arms	Adverse events (including serious adverse events)	Dropouts/withdrawals/discontinued interventions due to adverse events (if mentioned)
Ayurvedic medicine- single plant- or mineral-origin ingredient			
Samani 2016	A1= <i>Tribulus terrestris</i>	0	
	A2=Placebo	0	
<i>Trigonella foenum-graecum</i>			
Gupta 2001	A1= <i>Trigonella foenum-graecum</i>	Dyspepsia and mild abdominal distension-5	
	A2=Placebo		
Lu 2008	A1= <i>Trigonella foenum-graecum</i>	Stomach discomfort and nausea-2, Diarrhea-1	
	A2=Placebo		
Ansari 2011	A1= <i>Trigonella foenum-graecum</i>		
	A2=No additional medicine		
Rafraf 2014	A1= <i>Trigonella foenum-graecum</i>	0	
	A2=Placebo	0	
Suchitra 2015	A1= <i>Trigonella foenum-graecum</i>	0	
	A2=No additional medicine	0	
Kaur 2016	A1= <i>Trigonella foenum-graecum</i>	Mild diarrhea-1, Flatulence-1, Mild nausea/vomiting-1, Mild facial swelling-1, Mild itching-1	
	A2=No additional medicine	0	
Singh 2016	A1= <i>Trigonella foenum-graecum</i>	Mild dyspepsia-2, Flatulence/mild abdominal bloating-4, Mild diarrhea-1, Mild pain abdomen and mild abdominal bloating-1	
	A2= <i>Trigonella foenum-graecum</i> +OAD	Flatulence/mild abdominal bloating-2	
	A3=OAD	Mild nausea-1, Mild hypoglycemia-1, Mild headache-2	
Verma 2016	A1= <i>Trigonella foenum-graecum</i>		
	A2=Placebo		
Ranade 2017	A1= <i>Trigonella foenum-graecum</i>		
	A2=No additional medicine		
Gholaman 2018	A1= <i>Trigonella foenum-graecum</i>		
	A2=Placebo		
Kandhare 2018	A1= <i>Trigonella foenum-graecum</i>	Musculoskeletal system disorders-4, Central and peripheral nervous system-10, Vision disorders-1, Psychiatric disorders-2, Gastrointestinal system disorders-10, Liver and biliary system-9, Metabolic and nutritional disorders-42, Cardiovascular disorders-7, Heart rate and rhythm disorders-2, Respiratory system disorders-6, Red blood cell disorders-8, White cells disorders-8, Platelet bleeding and clotting disorders-1, Urinary system disorders-4, Female reproductive disorders-1, Body as a whole (general disorders)-30, Resistance mechanism disorders-4, Total drug-related adverse events (exact names not provided)-25 Hypoglycemia-10 (related), 2 (unrelated) Hypertriglyceridemia-1 (unrelated)	Failure of medicine and adverse event (exact name not provided)-1, Exact names not provided-3, Adverse events (exact names not provided) and other reasons-4

Author and year	Study arms	Adverse events (including serious adverse events)	Dropouts/withdrawals/discontinued interventions due to adverse events (if mentioned)
Ayurvedic medicine- single plant- or mineral-origin ingredient			
	A2=Placebo	Skin and appendages disorders-3, Musculoskeletal system disorders-2, Central and peripheral nervous system-8, Autonomic nervous system disorders-1, Vision disorders-1, Hearing and vestibular disorders-1, Psychiatric disorders-3, Gastrointestinal system disorders-13, Liver and biliary system-9, Metabolic and nutritional disorders-43, Cardiovascular disorders-2, Heart rate and rhythm disorders-2, Respiratory system disorders-6, Red blood cell disorders-2, White cells disorders-13, Platelet bleeding and clotting disorders-1, Urinary system disorders-3, Female reproductive disorders-1, Body as a whole (general disorders)-28, Total drug-related adverse events (exact names not provided)-19 Hypoglycemia-3 (related), 2 (unrelated) Leucocytosis-1	Failure of medicine-1, Exact names not provided-2, Adverse events (exact names not provided) and other reasons-9
Hassani 2019	A1= <i>Trigonella foenum-graecum</i> A2=Placebo		
Hota 2019	A1= <i>Trigonella foenum-graecum</i> A2=No additional medicine	0 0	
Najdi 2019	A1= <i>Trigonella foenum-graecum</i> A2=OAD	Hypoglycemia-1 0	Medicine amendment and other reasons-1 Medicine amendment and other reasons-2
Rashid 2019	A1= <i>Trigonella foenum-graecum</i> A2=Placebo	0	
Hadi 2020	A1= <i>Trigonella foenum-graecum</i> A2=No additional medicine	0	OAD dose amendment-1
<i>Urtica dioica</i>			
Namazi 2011, Esfanjani 2012a, Esfanjani 2012b	A1= <i>Urtica dioica</i> A2=Placebo		Insulin therapy-2, Nausea-1
Kianbakht 2013	A1= <i>Urtica dioica</i> A2=Placebo	0 0	
Khajeh-Mehrizi 2014	A1= <i>Urtica dioica</i> A2=Placebo		Illness (exact names not provided)-2 Illness (exact names not provided)-4
Dabagh 2016	A1= <i>Urtica dioica</i> A2=No additional medicine		
Hassani 2016	A1= <i>Urtica dioica</i> A2=Placebo		
Dadvar 2017	A1= <i>Urtica dioica</i> A2=No additional medicine		
Ghalavand 2017	A1= <i>Urtica dioica</i>		

Author and year	Study arms	Adverse events (including serious adverse events)	Dropouts/withdrawals/discontinued interventions due to adverse events (if mentioned)
Ayurvedic medicine- single plant- or mineral-origin ingredient			
	A2=No additional medicine		
Korani 2017	A1= <i>Urtica dioica</i>	Itching-1	
	A2=Placebo	0	
Mohammadnia 2017	A1= <i>Urtica dioica</i>		
	A2=Placebo		
<i>Vernonia cinerea</i>			
Sayeed 2013	A1= <i>Vernonia cinerea</i>	0	
	A2=Placebo		
<i>Withania coagulans</i>			
Hemalatha 2018	A1= <i>Withania coagulans</i>		
	A2=Placebo		
<i>Withania somnifera</i>			
Usharani 2014	A1= <i>Withania somnifera</i>		Abnormal laboratory reports? (exact names not provided)-4
	A2=Placebo		
<i>Zingiber officinale</i>			
Mahluji 2013	A1= <i>Zingiber officinale</i>	Slight heart burn-2	Medicine failure-2, Medicine amendment-1
	A2=Placebo		Medicine failure-1
Arablou 2014a, Arablou 2014b	A1= <i>Zingiber officinale</i>		Heartburn-1
	A2=Placebo		Insulin therapy-1
Mozaffari-Khosravi 2014, Talaei 2017, Talaei 2018	A1= <i>Zingiber officinale</i>	0	
	A2=Placebo	0	
Shidfar 2015	A1= <i>Zingiber officinale</i>		
	A2=Placebo		
Arzati 2017, Zarezadeh 2018	A1= <i>Zingiber officinale</i>		Insulin therapy-1
	A2=Placebo		Gastrointestinal intolerance-1
Mohammadi 2017, Mohammadi 2019	A1= <i>Zingiber officinale</i>		
	A2=Placebo		
Carvalho 2020	A1= <i>Zingiber officinale</i>	Diarrhoea-1, Gastrointestinal discomfort-1	Exact name not provided-1
	A2=Placebo		Exact name not provided-1
Gholinezhad 2020	A1= <i>Zingiber officinale</i>	0	
	A2=Placebo		
<i>Ziziphus mauritiana</i>			
Yazdanpanah 2017	A1= <i>Ziziphus mauritiana</i>		Hypotension-1, Hives-1
	A2=No additional medicine		Medicine amendment-1, Insulin therapy-2
<i>Acalypha indica</i>/<i>Allium cepa</i>/<i>Allium sativum</i>/<i>Azadirachta indica</i>/<i>Mangifera indica</i>/<i>Murraya koenigii</i>/<i>Musa sapientum</i>/<i>Ocimum tenuiflorum</i>/<i>Phyllanthus amarus</i>/<i>Tinospora cordifolia</i>			
Balasubramaniam 2010	A1= <i>Acalypha indica</i> / <i>Allium cepa</i> / <i>Allium sativum</i> / <i>Azadirachta indica</i> / <i>Mangifera indica</i> / <i>Murraya koenigii</i> / <i>Musa sapientum</i> / <i>Ocimum tenuiflorum</i> / <i>Phyllanthus amarus</i> / <i>Tinospora cordifolia</i>		

