Tackling Indonesia’s Diabetes Challenge with Indonesian Traditional Herbs as Dietary Supplementation to Reduce Development of Cardiovascular Complications: Promotion The Use of Natural Product

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ABSTRACT
Indonesia’s biggest challenge in the next 10-15 years is non-communicable diseases (NCD) like cardiovascular and diabetes with its complication which are accounted for nearly 50 percent of deaths in the country. As of 2014, Indonesia’s diabetes population was the fifth largest in the world, International Diabetes Federation (IDF) predicted more than 14 million Indonesians will suffer diabetes in 2035. Dietary supplementation can reduce the risk of diabetes development and its cardiovascular complication. Indonesia as a country that is rich in natural sources has the opportunity to maximise the utilization and benefits of its natural products. Indonesian traditional herbs have been used to treat disease and nowadays they are being scientifically developed for therapies. These natural products are considered to have potentials in delaying the development of diabetes and its complications and to be able to cure the metabolic abnormalities using a variety of mechanism. Comprehensive literatures were used to review Indonesian traditional herbs used in the management of diabetes. An online database research from Elsevier, Science Direct, and PubMed was conducted to find literature on herbs growth in Indonesia that improves health outcomes in the development of diabetes and its cardiovascular complication. Indonesian traditional herbs such as Momordica chataantia, Trigonella foenum-graecum, Tinospora cordifolia, Zingiber officinale, Allium sativum have been proven to produce significant improvement of blood glucose, 2 hours post load glucose, A1C, LDL-C, blood pressure level as compared with control which have antidiabetic and cardioprotective activity with various mechanism of action. Indonesian scientifically proven traditional herbs have great potentials to be used as dietary supplementation to reduce the development of diabetes and its complication. It can be the investment to tackle the global challenge for reducing deaths caused by diabetes and its cardiovascular complication.

Keywords: Indonesia, Diabetes, Cardiovascular, Complication, Herbs, Dietary

I. INTRODUCTION
Indonesia’s biggest challenge in the next 10-15 years is non-communicable diseases (NCD) like cardiovascular and diabetes with its complication which are accounted for nearly 50 percent of deaths in the country. As of 2014, Indonesia’s diabetes population was the fifth largest in the world, International Diabetes Federation (IDF) predicted more than 14 million Indonesians will suffer diabetes in 2035 [1].

Traditional herbs have an important role in primary health care of individuals in many developing countries e.g. Indonesia. In Indonesia, traditional herbs, known as “Jamu”, have been taken since long time ago and still popular on the Indonesian health care system. Traditional herbs are highly taken by people because it is cheaper than western medicines [2].

Dietary supplementation of traditional herbs can reduce the risk of diabetes development and its cardiovascular complication. Indonesia, as a country that is rich in natural sources, has the opportunity to maximise the utilization and benefits of its natural products. Indonesian traditional herbs have been used to treat disease and nowadays they are being scientifically developed for therapies. These natural products are considered to have potentials in delaying the development of diabetes and its complications and to be able to cure the metabolic abnormalities using a variety of mechanism [3].

II. DIABETES AND COMPLICATION
Diabetes mellitus is a chronic illness and define as “a metabolic disorder of multiple etiologies
characterized by chronic hyperglycemia with disturbances in carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both” [4]. In general, there are four classification of diabetes mellitus: type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, and specific type of diabetes due to other cause [5]. Type 1 diabetes mellitus is insulin-dependent diabetes which occur due to destruction of β-cell of pancreas. Type 2 diabetes mellitus (non-insulin-dependent) is insulin resistance due to progressive loss of insulin secretion. Type 2 diabetes mellitus (T2DM) is the most common diabetes mellitus in people with diabetes and the result of physical inactivity and excess body weight. Gestational diabetes is diabetes that occur in pregnancy [5].

Hyperglycemia is a pathological condition characterized by elevated blood glucose levels. It affects the mortality rate and caused the reduction of blood flow to the central nervous system area. It is a manifestation most commonly associated with such disease conditions as pre-diabetes and diabetes mellitus. The hyperglycemia seems to be involved in diabetic macrovascular complications [6,7,8]. It is a leading cause of nephropathy, retinopathy, and accelerated atherosclerosis [9].

In patients with T2DM, the frequency of atherosclerosis disease is increasing and causing the myocardial infarction, stroke, and gangrene in the lower part of the extremities. Increased risk of atherosclerosis in T2DM patients due to several reasons, those are the occurrence of hypertension and hyperlipidemia. The T2DM condition itself is the risk factor of atherosclerosis and has a synergistic activity with other risk factors that can increase the event of atherosclerosis. In T2DM, hypertension often occur on patient with obesity and those with insulin resistance [8].

