

The Herbal Supplements for Diabetes Mellitus Type II

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Abstract— *Diabetes is an endocrine disorder which due to its high prevalence in the worldwide the patients are at risk of its complications. The treatment used by T2DM patients is not only in conventional medicine, but there are patients who use complementary medicine like herbs. The present study aimed to analyzed 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 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 Integerrima root berberis and the other herbs therapy. Besides that 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; HbA1c*

I. INTRODUCTION

Diabetes is an endocrine disorder which due to its high prevalence in the 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 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, Javadi, Hashemipour, Koushan, & haghghian, 2019).

Diabetes is a set of metabolic abnormalities due to an impaired insulin secretion, insulin action, or the both. The rapid increase of prevalence of diabetes mellitus is the most challenging health problem of the 21 st century in the world. In 2007, 246 million people (6% of 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%) (Mohammadzadeh Honarvar et al., 2019).

The prevalence of 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, Joeliantina, Novitasari, & Purnamawati, 2020a).

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 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) (53mmol/mol) (Neto 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 systematic reviews (Ranasinghe 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. Notwithstanding limitations in studies involving demographic/cultural diversity (Sharif 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 there are patients who use complementary medicine in an effort 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 et al., 2020a).

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 supports the growth of a variety of plants. This is a potential that must be exploited and preserved for the purpose of human welfare (Proboningsih et al., 2020a). This study aim to analyzed the effectiveness of herbal therapy for Diabetes Mellitus Type 2.

II. MATERIAL AND METHODS

Database

The source of the articles in this systematic review used research databases such as Scopus, Sage, Science direct, Ebsco and ProQuest. Additional articles were selected by means of the article except included in this systematic review.

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 systematic review follows the diagrams flow and checklist guidelines set by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes) 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 in accordance with the questions and research objectives set out in this systematic review.

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 systematic review. Next, the other two reviewers will review the studies that have been selected to match the questions or objectives of the systematic review. In an effort 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).