Author and year	Study arms	Adverse events (including serious adverse events)	Dropouts/withdrawals/discontinued interventions due to adverse events (if mentioned)
Ayurvedic medicine- single plant- or mineral-origin ingredient			
	A2=Placebo		
Allium sativum; Cuminum cyminum			
Mansouri 2018	A1=Allium sativum	0?	
	A2=Cuminum cyminum	0?	
	A3=Placebo		
Aloe vera; Pterocarpus marsupium; Aloe vera+Pterocarpus marsupium			
Maurya 2017	A1=Aloe vera	0?	
	A2=Pterocarpus marsupium	Diarrhea and flatulence?-1	
	A3=Aloe vera+Pterocarpus marsupium	0?	
	A4=OAD		
Cinnamomum verum; Crocus sativus; Elettaria cardamomum; Zingiber officinale			
Azimi 2014, Azimi 2016	A1=Cinnamomum verum	0	
	A2=Crocus sativus	0	
	A3=Elettaria cardamomum	0	
	A4=Zingiber officinale	0	
	A5=Placebo		
Enicostemma axillare; Shilajit			
Kumar 2014	A1=Enicostemma axillare	0	
	A2=Shilajit	0	
	A3=OAD		
Enicostemma axillare+Emblica officinalis+Tinospora cordifolia			
Sharma 2019	A1=Enicostemma axillare+Emblica officinalis+Tinospora cordifolia		
	A2=No additional medicine		
Linum usitatissimum; Plantago ovata			
Ricklefs-Johnson 2017	A1=Linum usitatissimum	0	
	A2=Plantago ovata		
Syzygium cumini+Withania coagulans			
Siddiqui 2017	A1=Syzygium cumini+Withania coagulans	0	
	A2=OAD	0	
Trigonella foenum-graecum; Aegle marmelos; Trigonella foenum-graecum+Aegle marmelos			
Yaheya 2009	A1=Trigonella foenum-graecum	Flatulence-Exact numbers not provided, Headache-Exact numbers not provided	
	A2=Aegle marmelos		
	A3=Trigonella foenum-graecum+Aegle marmelos		
	A4=No additional medicine		
Ayurvedic medicine- combination of plant- and/or mineral-origin ingredients§			
AYUBES			
Godatwar 2019	A1=AYUBES	Exact names not provided-13 (mostly unrelated)	
	A2=Placebo	Exact names not provided-12 (mostly unrelated)	
BGR-34			
Gupta 2018	A1=BGR-34	0	

Author and year	Study arms	Adverse events (including serious adverse events)	Dropouts/withdrawals/discontinued interventions due to adverse events (if mentioned)
Ayurvedic medicine- single plant- or mineral-origin ingredient			
	A2=Placebo	0	
Bilvadi Churna; Kiratadi Churna			
Kumari 2016	A1=Bilvadi Churna		
	A2=Kiratadi Churna		
	A3=Placebo		
CardiPro			
Fatima 2012	A1=CardiPro	Diarrhea-2	
	A2=Placebo	Dyspepsia-1	
Cogent db			
Shekhar 2002	A1=Cogent db	Mild diarrhea-4	
	A2=No additional medicine	0	
DCBT 2345			
Mohan 2001	A1=DCBT 2345		Associated illness (vomiting, hepatitis, abdominal tuberculosis, urinary tract infection and coronary artery disease)-6, Insulin therapy due to severe hyperglycemia-6
	A2=Placebo		
Diabetea tea			
Mahmoud 2016	A1=Diabetea tea	0	
	A2=Placebo		
Emblica officinalis; Withania somnifera; Emblica officinalis, Withania somnifera			
Usharani 2014	A1=Emblica officinalis	Dyspepsia-3	
	A2=Withania somnifera		
	A3=Emblica officinalis, Withania somnifera		
Herbal combination			
Shokoohi 2017	A1=Herbal combination	0	
	A2=Placebo	0	
Hyponidd			
Poongothai 2002	A1=Hyponidd		Severe hyperglycemia-2, Transient increase in Serum Glutamate Oxaloacetate Transaminase (SGOT) and Serum Glutamate Pyruvate Transaminase (SGPT) levels-1
	A2=Placebo		
Inolter			
Agrawal 2002	A1=Inolter	0	
	A2=Placebo	0	
Kalpit			
Agarwal 2013	A1=Kalpit	0	
	A2=Kalpit+OAD		
	A3=OAD		
Khadira-Kramuka Kashaya Ghanavati; Nishamalaki, Shilajit; Khadira-Kramuka Kashaya Ghanavati+Nishamalaki, Shilajit			
Paliwal 2018	A1=Khadira-Kramuka Kashaya Ghanavati	0	
	A2=Nishamalaki, Shilajit	0	

Author and year	Study arms	Adverse events (including serious adverse events)	Dropouts/withdrawals/discontinued interventions due to adverse events (if mentioned)
Ayurvedic medicine- single plant- or mineral-origin ingredient			
	A3=Khadira-Kramuka Kashaya Ghanavati+Nishamalaki, Shilajit	0	
Lodhradi Kashaya Ghana Vati			
Bramhankar 2017	A1=Lodhradi Kashaya Ghana Vati		
	A2=Lodhradi Kashaya Ghana Vati+OAD		
	A3=OAD		
Madhumeha Nashini Gutika; Darvyadi Kwatha; Madhumeha Nashini Gutika+Darvyadi Kwatha			
Bhawana 2015	A1=Madhumeha Nashini Gutika	0	
	A2=Darvyadi Kwatha	0	
	A3=Madhumeha Nashini Gutika+Darvyadi Kwatha	0	
Mamajjaka Ghana Vati; Tejashiladi Vati			
Bhagat 2017	A1=Mamajjaka Ghana Vati	0	
	A2=Tejashiladi Vati	0	
Mamajjaka Ghana Vati; Trikatu Gutika			
Kataria 2017	A1=Mamajjaka Ghana Vati		
	A2=Trikatu Gutika		
Mehagni			
Gopalakrishna 2017	A1=Mehagni		
	A2=No additional medicine		
Mustadi Kwatha Ghana Vati			
Kushwaha 2017	A1=Mustadi Kwatha Ghana Vati	0	
	A2=Placebo		
Naga Bhasma, Nishamalaki; Nishamalaki, Hordeum vulgare			
Desale 2018	A1=Naga Bhasma, Nishamalaki	0	Hysterectomy-1
	A2=Nishamalaki, Hordeum vulgare	0	
Nigella sativa, Trigonella foenum-graecum			
Memon 2010a, Memon 2010b, Memon 2012	A1=Nigella sativa, Trigonella foenum-graecum		
	A2=No additional medicine		
Nisha Katakadi Kashaya; Yashad Bhasma; Nisha Katakadi Kashaya+Yashad Bhasma			
Srinivas 2018	A1=Nisha Katakadi Kashaya		
	A2=Yashad Bhasma		
	A3=Nisha Katakadi Kashaya+Yashad Bhasma		
Pancreas tonic			
Hsia 2004	A1=Pancreas tonic	Sore throat, Itchy eyes, Migraine headache-4?, Exacerbation of back and leg pain-1, Mild hypoglycemia-1 (unrelated)	
	A2=Placebo	Nightmares, Dizzy spells, Abdominal pain, Flank pain, Insomnia, Leg numbness, Weakness on exertion-5?	Hospitalization due to angina exacerbation-1
Polyherbal formulation			
Awasthi 2015	A1=Polyherbal formulation		OAD due to uncontrolled blood glucose level-6

