

The Herbal Supplements for Diabetes Mellitus Type II

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ABSTRACT

Diabetes is an endocrine disorder which due to its high prevalence worldwide the patients are at risk of its complications. The treatment used by T2DM (Diabetes Mellitus Type 2) patients is not only in conventional medicine, but some patients use Complementary Medicine (CM) like herbs. The present study aimed to analyze the effectiveness of herbal therapy for Diabetes Mellitus Type 2. Five databases (Scopus, Sage, Science direct, Ebsco, and ProQuest) were explored to find relevant articles published from 2015 to 2020. The boolean search used "herbal therapy" and Diabetes Mellitus Type 2" and Hemoglobin A1c (HbA1c) in the title, abstract, or keywords. The most common type of study was random control trial. This

study shows that various herbal therapies that can be used to lower blood glucose such as *Momordica charantia*, cinnamon, and Caucasian whortleberry, nano curcumin, walnut oil, and *Berberis integerrima* root, and other herbs therapy. Besides, those herbs have secondary results, namely being able to reduce stress, quality of life, body weight, and control moderate glycemic status.

Keywords: Blood glucose, Herbal, Diabetes Mellitus Type 2 (T2DM), Hemoglobin A1c (HbA1c)

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INTRODUCTION

Diabetes is an endocrine disorder which due to its high prevalence worldwide the patients are at risk of its complications. Based on the mechanisms studied in the pathology of diabetes, complications can be categorized in macrovascular, microvascular, and both micro and macrovascular such as a diabetic foot. According to the World Health Organization, financial and economic losses of the disease, as well as the deaths caused by it, is high. The main cause of most mortality and morbidity from diabetes is due to macrovascular complications as compared to the microvascular complications in patients (Afsharpour F, *et al.*, 2019).

Diabetes is a set of metabolic abnormalities due to impaired insulin secretion, insulin action, or both. The rapid increase in the prevalence of Diabetes Mellitus is the most challenging health problem of the 21st century in the world. In 2007, 246 million people (6% of the world population) had diabetes, and it is expected that by 2025 the number of people with diabetes in the world reaches to about 380 million (7.3%) (Honarvar NM, *et al.*, 2019).

The prevalence of Diabetes Mellitus (DM) in Indonesia is ranked seventh in the world along with China, India, the United States, Brazil, and Mexico with an estimated number of people with diabetes of 10 million in 2015 and will increase to 16.2 million in 2040. The percentage of deaths due to DM in Indonesia is the second-highest after Sri Lanka (Proboningsih J, *et al.*, 2020).

Type 2 Diabetes Mellitus (T2DM) is a metabolic disorder known as a global health problem, characterized by elevated blood glucose levels. It is estimated that nearly 200 million people with diabetes are undiagnosed and; therefore, at greater risk of developing complications including kidney failure, blindness, amputations, heart disease, and stroke (Neto JC, *et al.*, 2020). According to the International Diabetes Federation, the general target for glucose control in T2DM should be less than 7% of Hemoglobin A1c (HbA1c) (53 mmol/mol) (Neto JC, *et al.*, 2020).

This has resulted in numerous studies focusing on dietary components that are beneficial either in the prevention and/or treatment of Type-2 Diabetes and the findings of these individual studies have been summarized in this study (Ranasinghe P, *et al.*,

2017). Based on data from the Fremantle Diabetes Study Phase II (FDS2) and consistent with other studies identifying relatively high use in diabetes, 44% of Australians with Type 2 Diabetes take Complementary Medicine (CM). To understand why this percentage was large, it is important to assess the treatment beliefs of CM users. The Complementary and Alternative Medicine Beliefs Inventory (CAMBI) was developed and validated for this purpose. No withstanding limitations in studies involving demographic/cultural diversity (Sharif I, *et al.*, 2020).

T2DM patients must carry out treatments related to blood sugar control so that the body's metabolism can function properly. T2DM treatment must be carried out for a lifetime. The treatment used by T2DM patients is not only in conventional medicine, but some patients use Complementary Medicine to complement conventional treatments that have been done. Types of Complementary Medicine that are widely used by DM patients are herbs, supplements (vitamins and minerals), and mind-body therapy. The use of herbs as Complementary Medicine must pay attention to aspects of efficacy and safety (Proboningsih J, *et al.*, 2020).