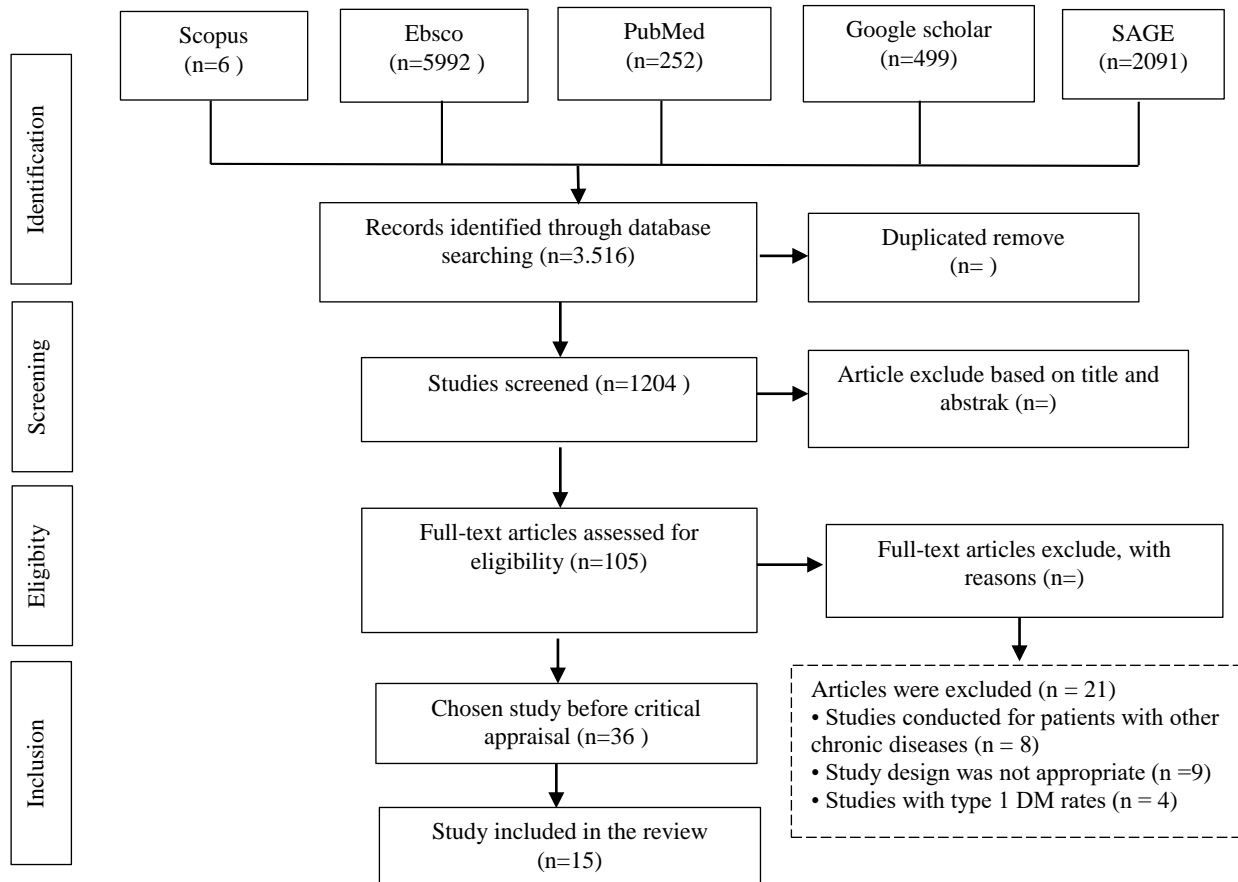


Figure 1. Articles selection process using PRISMA

PICOS Framework

We use PICOS framework to identify the articles, start from population, intervention, comparators, outcome and study design.

Tabel 1. PICOS Framework

| PICOS | Inclusion | Exclusion |
|----------------------|---|--|
| Population | Population in this study are people who have diabetes mellitus type 2, adolescent to adult. | Peoples who does 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 | RCT, Quasy experimental study, | Systematic review, cross sectional |
| Years of publication | 2015-2020 | Before 2015 |

Risk of Bias

The risk of bias was measured using The JBI 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 review >50 %.

| No | Title (Sitasi) | Kriteria (Jika ada di beri "√") | | | | | | | | | | | | | Hasil (%) |
|----|---|---------------------------------|---|---|---|---|---|---|---|---|----|----|----|----|-----------|
| | | 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 et al., 2017) | √ | √ | √ | √ | √ | - | √ | √ | √ | √ | √ | √ | √ | 92,30 |
| 2 | Complementary treatment to reduce blood sugar levels of type 2 diabetes mellitus | √ | √ | √ | √ | √ | √ | - | √ | √ | √ | √ | - | - | 76,92 |

| | | | | | | | | | | | | | | | |
|----|--|---|---|---|---|---|---|---|---|---|---|---|---|---|-------|
| 12 | Therapeutic Effect of <i>Abelmoschus manihot</i> on Type 2 Diabetic Nonproliferative Retinopathy and the Involvement of VEGF (Zhao et al., 2020) | √ | √ | √ | √ | √ | - | √ | √ | √ | √ | √ | √ | - | 84,61 |
| 13 | Therapeutic effect of Chinese prescription Kangen-karyu in patients with diabetic nephropathy (Park, Hiratani, Natazuka, & Yokozawa, 2020) | √ | √ | √ | - | - | √ | √ | √ | √ | √ | - | √ | √ | 76,92 |
| 14 | The effect of walnut oil consumption on blood sugar in patients with diabetes mellitus type 2 (Javad, Nezhad, Aghasadeghi, & Hakimi, 2016) | √ | √ | √ | √ | √ | - | √ | √ | √ | √ | √ | √ | √ | 90,30 |
| 15 | Comparison of topical capsaicin and topical turpentine oil for treatment of painful diabetic neuropathy (Musharraf, Ahmad, & Yaqub, 2017) | √ | √ | √ | √ | √ | - | √ | √ | √ | √ | √ | √ | - | 84,61 |

III. RESULT

General Characteristics

Based on 15 articles that have been analyzed (Table 1), the most common type of study was random control-trial with 12 articles (80%) and the most common time of evaluate the intervention was 90 day with 5 articles (33,33%). The type of the herbal that used to interventions for diabetes mellitus type-2 from the articles are various.

Table 1. 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>syzigium polyanthum</i>), and pegagan leaves (<i>centella asiatica</i>) | 1 | 6,67 |
| Cinnamon and caucasian whortleberry | 1 | 6,67 |
| American gingseng | 1 | 6,67 |
| Momordica charantia | 2 | 13,33 |