Author and year	Study arms	Adverse events (including serious adverse events)	Dropouts/withdrawals/discontinued interventions due to adverse events (if mentioned)
Ayurvedic medicine- single plant- or mineral-origin ingredient			
	A2=OAD		OAD amendment due to uncontrolled blood glucose level-5
Salasaradi Kashaya+Shilajit+Trivanga Bhasma+Tinospora cordifolia, Azadirachta indica; Hyponidd			
Bhat 2012	A1=Salasaradi Kashaya+Shilajit+Trivanga Bhasma+Tinospora cordifolia, Azadirachta indica		Aggravation of T2DM symptoms-Few (exact names and numbers not provided)
	A2=Hyponidd		
Shilajit; Asanadi Ghana Vati			
Gupta 2016	A1=Shilajit	0	
	A2=Asanadi Ghana Vati	0	
Swarnamakshika Bhasma			
Taviad 2016	A1=Swarnamakshika Bhasma	0	
	A2=Placebo	0	
Talapotaka Churna			
Nille 2018	A1=Talapotaka Churna	0	
	A2=Talapotaka Churna+OAD		
	A3=OAD		
Trigonella foenum-graecum, Ocimum tenuiflorum			
Mitra 2006	A1=Trigonella foenum-graecum, Ocimum tenuiflorum		
	A2=No medicine		
Triticum aestivum; Nishamalaki; Triticum aestivum+Nishamalaki			
Samagandi 2012	A1=Triticum aestivum		
	A2=Nishamalaki		
	A3=Triticum aestivum+Nishamalaki		
Vidangadi Yoga			
Deshpande 2018	A1=Vidangadi Yoga	A1=4 and A2=7; Fever with chills-2, Upper respiratory tract infection-4, Hypertension-3, Knee joint pain-1, Left foot abscess-1 (all unrelated)	
	A2=OAD		
Vijaysaradi Ghana Vati; Madhumehari Vati			
Sharma 2018	A1=Vijaysaradi Ghana Vati		
	A2=Madhumehari Vati		

A1, A2, A3, A4, A5=Eligible study arms, OAD=Oral antidiabetic drug, T2DM=Type 2 diabetes mellitus

§Some of the Ayurvedic medicines contain single plant- or mineral-origin ingredient.

Chattopadhyay K, Kapoor N, Heinrich M, Mitra A, Mittal M, Lewis SA, Greenfield SM, Mukherjee S, Pischel I, Jeemon P, Tandon N, Kinra S, Biswas TK, Leonardi-Bee J. Development process of a clinical guideline to manage type 2 diabetes in adults by Ayurvedic practitioners. *Front Med.* 2023;10:1043715.

In this fourth empirical chapter, which follows the third empirical chapter on evidence synthesis (i.e., effectiveness and safety of Ayurvedic medicines for managing T2DM), a clinical guideline for Ayurvedic practitioners was systematically developed to manage T2DM in adults. Using the evidence synthesis findings and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, the Evidence-to-Decision framework was developed, focusing on glycaemic control and adverse events. Subsequently, based on the Evidence-to-Decision framework, a Guideline Development Group of 17 international members made recommendations on Ayurvedic medicines' effectiveness and safety in T2DM. These recommendations formed the basis of the clinical guideline, and additional generic content and recommendations were adapted from the T2DM Clinical Knowledge Summaries of the Clarity Informatics (UK). The feedback given by the Guideline Development Group on the draft version was used to amend and finalise the clinical guideline.



OPEN ACCESS

EDITED BY

Luciana Nobre,
Universidade Federal dos Vales do
Jequitinhonha e Mucuri (UFVJM), Brazil

REVIEWED BY

Ozra Tabatabaei-Malazy,
Tehran University of Medical Sciences, Iran
Saikat Sen,
Assam Down Town University, India

*CORRESPONDENCE

Kaushik Chattopadhyay
✉ kaushik.chattopadhyay@nottingham.ac.uk

SPECIALTY SECTION

This article was submitted to
Family Medicine and Primary Care,
a section of the journal
Frontiers in Medicine

RECEIVED 13 September 2022

ACCEPTED 12 January 2023

PUBLISHED 30 January 2023

CITATION

Chattopadhyay K, Kapoor N, Heinrich M,
Mitra A, Mittal M, Lewis SA, Greenfield SM,
Mukherjee S, Pischel I, Jeemon P, Tandon N,
Kinra S, Biswas TK and Leonardi-Bee J (2023)
Development process of a clinical guideline
to manage type 2 diabetes in adults by
Ayurvedic practitioners.
Front. Med. 10:1043715.
doi: 10.3389/fmed.2023.1043715

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Development process of a clinical guideline to manage type 2 diabetes in adults by Ayurvedic practitioners

Kaushik Chattopadhyay^{1,2*}, Nitin Kapoor^{3,4}, Michael Heinrich⁵,
Achintya Mitra⁶, Madhukar Mittal⁷, Sarah Anne Lewis¹,
Sheila Margaret Greenfield⁸, Shyamalendu Mukherjee⁹,
Ivo Pischel⁵, Panniyammakal Jeemon¹⁰, Nikhil Tandon¹¹,
Sanjay Kinra¹², Tuhin Kanti Biswas^{13,14} and Jo Leonardi-Bee^{1,2}

¹Lifespan and Population Health Academic Unit, School of Medicine, University of Nottingham, Nottingham, United Kingdom, ²The Nottingham Centre for Evidence-Based Healthcare: A JBI Centre of Excellence, Nottingham, United Kingdom, ³Department of Endocrinology, Metabolism and Diabetes, Christian Medical College, Vellore, India, ⁴Non-communicable Diseases and Implementation Science, Baker Heart and Diabetes Institute, Melbourne, VIC, Australia, ⁵Centre for Pharmacognosy and Phytotherapy, School of Pharmacy, University College London, London, United Kingdom, ⁶Central Ayurveda Research Institute Under Central Council for Research in Ayurvedic Sciences (Ministry of Ayush), Kolkata, India, ⁷Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, Jodhpur, India, ⁸Institute of Applied Health Research, University of Birmingham, Birmingham, United Kingdom, ⁹West Bengal State Medicinal Plants Board, Kolkata, India, ¹⁰Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, India, ¹¹Department of Endocrinology, Metabolism and Diabetes, All India Institute of Medical Sciences, New Delhi, India, ¹²Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom, ¹³Department of Kayachikitsa, J. B. Roy State Ayurvedic Medical College and Hospital, Kolkata, India, ¹⁴West Bengal Ayurvedic Practitioners Association (Paschim Banga Ayurved Chikitsak Samity), Kolkata, India

Background: Type 2 diabetes mellitus (T2DM), a common chronic health condition, has major health and socioeconomic consequences. In the Indian subcontinent, it is a health condition for which individuals commonly consult Ayurvedic (traditional medical system) practitioners and use their medicines. However, to date, a good quality T2DM clinical guideline for Ayurvedic practitioners, grounded on the best available scientific evidence, is not available. Therefore, the study aimed to systematically develop a clinical guideline for Ayurvedic practitioners to manage T2DM in adults.