The use of herbs as a treatment in Indonesia has been regulated in the Decree of the Minister of Health of the Republic of Indonesia number HK.01.07/MENKES/187/2017 regarding the Formulary of Indonesian Traditional Medicinal Herbs. Nurses as part of health workers are authorized to perform complementary and alternative nursing management in carrying out their duties as providers of Nursing Care in the field of public health efforts. Indonesia is a country that is very rich in natural biological resources because Indonesia's topography and tropical climate support the growth of a variety of plants. This is a potential that must be exploited and preserved for human welfare (Proboningsih J, *et al.*, 2020). This study aims to analyze the effectiveness of herbal therapy for Diabetes Mellitus Type 2.

MATERIALS AND METHODS

Database

The sources of the articles in this study used are research databases such as Scopus, Sage, Science direct, Ebsco, and ProQuest. Additional articles were selected using the article except included in this study.

Keywords and search terms

Search for articles in the database using the hep boolean operators with a combination of keywords and search terms as follows: “Herbal therapy” OR “herbs” OR “herbalism” AND “Diabetes Mellitus Type 2” OR “DM Type 2” and “HbA1c” OR “glucose index” during 2015-2020.

Article selection

The preparation of this study follows the diagrams flow and checklist guidelines set by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) in 2009. We obtained articles from all research electronic databases that used a total of 8,840 documents. After performing the first stage of screening with inclusion criteria, the remaining 105 documents were deemed suitable. The second stage of screening resulted in 36 selected articles, then before going to the Critical appraisal stage, the remaining 15 journals were by the questions and research objectives set out in this study.

During the screening of articles, three reviewers were tasked with selecting titles, abstracts, and keywords relevant to the inclusion criteria. The reviewer notes the reasons why a study is considered relevant for inclusion in this work. Next, the other two reviewers will review the studies that have been selected to match the questions or objectives of the study. To minimize the risk of the study input being wrong or not meeting the criteria, all reviewers conducted a joint discussion to obtain agreement. The process of selecting this article is shown in more detail in the PRISMA 2009 Flow Diagram (Figure 1).

Population, Intervention, Comparison, Outcomes and Study (PICOS) framework

We use the PICOS framework to identify the articles, start from population, intervention; comparators, outcome, and study design (Table 1).

Risk of bias

The risk of bias was measured using The JBI (Joanna Briggs Institute) Critical Appraisal to assess the quality of each study. Studies with RCT research designs were assessed using the JBI Critical Appraisal Checklist. The checklist consists of some questions with answers to “yes”, “no”, “unclear” and “not valid”. An assessment score that reaches a minimum of 50% then meets the critical appraisal with the cut-off point value agreed upon by the researcher. We did not include studies with scores below 50% to avoid bias in results and discussion. The JBI scores for each journal in this study are >50 % (Table 2).

RESULTS

General characteristics

Based on 15 articles that have been analyzed (Table 3), the most common type of study was random control-trial with 12 articles (80%), and the most common time of evaluation the intervention was 90 days with 5 articles (33,33%) (Asadi S, et al., 2019). The type of herbal that is used to interventions for Diabetes Mellitus Type-2 from the articles is various (Table 3).

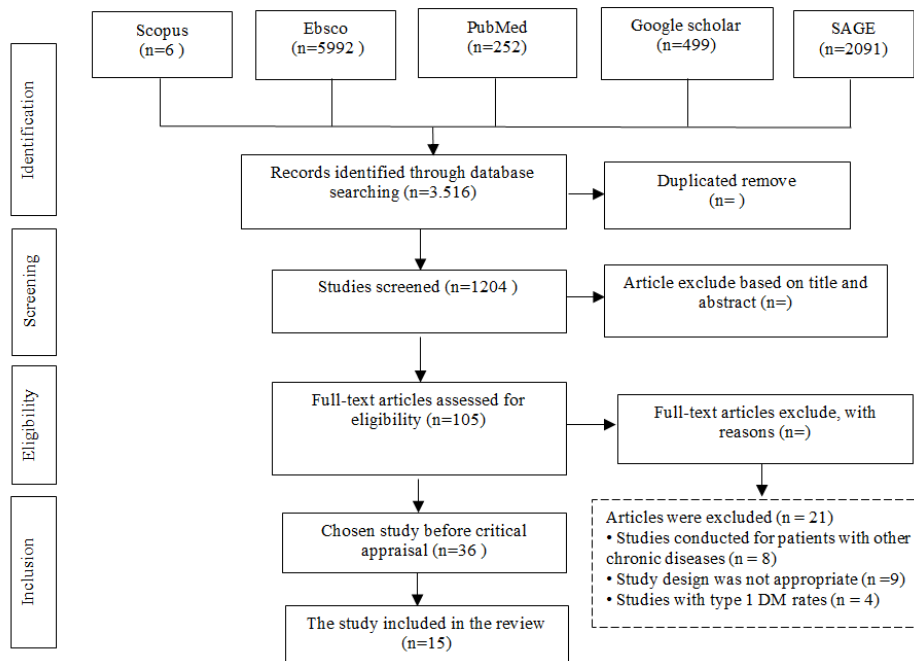


Figure 1: Articles selection process using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Table 1: Population, Intervention, Comparison, Outcomes and Study (PICOS) framework