| Category | n | % |
|---|----|-------|
| Nano curcumin | 1 | 6,67 |
| Propolis supplement | 1 | 6,67 |
| Extract berberis integerrima root | 1 | 6,67 |
| Glucoherbs | 1 | 6,67 |
| Combination of silymarine, olibanum and nettle extracts | 1 | 6,67 |
| Oral ginger supplementation | 1 | 6,67 |
| Topical capcaisine and turpentine oil | 1 | 6,67 |
| Abelmoschus manihot | 1 | 6,67 |
| Kangen-karyu | 1 | 6,67 |
| Walnut oil | 1 | 6,67 |
| Type of study | | |
| random control-trial | 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 antiamilase, antiglucosidase and antioxidant than *Bay Leaves (Syzigium Polyanthum)*, and *Pegagan Leaves (Centella Asiatica)*. *Momordica charantia* 200gr / 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 2,380mg / day for 56 days has no significant effect in reducing HbA1c levels but has an effect in lowering blood glucose levels. Giving *Cinnamon* and *Caucasian whortleberry* as much as 1g / day for 90 days can reduce blood glucose levels and body weight and control moderate glycemic status. Giving *American ginseng* as much as 3g / day for 56 days can reduce HbA1c and systolic blood pressure. 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.

Provision of Propolis supplements of 1,500 mg / day for 60 days can reduce HbA1c, fasting blood sugar, post pandrial blood sugar and increase total antioxidant capacity (TAC) and glutathione peroxidase (GPx). Giving an extract of 1gr / day of *Integerrima root berberis* for 90 days can reduce blood glucose levels, body weight and cholesterol. Giving *Glucoherbs* for 360 days can reduce HbA1c, blood glucose levels, and BMI in pre-diabetic patients. The combination of *Silymarine, Olibanum* and *Nettle extracts* as much as 6gr / day for 90 days can reduce HbA1c, fasting blood sugar and triglycerides. Oral *Ginger* supplementation of 2 gr / day for 300 days was significant for anthropometric evaluation and decreased the concentration of NF-xB 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 VEGF, NPDR, ETDRS vision scores and macular edema. It could be taken as a novel complementary and alternative strategy for treating type 2 diabetic nonproliferative retinopathy. Giving *Kangen Karyu* as much as 7.5 gr / day for 120 days can reduce somatic and subjective symptoms, reduce serum creatinine levels and increase glomerular

filtration. Giving *Walnut oil* as much as 15gr / day for 30 days can reduce HbA1c, fasting blood sugar, and increase blood glucose homeostasis in type 2 DM patients.

IV. DISCUSSION

The effect of consumption of walnut oil, which contains high levels of PUFAs especially Alpha linolenic acid (ALA) was investigated on blood sugar control in DM type 2 patients. 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, Sun, Manson, Willett, & Hu, 2013) (Javad et al., 2016).

Walnuts has the highest antioxidant capacity. These antioxidants are possibly of phenolic compounds, including hydrolyzed tannins, tocopherol (Anderson, Teuber, Gobeille, Cremin, & Waterhouse, AL Steinberg, 2014), 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 body weight remains unchanged (Javad 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 (Javad et al., 2016). Also in another clinical trial have been reported that consumption 1200 mg turmeric for a period of 8 weeks could reducing BMI in patients with type 2 diabetes (Maithilikarpagaselvi, Sridhar, Swaminathan, & Zachariah, 2016). There are various mechanisms for anti-diabetic effect of curcumin. One of the most fundamental of these mechanisms is that improvement in beta-cells function through its anti-inflammatory and anti-oxidant properties (Rivera-Mancía, Lozada-García, & Pedraza-Chaverri, 2015) (Chuengsamarn, S, Rattanamongkolgul, S, Luechapudiporn, R, Phisalaphong & Jirawatnotai, 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, Krishna, Rao, Saradhi, & Rao, 2012). The intake of *Momordica charantia* or bitter melon for 12 weeks and improved fasting glucose levels and insulin resistance index in patients with type 2 diabetes mellitus (Kyoung et al., 2020). The bitter melon extract potentiated OHAs in patients with type 2 diabetes. However, the size of these studies were small, and others were not randomized or double-blinded. Marisol et al. conducted the randomized, double-blinded, placebo-controlled study (Cortez-Navarrete Marisol, Martí nez-Abundis Esperanza & Gonzalez-Ortiz Manuel, 2018).

The experimental studies established that propolis could practically control the hyperglycemia in the STZ-induced diabetic rat model (Afsharpour, Javadi, Hashemipour, Koushan, et al., 2019). This finding are similar with The results of Samadi et al. investigation that conducted in patients with type 2 diabetes, showed that daily intake of 900 mg of bee propolis supplement for 12 weeks results in improvement of glycemic in patients with T2D (Samadi N, Mozaffari-Khosravi H, Rahmanian M, 2017).

V. CONCLUSION

There are many ways to lower blood glucose levels in patients with DM, one of which is 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 *Integerrima* root *berberis* and the other herb therapy. Besides that herbs have secondary results, namely being able to reduce stress, quality of life, body weight and control moderate glycemic status.

CONFLICT OF INTEREST

No conflict of interest have declared

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