Methods: The development work was guided by the UK's National Institute for Health and Care Excellence (NICE) manual for developing guidelines, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument. First, a comprehensive systematic review was conducted which evaluated Ayurvedic medicines' effectiveness and safety in managing T2DM. In addition, the GRADE approach was used for assessing the certainty of the findings. Next, using the GRADE approach, the Evidence-to-Decision framework was developed, and we focused on glycemic control and adverse events. Subsequently, based on the Evidence-to-Decision framework, a Guideline Development Group of 17 international members made recommendations on Ayurvedic medicines' effectiveness and safety in T2DM. These recommendations formed the basis of the clinical guideline, and additional generic content and recommendations were adapted from the T2DM Clinical Knowledge Summaries of the Clarity Informatics (UK). The feedback given by the Guideline Development Group on the draft version was used to amend and finalize the clinical guideline.

Results: A clinical guideline for managing T2DM in adults by Ayurvedic practitioners was developed, which focuses on how practitioners can provide appropriate care, education, and support for people with T2DM (and their carers and family). The clinical guideline provides information on T2DM, such as its definition, risk factors, prevalence, prognosis, and complications; how it should be diagnosed and managed through lifestyle changes like diet and physical activity and Ayurvedic medicines; how the acute and chronic complications of T2DM should be detected and managed (including referral to specialists); and advice on topics like driving, work, and fasting including during religious/socio-cultural festivals.

Conclusion: We systematically developed a clinical guideline for Ayurvedic practitioners to manage T2DM in adults.

KEYWORDS

development, clinical guideline, type 2 diabetes mellitus, Ayurveda, management

Background

The prevalence of diabetes mellitus, one of the most common chronic diseases, is increasing (1). Currently, one in 10 adults is living with the disease, and approximately 44% are undiagnosed (1). Around 90% of adults diagnosed with the disease have type 2 diabetes mellitus (T2DM), and a large population with T2DM is undiagnosed (1). It is a complex metabolic disorder with major health and socioeconomic consequences (1, 2). In T2DM, chronic hyperglycemia is related to macro- and micro-vascular complications and death (1, 2).

Ayurveda, a major traditional medical system, is in use for thousands of years in the Indian subcontinent, such as in Nepal and India (3, 4). In the public healthcare system, qualified and registered Ayurvedic practitioners are deployed, often as the lead clinical provider (5, 6). Ayurvedic practitioners also practice medicine in private clinics (5, 7). In Ayurveda, the corresponding term for diabetes mellitus is madhumeha, and the meaning of madhu is sweetness and meha is excessive urination (8, 9). In classical Ayurvedic texts, written in Sanskrit, this disease and its management have been described in detail (8, 9). Briefly, a multi-pronged and individualized approach is used to manage the disease, for example, through lifestyle modification (including diet) and Ayurvedic medicines (containing plant-, animal-, or mineral-origin ingredients—single or in combination). It is postulated that the mechanism of action includes pancreatic and extrapancreatic effects (8, 9). One of the leading diseases for which people visit Ayurvedic practitioners and use their medicines is T2DM, often uninterruptedly from the time of diagnosis (5, 6, 10–15). Ayurveda is commonly used by people with T2DM in the Indian subcontinent as it fits with their culture and health beliefs, and therefore, its acceptability, perceived relief, and satisfaction are generally high, particularly among older, poor, rural, and indigenous/minority people (13, 15, 16). Many individuals with T2DM do not prefer using western medicines because of the related side effects, administration mode (e.g., injections), and cost (12–15).

A lack of consistency can be seen in how Ayurvedic practitioners manage the disease, and many actions at the various stages of the care pathway (including screening for complications and referral to specialists) are mostly left to the individual Ayurvedic practitioner's

judgment, leading to unacceptable variations (11, 17, 18). They prescribe many non-evidence-based Ayurvedic medicines, which can have serious adverse effects on individuals, including heavy metal poisoning (19). They often follow claims made by peers or opt for an approach like “trial and error” (18, 20). One of the key hurdles highlighted by them is the lack of a good quality T2DM clinical guideline that can assist their clinical decision-making process and delivery of high-quality care to individuals (18).

High-quality T2DM clinical guidelines are effectively used in western medicine for improving the clinical care of individuals (21, 22). However, no such T2DM clinical guideline is available in Nepal for Ayurvedic practitioners, but such clinical guidelines are available in India (8, 9, 23–25). However, their quality is questionable due to several factors, including whether the best available scientific evidence was taken into consideration (26). Most of these clinical guidelines are short and limited in scope and have heterogeneous content with no clear recommendations for action at the different stages of the care pathway (26). Based on the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument, which covers domains like scope and purpose of the guideline, stakeholder involvement, the rigor of development, clarity of presentation, applicability, and editorial independence (27), the overall quality of these clinical guidelines is poor, and these guidelines cannot be recommended for use in clinical practice (26). Poor quality clinical guidelines can lead to ineffective interventions' usage and limited resources' inefficient usage and can harm patients (28).

A good quality T2DM clinical guideline for Ayurvedic practitioners, grounded on the best available scientific evidence, may address the existing problems, discourage the use of Ayurvedic medicines of no, minimal, or questionable value, and encourage the use of effective and safe Ayurvedic medicines. Additionally, the clinical guideline may close the gap between what they do to manage T2DM and what the scientific evidence supports. Therefore, the study aimed to systematically develop a clinical guideline to manage T2DM in adults by qualified and registered Ayurvedic practitioners. The purpose is to provide them with a readily accessible summary of the current scientific evidence base and practical guidance on best practices for the management of T2DM.

Methods

We followed a systematic process for developing this clinical guideline as shown in **Figure 1**, and it was guided by the UK's National Institute for Health and Care Excellence (NICE) manual for developing guidelines, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, and the AGREE II instrument (27, 29, 30).