PICOS	Inclusion	Exclusion
Population	The population in this study is people who have Diabetes Mellitus Type 2 (DMT2), adolescent to adult.	Peoples who do not have Diabetes Mellitus Type 2, gestational DM
Intervention	Interventions using herbal remedies	Pharmacological treatment of diabetes
Comparators	The comparison was a combination intervention of herbs and pharmacology	There are no exceptions

Outcome	HbA1c, glucose index	Studies that do not discuss the effects of herbal therapy for patients with DMT2
Study design	Randomized Controlled Clinical Trial (RCT), Quasy experimental study	A systematic review, cross-sectional
Years of publication	2015-2020	Before 2015

Table 2: JBI Critical Appraisal Checklist

No	Title (Citation)	Criteria (If it is given“√”)													Result (%)
		1	2	3	4	5	6	7	8	9	10	11	12	13	
1	Comparison effectiveness of antidiabetic activity extract herbal mixture of Soursop leaves (<i>Annona muricata</i>), Bay leaves (<i>Syzygium polyanthum</i>), and Pegagan leaves (<i>Centella Asiatica</i>) (Berawi KN, <i>et al.</i> , 2017)	√	√	√	√	√	-	√	√	√	√	√	√	√	92,30
2	Complementary treatment to reduce blood sugar levels of type 2 diabetes mellitus patients (Proboningsih J, <i>et al.</i> , 2020)	√	√	√	√	√	√	-	√	√	√	√	-	-	76,92
3	Controlling type 2 diabetes mellitus with herbal medicines: A triple-blind randomized clinical trial of efficacy and safety (Mirfeizi M, <i>et al.</i> , 2016)	√	√	√	√	√	-	√	√	√	√	√	√	-	84,61
4	Efficacy and safety of American ginseng (<i>Panax quinquefolius L.</i>) extract on glycemic control and cardiovascular risk factors in individuals with type 2 diabetes: A double-blind, randomized, crossover clinical trial (Vuksan V, <i>et al.</i> , 2019)	√	√	√	√	√	-	√	√	√	√	√	√	√	92,30
5	Glucoherb versus metformin on glycemic markers and glycosylated hemoglobin in prediabetes patients: A clinical trial study (Izadi I, <i>et al.</i> , 2020)	√	√	√	√	√	√	√	√	√	√	√	√	-	92,30
6	Hypoglycemic efficacy and safety of <i>Momordica charantia</i> (bitter melon) in patients with Type 2 Diabetes Mellitus (Kim SK, <i>et al.</i> , 2020)	√	√	√	√	√	-	√	√	√	√	√	√	√	92,30
7	Nano curcumin supplementation reduced the severity of diabetic sensorimotor polyneuropathy in patients with Type 2 Diabetes Mellitus: A randomized double-blind placebo-controlled clinical trial (Asadi S, <i>et al.</i> , 2019)	√	√	√	√	√	-	√	√	√	√	√	√	√	92,30
8	Propolis supplementation improves glycemic and antioxidant status in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled study (Afsharpour F, <i>et al.</i> , 2019)	√	√	√	-	-	√	√	√	√	√	-	√	√	76,92
9	Safety and efficacy of <i>Berberis integerrima</i> root extract in patients with type 2 diabetes. A parallel intervention based triple-blind clinical trial (Sanjari M, <i>et al.</i> , 2020)	√	√	√	√	√	-	√	√	√	√	√	√	-	84.61
10	Silymarin, Olibanum, and Nettle, a mixed herbal formulation in the treatment of type II diabetes: A randomized, double-blind, placebo-controlled, clinical trial (Khalili N, <i>et al.</i> , 2017)	√	√	√	√	√	-	√	√	√	√	√	√	√	92,30
11	The effect of oral ginger supplementation on NF-κB concentration in peripheral blood mononuclear cells and anthropomorphic data of patients with type 2 diabetes: A randomized double-blind, placebo-controlled clinical trial (Honarvar NM, <i>et al.</i> , 2019)	√	√	√	√	√	-	√	√	√	√	√	√	-	84.61
12	Therapeutic effect of <i>Abelmoschus manihot</i> on Type 2 diabetic nonproliferative retinopathy and the involvement of Vascular Endothelial Growth Factor (VEGF) (Zhao Y, <i>et al.</i> , 2020)	√	√	√	√	√	-	√	√	√	√	√	√	-	84,61
13	The therapeutic effect of Chinese prescription Kangen-karyu in patients with diabetic nephropathy (Park CH, <i>et al.</i> , 2020)	√	√	√	-	-	√	√	√	√	√	-	√	√	76,92
14	The effect of walnut oil consumption on blood sugar in patients with Diabetes Mellitus Type 2 (Zibaenezhad M, <i>et al.</i> , 2016)	√	√	√	√	√	-	√	√	√	√	√	√	√	90,30
15	Comparison of topical capsaicin and topical turpentine oil for treatment of painful diabetic neuropathy (Musharraf MU, <i>et al.</i> , 2017)	√	√	√	√	√	-	√	√	√	√	√	√	-	84,61