First, a comprehensive systematic review (and meta-analysis) was conducted to evaluate and synthesize the scientific evidence on Ayurvedic medicines' effectiveness and safety in managing T2DM. The details are published elsewhere (31). Briefly, we followed the JBI systematic review methodology to ensure the findings from the review were scientifically robust (32). Randomized controlled trials (RCTs) assessing Ayurvedic medicines' effectiveness and safety to manage newly diagnosed T2DM (treatment naïve) or existing cases of T2DM (on treatment) in adults (≥ 18 years) were included. RCTs were eligible if evaluated any classical or proprietary Ayurvedic medicine (e.g., containing plant- or mineral-origin ingredients—single or in combination) in any form (e.g., capsules, tablets, decoction, powder) with no intervention, placebo, non-pharmaceutical intervention (e.g., yoga), or pharmaceutical intervention (i.e., western oral antidiabetic drug or head-to-head comparison with another Ayurvedic medicine). The Ayurvedic medicines had to be administered for at least 8 weeks, and the timing of outcome measurements had to be at least 8 weeks from randomization. We conducted a comprehensive search of sources (including 18 electronic databases) till 16 January 2021 for finding published and unpublished RCTs. We developed the search strategies based on relevant previous systematic reviews and clinical guidelines and in consultation with an experienced information specialist. There were no language restrictions. We conducted data synthesis using random effects meta-analysis and reported pooled results as mean differences (MD) with 95% confidence intervals (CI). We used the GRADE approach for assessing the certainty of the findings—the findings were initially ranked as high ($\oplus\oplus\oplus\oplus$),

and if there was serious evidence of the following five: risk of bias, inconsistency of results, indirectness of evidence, imprecision, and/or publication bias, the findings were downgraded to moderate ($\oplus\oplus\oplus\circ$), low ($\oplus\oplus\circ\circ$), or very low ($\oplus\circ\circ\circ$) (28). The review included 219 articles on 199 RCTs (21,191 participants), evaluating 98 Ayurvedic medicines. We conducted meta-analysis on 33 Ayurvedic medicines (including 32 single herbs), and the effects on glycemic control are shown in **Table 1**. Unfortunately, we could not include 65 Ayurvedic medicines in any meta-analysis, administered either as a single medicine or in combination with other Ayurvedic medicines, due to being evaluated in a single study. Few RCTs reported on adverse events, and if reported, adverse events were mostly none to mild, and mainly gastrointestinal tract related.

Next, the GRADE approach was used to develop the Evidence-to-Decision framework for each of the 33 Ayurvedic medicines, and we focused on glycemic control and adverse events (28). A societal perspective (including all costs, regardless of who pays) was taken, and the following domains were considered in the Evidence-to-Decision framework: (i) Is the problem a priority? (ii) How substantial are the desirable anticipated effects? (iii) How substantial are the undesirable anticipated effects? (iv) What is the overall certainty of the evidence of effects? (If the quality of the scientific evidence was the same for glycated hemoglobin (HbA1c) and fasting blood glucose (FBG), then this became the overall quality of evidence, but if it differed across HbA1c and FBG, then the lowest quality of evidence for these became the overall quality of evidence.) (v) Is there important uncertainty about or variability in how much people value the main outcomes? (vi) Does the balance between desirable and undesirable effects favor the intervention or the comparison? (vii) Is the intervention acceptable to key stakeholders? (viii) Is the intervention feasible to implement?

A Guideline Development Group was formed, which comprised 17 internationally based members consisting of Ayurvedic practitioners, western medicine practitioners (including diabetologists), pharmacognosists and experts in medicinal plants and phytochemistry, systematic review methodologists, medical statisticians, epidemiologists, sociologists, and people with T2DM. The direct and indirect interests of the members were considered, but no potential conflicts of interest were identified. A Delphi consensus-based technique was used to develop the recommendations (along with justification), using the scientific evidence presented in the Evidence-to-Decision framework (and their expertise and/or experience) (28). The following recommendations were available: a strong recommendation for or against the intervention (i.e., Ayurvedic medicine), a conditional recommendation for or against the intervention (i.e., weak recommendation), or no recommendation/recommendation to use the intervention only in research. A strong recommendation was given where a high or moderate overall quality of evidence was reported, and the wording of the recommendation included either “offer” ($\uparrow\uparrow$) or “do not offer” ($\downarrow\downarrow$), depending on the direction (for or against, respectively). A weak recommendation was given where a low or very low overall quality of evidence was reported, and the wording of the recommendation included either “consider offering” ($\uparrow?$) or “do not consider offering” ($\downarrow?$), depending on the direction (for or against, respectively). In the systematic review, we found that the daily doses of Ayurvedic medicines varied in the included RCTs, depending on their type and form and timing of administration (31). Therefore, the Guideline Development Group considered the information available

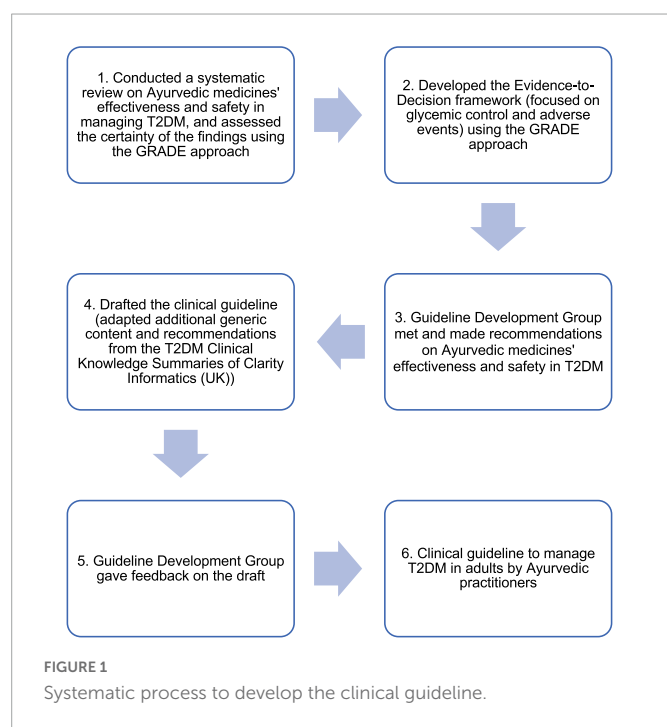


TABLE 1 Effects of Ayurvedic medicines on HbA1c and FBG.

Ayurvedic medicine compared to no medicine, no additional medicine, or placebo (unless mentioned otherwise)	HbA1c (%) MD; 95% CI (Number of RCTs)	FBG (mg/dl) MD; 95% CI (Number of RCTs)
<i>Aegle marmelos</i> (L.) Corrêa	−1.6; −3 to −0.3 (2 RCTs)	−56; −104 to −9 (3 RCTs)
<i>Allium sativum</i> L.	−0.4; −0.9 to 0.1 (3 RCTs)	−1; −14 to 11 (4 RCTs)
<i>Aloe vera</i> L.	−0.9; −2.1 to 0.3 (3 RCTs)	−11; −32 to 10 (4 RCTs)
<i>Anethum graveolens</i> L.	Meta-analysis not possible (<2 RCTs)	−12; −30 to 7 (2 RCTs)
<i>Azadirachta indica</i> A. Juss.	Meta-analysis not possible (<2 RCTs)	−8; −13 to −4 (2 RCTs)
<i>Boswellia serrata</i> Roxb.	−0.5; −0.7 to −0.4 (2 RCTs)	−24; −28 to −21 (2 RCTs)
<i>Camellia sinensis</i> (L.) Kuntze	−0.1; −0.4 to 0.2 (6 RCTs)	−11; −26 to 5 (4 RCTs)
<i>Cinnamomum aromaticum</i> Nees	−0.2; −0.5 to 0.1 (10 RCTs)	1; −6 to 9 (9 RCTs)
<i>Cinnamomum verum</i> J. Presl	−0.1; −0.5 to 0.3 (6 RCTs)	−11; −19 to −3 (6 RCTs)
<i>Citrullus colocynthis</i> (L.) Schrad.	−0.2; −0.7 to 0.4 (2 RCTs)	−3; −18 to 12 (2 RCTs)
<i>Coccinia grandis</i> (L.) Voigt	−0.5; −1.1 to 0 (2 RCTs)	−22; −25 to −19 (2 RCTs)
<i>Crocus sativus</i> L.	0.2; −0.1 to 0.4 (4 RCTs)	−9; −26 to 8 (5 RCTs)
<i>Cuminum cyminum</i> L.	−1.5; −3.7 to 0.7 (2 RCTs)	−14; −35 to 6 (2 RCTs)
<i>Curcuma longa</i> L.	−0.2; −0.7 to 0.4 (6 RCTs)	−10; −15 to −5 (6 RCTs)
<i>Cyamopsis tetragonoloba</i> (L.) Taub.	Meta-analysis not possible (<2 RCTs)	−7; −58 to 44 (2 RCTs)
<i>Elettaria cardamomum</i> (L.) Maton	0.2; −0.2 to 0.5 (2 RCTs)	1; −9 to 12 (2 RCTs)
<i>Enicostemma axillare</i> (Lam.) Raynal (versus oral antidiabetic drug)	Meta-analysis not possible (<2 RCTs)	23; −20 to 66 (2 RCTs)
<i>Gynostemma pentaphyllum</i> (Thunb.) Makino	−1; −1.5 to −0.6 (2 RCTs)	−29; −43 to −15 (2 RCTs)
<i>Ipomoea batatas</i> (L.) Lam.	−0.2; −0.5 to 0.1 (2 RCTs)	−8; −13 to −3 (2 RCTs)
<i>Juglans regia</i> L.	−0.3; −0.6 to 0 (5 RCTs)	−14; −24 to −4 (5 RCTs)
<i>Momordica charantia</i> L.	−0.3; −0.4 to −0.1 (7 RCTs)	−14; −23 to −4 (7 RCTs)
<i>Momordica charantia</i> L. (versus oral antidiabetic drug)	0.4; 0.2 to 0.7 (2 RCTs)	14; 9 to 19 (2 RCTs)
<i>Nigella sativa</i> L.	−0.4; −0.6 to −0.1 (4 RCTs)	−15; −30 to 0 (7 RCTs)
<i>Plantago ovata</i> Forssk.	−0.9; −1.4 to −0.3 (3 RCTs)	−32; −40 to −23 (3 RCTs)
<i>Portulaca oleracea</i> L.	Meta-analysis not possible (<2 RCTs)	−10; −34 to 14 (3 RCTs)
<i>Pterocarpus marsupium</i> Roxb. (versus oral antidiabetic drug)	Meta-analysis not possible (<2 RCTs)	16; −7 to 39 (2 RCTs)

(Continued)

TABLE 1 (Continued)

Ayurvedic medicine compared to no medicine, no additional medicine, or placebo (unless mentioned otherwise)	HbA1c (%) MD; 95% CI (Number of RCTs)	FBG (mg/dl) MD; 95% CI (Number of RCTs)
<i>Punica granatum</i> L.	−0.1; −0.5 to 0.4 (6 RCTs)	−8; −16 to 1 (6 RCTs)
<i>Sesamum indicum</i> L.	−0.7; −1.4 to 0 (2 RCTs)	−46; −116 to 25 (2 RCTs)
Shilajit	−0.3; −0.7 to 0.2 (2 RCTs)	Meta-analysis not possible (<2 RCTs)
<i>Syzygium cumini</i> (L.) Skeels	−0.1; −1.5 to 1.3 (2 RCTs)	−5; −40 to 29 (2 RCTs)
<i>Tinospora cordifolia</i> (Willd.) Hook. f. and Thomson	−0.5; −0.6 to −0.5 (2 RCTs)	−4; −6 to −3 (2 RCTs)
<i>Trigonella foenum-graecum</i> L.	−0.6; −0.9 to −0.4 (12 RCTs)	−14; −22 to −5 (13 RCTs)
<i>Trigonella foenum-graecum</i> L. (versus oral antidiabetic drug)	0.3; −1 to 1.6 (2 RCTs)	27; −24 to 79 (2 RCTs)
<i>Urtica dioica</i> L.	−1.3; −2.4 to −0.2 (3 RCTs)	−20; −41 to 1 (8 RCTs)
<i>Zingiber officinale</i> Roscoe	−0.3; −0.6 to 0.1 (9 RCTs)	−8; −17 to 1 (8 RCTs)

Results reported in bold are statistically significant at the 5% level.

in the systematic review before providing recommended doses for the different Ayurvedic medicines.

The recommendations from the Guideline Development Group on Ayurvedic medicines' effectiveness and safety in T2DM were used to form the basis of the clinical guideline, and additional generic content and recommendations were adapted from the T2DM Clinical Knowledge Summaries (June 2021 version; accredited by NICE) of the Clarity Informatics (UK) with permission (33). This approach was taken because the basic principle of T2DM management is the same in western and Ayurvedic medical systems i.e., a combination of a healthy lifestyle and medicinal products (8, 9, 33); however, the scientific evidence base is extremely limited for components like the Ayurvedic lifestyle.

Finally, the draft version of the clinical guideline was shared with the Guideline Development Group. Experts mainly gave feedback on the applicability and feasibility of the content and readability and understandability of the clinical guideline, and people with T2DM primarily provided their views and preferences. The feedback was used to amend and finalize the clinical guideline.

Results

A clinical guideline for managing T2DM in adults by Ayurvedic practitioners was developed, which focuses on how practitioners can provide appropriate care, education, and support for people with T2DM (and their carers and family). Table 2 summarizes the broad topics covered in the clinical guideline. Briefly, it provides information on T2DM, such as its definition, risk factors, prevalence, prognosis, and complications; how it should be diagnosed and managed through lifestyle changes like diet and physical activity and Ayurvedic medicines; how the acute and chronic complications of T2DM should be detected and managed (including referral to specialists); and advice on topics like driving, work, and fasting

including during religious/socio-cultural festivals. The following issues are outside the scope of the clinical guideline: people with other types of diabetes or at high risk of developing T2DM; women with T2DM who are pregnant, planning a pregnancy, or breastfeeding; management of T2DM using western medicines or insulin; and detailed recommendations on the management of comorbidities, emergencies, and complications related to T2DM.

Discussion

We report the systematic development process of a clinical guideline to manage T2DM in adults by Ayurvedic practitioners. Ayurvedic practitioners based in the Indian subcontinent, such as Nepal and India, may find this clinical guideline useful due to many similarities, such as in the population, context, and setting. The clinical guideline may also be highly relevant in countries with South Asian ethnic minorities who often rely heavily on such treatments (34, 35), as the guideline is based on a systematic review of the worldwide literature.

There is a need to evaluate clinical guidelines and scale these up if found to be effective in improving outcomes (27, 36, 37). In this case, the evaluation is specifically important, as we used an innovative approach to integrate Ayurvedic and western medical systems. Here, integration does not mean the prescription of western medicines by Ayurvedic practitioners (and vice-versa) but focusing on management issues like generic advice given to patients and referral to specialists for complications. Therefore, a feasibility cluster RCT is currently in progress in Nepal to determine the feasibility of undertaking the definitive cluster RCT (38). As part of the feasibility study, we will also be conducting semi-structured interviews with Ayurvedic practitioners to explore their acceptability of the clinical guideline and factors that can facilitate or impede its uptake and adherence. If the feasibility of undertaking the definitive cluster RCT

TABLE 2 Broad topics covered in the clinical guideline.