Table 3: General characteristics of selected studies (n=15)

Category	n	%
Year of publishing		
2015	1	6,67
2016	1	6,67
2017	3	20
2018	1	6,67
2019	4	26,67
2020	4	26,67
2021	1	6,67
Type of herbal		
Soursop leaves (<i>Annona muricata</i>), bay leaves (<i>Syzygium polyanthum</i>), and pegagan leaves (<i>Centella asiatica</i>)	1	6,67
Cinnamon and caucasian whortleberry	1	6,67
American ginseng	1	6,67
<i>Momordica charantia</i>	2	13,33
Nano curcumin	1	6,67
Propolis supplement	1	6,67
Extract <i>Berberis integerrima</i> root	1	6,67
Glucoherbs	1	6,67
Combination of silymarin, olibanum, and nettle extracts	1	6,67
Oral ginger supplementation	1	6,67
Topical capcaisine and turpentine oil	1	6,67
<i>Abelmoschus manihot</i>	1	6,67
Kangen-karyu	1	6,67
Walnut oil	1	6,67
Type of study		
Random Control-Trial (RCT)	12	80
Quasi-experimental	2	13,33
Case study	1	7,69
Time of evaluate		
Not explained	1	7,69
8 day	1	7,69
56 day	2	13,33
60 day	1	7,69
84 day	1	7,69
90 day	5	33,33
120 day	2	13,33
300 day	1	7,69
360 day	1	7,69

Single extract of Soursop leaves (*Annona muricata*) has the highest potential effectiveness of anti-amylase, anti-glucosidase, and antioxidant than Bay leaves (*Syzygium polyanthum*), and Pegagan leaves (*Centella asiatica*). *Momordica charantia* 200 gm/day for 8 days has the effect of lowering blood glucose levels better than Bay leaves and Cinnamon in Type 2 Diabetes patients. Giving *Momordica charantia* as much as 2,380 mg/day for 56 days has no significant effects on reducing the HbA1c levels but it has an effect in lowering blood glucose levels. Giving Cinnamon and Caucasian whortleberry as much as 1 g/day for 90 days can reduce blood glucose levels and body weight and control moderate glycemic status (Berawi KN, *et al.*, 2017). Along with that, American ginseng as much as 3 g/day for 56 days can reduce systolic blood pressure and HbA1c. The administration of 80 mg Nano curcumin capsules for 56 days showed a significant reduction in HbA1c, blood glucose, and body weight and reduced the severity of Diabetic Sensorimotor Polyneuropathy (Izadi I, *et al.*, 2020).

Provision of Propolis supplements of 1,500 mg/day for 60 days can reduce

HbA1c, fasting blood sugar, postprandial blood sugar, and increase Total Antioxidant Capacity (TAC) and Glutathione Peroxidase (GPx). Giving an extract of 1 g/day of *Berberis integerrima* root for 90 days can reduce blood glucose levels, body weight, and cholesterol (Khalili N, *et al.*, 2017). Giving glucoherbs for 360 days can reduce HbA1c, blood glucose levels, and Body Mass Index (BMI) in pre-diabetic patients. The combination of Silymarin, Olibanum, and Nettle extracts as much as 6 g/day for 90 days can reduce HbA1c, fasting blood sugar, and triglycerides (Mirfeizi M, *et al.*, 2016). Oral Ginger supplementation of 2 g/day for 300 days was significant for anthropometric evaluation and decreased the concentration of NF-κB p65 or Nuclear Factor kappa B. Administration of Topical capcaisine and turpentine oil for 90 days was effective in reducing pain in diabetic neuropathy. Administration of *Abelmoschus manihot* as much as 5.4 g/day for 120 days can increase Vascular Endothelial Growth Factor (VEGF), Non-Proliferative Diabetic Retinopathy (NPDR), Early Treatment Diabetic Retinopathy Study (ETDRS) vision scores, and macular edema (Musharraf MU, *et al.*, 2017). It could be taken as a novel complementary and alternative