Section	Topics included
Background information	What is T2DM?
	What causes T2DM?
	What are the risk factors for T2DM?
	How common is T2DM?
	What is the prognosis of T2DM?
	What are the complications of T2DM?
Diagnosis	When should I suspect T2DM in an adult? <i>Interpreting HbA1c results</i>
	When should I suspect a hyperglycemic emergency? <i>Precipitating factors</i>
	When should I suspect hypoglycemia in a person with T2DM?
Management	What initial information and advice should I offer a person with T2DM?
	What are the treatment targets for people with T2DM?
	Which Ayurvedic antidiabetic medicines are available for people with T2DM?
	What lifestyle advice should I give to people with T2DM? <i>Diet</i> <i>Exercise and physical activity</i> <i>Alcohol intake</i> <i>Smoking and drug misuse</i>
	How should I screen for and manage complications in people with T2DM? <i>Retinopathy</i> <i>Foot problems</i> <i>Diabetic kidney disease</i> <i>Cardiovascular risk factors</i> <i>Peripheral and autonomic neuropathy</i>
	How should I manage a person with a suspected hyperglycemic emergency?
	How should I manage intercurrent illness in a person with T2DM? <i>"Sick-day rules"</i>
	How should I manage hypoglycemia in a person with T2DM? <i>Recognizing hypoglycemia</i> <i>Managing a person with impaired awareness of hypoglycemia</i> <i>Managing an acute episode of hypoglycemia</i> <i>Managing nocturnal hypoglycemia</i> <i>Preventing hypoglycemic episodes</i>
	What additional information and advice should I give people with T2DM? <i>Advice on driving</i> <i>Advice on insurance</i> <i>Advice on fasting, including religious/socio-cultural festivals</i> <i>Advice on work</i> <i>Advice on holidays and travel</i>

is promising, the definitive trial will be conducted for determining the effectiveness of the intervention. If it is found to be effective, individuals with T2DM will have improved health outcomes, such as better blood glucose control and lower T2DM complications. The

related future clinical, personal, and economic burden on individuals with T2DM, their carers and family, and the health system and the economy will be reduced. Individuals with T2DM will be cared for in line with the best available scientific evidence and in the same way irrespective of where or by which Ayurvedic practitioner they are treated.

To the best of our knowledge, this was the first time a systematic process was followed to develop a clinical guideline for Ayurvedic practitioners. The process was guided by some of the best guideline development methods and manuals. A significant challenge was to systematically integrate Ayurvedic and western medical systems for managing T2DM, and the best available scientific evidence on effective and safe Ayurvedic medicines in T2DM was used. We also involved a range of experts and people with T2DM, and the process helped us to reach a consensus on such a complex health intervention. If both Ayurvedic and western medical systems work together for the better management of T2DM, it will reduce the large gap in the doctor-patient ratio in South Asian countries (39). As we are evaluating the intervention (i.e., the clinical guideline) and the evaluation will take a number of years to complete, we are unable to publish the complete clinical guideline at this stage to avoid contamination in the control group. However, we have published its development process so that similar approaches could be used to develop clinical guidelines for managing other health conditions by Ayurvedic practitioners or in other traditional medical systems throughout the world. Clinical guidelines should be developed to reflect current research. At the time of the development of the clinical guideline, the comprehensive systematic review from which the evidence was considered was up to date (last searched to 16 January 2021). However, it would be prudent to consider updating the searches of the systematic review to capture more recent evidence before the clinical guideline is implemented more widely (and should include other essential aspects, such as monitoring and auditing criteria to measure the application of guideline recommendations). There is uncertainty around issues like the interaction of Ayurvedic and western medicines, which needs more research before making any recommendation in the clinical guideline. We only considered Ayurvedic medicines for which there was evidence of effectiveness from a comprehensive systematic review and meta-analysis of RCTs (31), which will mean that some potentially effective interventions may have been missed from either not having been tested in an RCT or those which could not be included in any meta-analysis due to being evaluated in a single RCT.

In conclusion, we systematically developed a clinical guideline for Ayurvedic practitioners to manage T2DM in adults. A feasibility cluster RCT is in progress.

Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethics approval was obtained from the Research Ethics Committee, Faculty of Medicine and Health Sciences, University of Nottingham, UK (511-2003). Written informed consent for

participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

KC conceptualized and designed the clinical guideline development process with the help of MH, SL, SG, PJ, NT, SK, TB, and JL-B. KC developed the clinical guideline with the help of other authors (i.e., the Guideline Development Group comprising NK, MH, MM, AM, SL, SG, SM, IP, PJ, NT, SK, TB, JL-B, and people with T2DM). KC wrote the first draft of the manuscript. All authors contributed significantly to the revision of the manuscript and read and approved the final manuscript.

Funding

This work was funded by a grant from the UK's Department of Health and Social Care, Foreign, Commonwealth and Development Office, Medical Research Council, and Wellcome Trust Joint Global Health Trials (MR/T003537/1).

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Acknowledgments

We thank people with T2DM for their contribution as members of the Guideline Development Group.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Discussion and Conclusion

In summary, in the first empirical study, a systematic iterative process was followed to develop a novel Yoga-based intervention (YOGA-DP) for T2DM prevention. First, a systematic review of the scientific literature was conducted to generate a list of Yogic practices that improves blood glucose levels among adults at high risk of or with T2DM. RCTs conducted among adults at high risk of or with T2DM were included if one or more authentic Yogic practices improved one or more blood glucose parameters (i.e., fasting blood glucose, HbA1c and/or postprandial blood glucose) in the intervention group compared to control. Databases were searched from inception to 7 May 2018. No language restrictions were applied. Nine RCTs were included in the review, conducted among people with T2DM. One study also included people with prediabetes. The Jadad score of only four RCTs was high, and only four RCTs mentioned allocation concealment (two provided only limited information). 58 Yogic practices that improve blood glucose levels among adults at high risk of or with T2DM were identified. One RCT mentioned that no adverse event occurred, and four reported limited information on adverse events. Next, validation of these 58 Yogic practices was completed by 41 Yoga experts, highly qualified and experienced Yoga practitioners and/or Yoga researchers with an interest in diabetes in India. They recommended 32 Yogic practices, namely, Shithilikarana Vyayama, Surya Namaskar, 23 Asana, five Pranayama, and two Dhyana and relaxation practices. Next, the intervention was drafted, and the generic lifestyle advice was adapted from a booklet of the Leicester Diabetes Centre (UK) and Diabetes UK website.^{1,2} Subsequently, the draft intervention was shared with 16 experts in India and the UK, covering areas, such as Yoga, exercise, physical activity, diet, behaviour change, and/or diabetes. Their feedback was used to amend it for the next step. Next, the amended draft intervention was pretested in India among eight Yoga teachers and six laypeople. Their feedback was used to amend and finalise it. YOGA-DP is a structured lifestyle education and exercise (based on Yoga) programme, provided over 24 weeks. Once people complete the programme, they are strongly encouraged to maintain a healthy lifestyle in the long term, using the intervention booklet and video.