strategy for treating type-2 diabetic non-proliferative retinopathy (Park CH, *et al.*, 2020). Giving Kangen karyu as much as 7.5 g/day for 120 days can reduce somatic and subjective symptoms, reduce serum creatinine levels and increase glomerular filtration. Giving Walnut oil as much as 15 g/day for 30 days can reduce HbA1c, fasting blood sugar, and increase blood glucose homeostasis in type 2 DM patients (Sanjari M, *et al.*, 2020).

DISCUSSION

The effect of consumption of walnut oil, which contains high levels of Polyunsaturated Fatty Acids (PUFAs) especially Alpha-Linolenic Acid (ALA) was investigated on blood sugar control in DM type 2 patients (Vuksan V, *et al.*, 2019; Zhao Y, *et al.*, 2020). These results are in line with research finding that in 2 large prospective cohorts of U.S. women, we found an inverse association between walnut consumption and risk of Type 2 Diabetes. This association was attenuated but remained significant after adjusting for BMI. Consistent with our previous analyses, regular consumption of peanut and tree nuts was also associated with a significantly lower risk of Type 2 Diabetes, but these associations were largely explained by body weight (Pan A, *et al.*, 2013; Zibaenezhad M, *et al.*, 2016).

Walnuts have the highest antioxidant capacity. These antioxidants are possible of phenolic compounds, including hydrolyzed tannins, tocopherol (Anderson KJ, *et al.*, 2001), and melatonin; all of which have a high antioxidant capacity. Effect of daily consumption of alpha-lipoic acid, as an antioxidant, for two months compared to placebo in type 2 DM patients. It was observed that in the group receiving alpha-lipoic acid, FBS and demand for Insulin Resistance Homeostasis model (IR-HOMA) decreased significantly but bodyweight remains unchanged (Zibaenezhad M, *et al.*, 2016).

Our finding indicated that treatment with nano curcumin improved and reduced the severity of Diabetic Sensorimotor Polyneuropathy (DSPN) in patients with T2DM. In addition, we found a significant effect of curcumin supplementation on Fast Blood Sugar (FBS) and HbA1c levels (Zibaenezhad M, *et al.*, 2016). Also the reports of another clinical trial have been showed that consumption of 1200 mg turmeric for 8 weeks could reduce BMI in patients with Type 2 Diabetes (Maithilikarpagaselvi N, *et al.*, 2016). There are various mechanisms for the anti-diabetic effect of curcumin. One of the most fundamental of these mechanisms is the improvement in beta-cell function through its anti-inflammatory and anti-oxidant properties (Rivera-Mancía S, *et al.*, 2015; Chuengsamarn S, *et al.*, 2012).

Complementary and alternative medicine involves the use of herbs and other dietary supplements as alternatives to mainstream western medical treatment. A recent study has estimated that up to 30% of patients with Diabetes Mellitus use complementary and alternative medicine (Raman BV, *et al.*, 2012). The intake of *Momordica charantia* or bitter melon for 12 weeks has improved fasting glucose levels and insulin resistance index in patients with Type 2 Diabetes Mellitus (Kim SK, *et al.*, 2020). The bitter melon extract potentiated Optimal Oral Hypoglycemic Agents (OHAs) in patients with Type 2 Diabetes. However, the size of these studies was small, and others were not randomized or double-blinded. Researchers conducted the randomized, double-blinded, placebo-controlled study (Cortez-Navarrete M, *et al.*, 2018).

The experimental studies established that propolis could practically control hyperglycemia in the Streptozotocin (STZ)-induced diabetic rat model (Afsharpour F, *et al.*, 2019). This finding is similar to the results of Samadi N, *et al.* investigation conducted in patients with Type 2 Diabetes, which showed that daily intake of 900 mg of bee propolis supplement for 12 weeks results in improvement of glycemic in patients with Type 2 Diabetes (T2D) (Samadi N, *et al.*, 2017).

CONCLUSION

There are many ways to lower blood glucose levels in patients with DM, one of which is a complementary treatment. This study shows that various herbal therapies that can be used to lower blood glucose such as *Momordica charantia*, cinnamon, and Caucasian whortleberry, nano curcumin, walnut oil, and *Berberis integerrima* root, and other herb therapy. Besides, those herbs have secondary results, namely being able to reduce stress, quality of life, body weight, and control moderate glycemic status.

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