In the second empirical study, a multicentre, two-arm, parallel-group, feasibility RCT was conducted in India. Adults at high risk for T2DM (i.e., fasting blood glucose 100 to 125 mg/dL) were eligible for recruitment. Sixty-five participants (33 in the intervention group and 32 in the control group) were randomised. In the intervention group, participants received YOGA-DP. In the control group, participants received enhanced standard care. Central randomisation was used for allocation concealment. The outcome assessors and data analysts were blinded to intervention status. In conclusion, the participant recruitment and follow-up and their

adherence to YOGA-DP were found to be promising in this feasibility study. The potential contamination of the intervention in the control group was low. Therefore, this study has demonstrated it is feasible to undertake a definitive RCT that will evaluate the effectiveness of YOGA-DP among people at high risk for T2DM in India. Semi-structured qualitative interviews, with feasibility trial non-participants, participants, YOGA-DP instructors, and staff to explore trial- and intervention-related barriers and facilitators, will inform decisions on modifying the definitive RCT and intervention to further improve participation and adherence.³⁻⁵

In the third empirical study, a comprehensive systematic review and meta-analysis was conducted to synthesise evidence on the effectiveness and safety of Ayurvedic medicines for managing T2DM. The JBI systematic review methodology was followed.⁶ Published and unpublished RCTs assessing the effectiveness and safety of Ayurvedic medicines for managing T2DM in adults were included. A comprehensive search of sources (including 18 electronic databases) was performed from inception to 16 January 2021. No language restrictions were applied. Data synthesis was conducted using narrative synthesis and random effects meta-analyses. 219 articles were included in the review representing 199 RCTs (21,191 participants) of 98 Ayurvedic medicines. Overall, the methodology was not adequately reported in the included studies, resulting in poorer methodological quality scoring. Compared to the control, HbA1c and fasting blood glucose levels were reduced using several Ayurvedic medicines. Very few studies assessed health-related quality of life. Adverse events were not reported in many studies, and if reported, these were mostly none to mild and predominately related to the gastrointestinal tract. In conclusion, the current evidence suggests the benefit of a range of Ayurvedic medicines in improving glycaemic control in people with T2DM. Given the limitations of the available evidence and to strengthen the scientific evidence base, high-quality RCTs should be conducted and reported.

In the fourth empirical study, a novel clinical guideline was systematically developed for Ayurvedic practitioners to manage T2DM in adults. The development work was guided by the UK's National Institute for Health and Care Excellence (NICE) manual for developing guidelines, the GRADE approach, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument.⁷⁻⁹ First, a systematic review was conducted (see third empirical study above). The GRADE approach was used to assess the certainty of the findings from the systematic review. Next, using the GRADE approach and focusing on glycaemic control and adverse events as critical/important outcomes, the Evidence-to-Decision framework was developed. Subsequently, based on the Evidence-to-Decision framework, a Guideline Development Group made recommendations on Ayurvedic medicines' effectiveness and safety in T2DM. These recommendations formed the basis of the clinical guideline, and

additional generic content and recommendations were adapted from the T2DM Clinical Knowledge Summaries of the Clarity Informatics (UK).¹⁰ The Guideline Development Group gave feedback on the draft version of the clinical guideline, which was then amended and finalised. The clinical guideline focuses on how Ayurvedic practitioners can provide appropriate care, education, and support for people with T2DM (and their carers and family). It provides information on T2DM, how T2DM should be diagnosed and managed through lifestyle changes and Ayurvedic medicines, how the acute and chronic complications of T2DM should be detected and managed, and advice on relevant topics. A feasibility cluster RCT is currently in progress to determine the feasibility of undertaking the definitive cluster RCT in the future that will evaluate the effectiveness of this clinical guideline for managing T2DM by Ayurvedic practitioners.

The studies collectively aimed to enhance T2DM prevention and management through novel Yoga- and Ayurveda-based interventions. The first study meticulously crafted the YOGA-DP, a structured programme integrating Yogic practices, derived from a systematic literature review and expert validation, with lifestyle advice. Building on this groundwork, the second study conducted a feasibility RCT in India, demonstrating promising recruitment and adherence and low intervention contamination, supporting the viability of a larger RCT to evaluate YOGA-DP's effectiveness. Additionally, the third study conducted a comprehensive systematic review and meta-analysis, revealing the potential of Ayurvedic medicines in improving glycaemic control in T2DM. Lastly, a novel clinical guideline for Ayurvedic practitioners was systematically developed, using evidence from the systematic review and expert recommendations. This guideline offers comprehensive guidance on T2DM diagnosis and management, using lifestyle modification and Ayurvedic medicines, as well as detection and basic management of complications. Together, these studies represent a concerted effort to integrate traditional practices and evidence-based approaches into T2DM prevention and management. They provide valuable insights into the development, feasibility, and potential effectiveness of interventions rooted in Yoga and Ayurveda, aiming to improve health outcomes in individuals at risk of or living with T2DM.

The strengths and limitations of individual empirical studies have been reported in the publications. Overall, robust methodologies were used in conducting these innovative projects, which met several Sustainable Development Goals (SDGs) of the United Nations (UN) e.g., Goal 3 - Good Health and Well-being and Goal 10 - Reduced Inequalities. SDGs' 'leave no one behind' agenda is relevant here, as what is often left behind in global health research is this broad landscape of indigenous, non-'Western', and culture-specific knowledge. Two other major achievements in these high-quality projects were the

engagement and involvement of key stakeholders and the capacity strengthening of early career researchers especially in low- and middle-income countries (LMICs). The main limitation of the work will lead to future studies. In other words, the research has contributed to the early phases of MRC/NIHR's framework for intervention development and evaluation (i.e., feasibility work).¹¹ However, the effectiveness of these interventions is still unknown. Initial estimates show some beneficial effects in the YOGA-DP feasibility trial. However, the feasibility trial was not powered for effectiveness. Therefore, the main evaluation needs to be conducted that will determine the effectiveness of these interventions in adequately powered RCTs. The definitive RCTs need to have integral health economic and qualitative process evaluations, which will answer questions related to interventions' cost-effectiveness and how interventions worked or why these didn't work, respectively. The process of writing and submitting research grant applications has already started. The COVID-19 pandemic and related travel restrictions had an impact on these studies, especially on the second, third, and fourth. Digital approaches were used for conducting the research, and it has its own challenges, especially in LMICs.

If these innovative interventions are found to be effective in future RCTs, people will have better health outcomes e.g., T2DM prevention among people at high risk and better blood glucose control and lower T2DM complications among people with T2DM. The related clinical, personal, and economic burden on people, their families, the health system, and the economy will be reduced. Work will be done with key stakeholders to implement/adopt these effective interventions. Given that T2DM is a global concern, the research summarised in this thesis will be of interest in other countries, particularly in other South Asian nations and in countries with South Asian ethnic minorities. Therefore, future work will focus on the evaluation and implementation/adoption of the interventions developed, not only in India but also in neighbouring countries, such as Nepal, considering the similarities in population characteristics, settings, contexts, and popularity of these traditional therapies.

In recognition of my work in this area as an internationally leading researcher, I received Indian diaspora awards, such as the Nav Rattan (Nine Jewels) Award 2023 and Hind Rattan (Jewel of India) Award 2020 on the eve of India's Republic Day. I was invited by a government agency in India to validate a Yoga protocol for managing diabetes mellitus, to join the JBI Endocrine and Diabetes Expert Reference Group, JBI Evidence-based Practice (EBP) Database, and Academic Management Board, Asia Research Institute, Nottingham. The research work was widely covered in the media, and I was interviewed on several occasions. I was invited as a guest speaker and to write editorials and book chapters, edit journal special issues, review research grant applications by major funders, and examine doctoral theses.

In conclusion, my work on traditional Indian therapies has contributed to the strengthening of its scientific evidence base for preventing and managing T2DM.

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