The central pathologic mechanism of cardiovascular disease is the process of atherosclerosis that causes narrowing the arterial wall in the body. Other risk factors are as follows: (a) changes in lipoprotein composition in T2DM make the particles in the blood vessels become more atherogenic; (b) procoagulant state in T2DM patients such as increased blood clotting factor and platelet aggregation; (c) proatherogenic changes in blood vessel walls; (d) proatherogenic changes in blood vessel walls due to the direct effect of blood hyperglycemia like the sedimentation of protein glycation only happened in microvascular complication; (e) pro-inflammation associated with the occurrence of insulin resistance [8,10].

III. INDONESIAN HERBS WITH ANTIDIABETIC AND RELATED BENEFICIAL EFFECTS

Nowadays, there has been increasing use of complementary and alternative medicine among global society. There were studies reported that almost 8% respondents with diabetes use alternative medicine. Another survey in specific diabetes populations two-thirds and 49% of Hispanic population in South Texas used alternative medicine [11]. Part of plants and its derivates have been used in traditional medicine around the world including Indonesia [11]. As a tropical country with thousands of islands, Indonesia is gifted with a rich and unique biodiversity [3]. Indonesia is the world’s second largest biodiversity after Brazil and home for about 90% of medicinal plants species found in Asia [11]. The area of Indonesian tropical forests is very wide and contain about 80% of the world’s medicinal plants. About 40 million Indonesian people have historically used the herbal medicines (known as “jamu”) for the treatment of diseases and dietary supplement [3]. This biodiversity rich have potential for future development of medicinal plants [12]. There are many herbal plants suggested for diabetes and its complication as follow:

A. Momordica charantia

*Momordica charantia* (MC) or usually called bitter melon is a flowering vine from the family of Cucurbitaceae. It is a tropical plant that is widely cultivated in Asia, India, East Africa, and South America for its intensely bitter fruits that are commonly used in cooking and as a natural remedy for treating diabetes. Bitter melon is one of the most beneficial plants for treating diabetes [13,14].

Many parts of the plant had been used by the public for treating the T2DM, those parts were the leaves, the stem, and the green fruits or seed. It also often being extracted into a dry powder and consumed in the form of capsules, aqueous extract, powdered dried fruit or fresh juice. The main constituents of MC which are believed to have the antidiabetic effects and possessed
insulin-like chemical structure and properties are momocharin and momordin. The momordin belongs to alkaloid group which is responsible for the bitter taste of MC and momorcharin belongs to glycoproteins group that possessed hypoglycemic properties [13,14].

Many research reported the various mechanism of bitter melon as the antidiabetic agent for the patient with T2DM. It is believed to exert the hypoglycemic effect by involving the stimulation or inhibition of the key enzymes of metabolic pathways, it stimulates the key enzymes of hexose monophosphate pathway, increases the utilization of peripheral and skeletal muscle glucose, inhibits the intestinal glucose uptake and hexokinase activity, suppress the gluconeogenic enzymes, and maintain the normal function of islet β-cells [15].

Rahman et al (2015) conducted a randomized control trial in human that proved the hypoglycemic and antiatherogenic effects of bitter melon compared to glibenclamide in T2DM patients [15]. The randomized controlled trial, double blind, and parallel group trial were involving 95 participants and divided into 3 groups. The first group received bitter melon 2 g/day, the second group received bitter melon 4 g/day, and the third group received glibenclamide 2.5 mg/day for 10 weeks. The result showed that there was significant reduction in A1C levels among patients in group 1, 2, and 3 from baseline to end-point after receiving the interventions. In group 1 and 2 which received bitter melon, the changes in 2 hours plasma glucose after oral glucose tolerance test (OGTT) were not statistically significant but the changes in fasting plasma glucose (FPG) were significant. Group 1 and 2 showed improvement in the changes of the blood lipid levels from baseline to end point but were not statistical significant except for triglyceride (TG), it also showed the favorable changes in body weight and systole blood pressure at the endpoint. The improvement on diabetes associated CV risk factor was better by bitter melon than glibenclamide, it might show that bitter melon less hypoglycemic but more antiatherogenic than glibenclamide [15].

A pilot study was conducted by Trakoon-osot et al in 2013 also showed that there was a significant reduction in A1C levels by consuming bitter melon for 16 weeks [16]. The participants were divided into two groups and each group received 6 g/d of bitter melon dried-fruit pulp or placebo. After 8 weeks of the treatment the reduction of A1C from baseline in the group which was taking bitter melon was greater than that of the placebo group. Although the result of this study showed there was no significant reduction in FPG, but it proved that bitter melon was beneficial on the glycemic control and potential systemic complication of T2DM [16].

B. Trigonella foenum-graecum

*Trigonella foenum-graecum* L. seeds (TFG), family Fabaceae, known as fenugreek, halba or helba, kelabat is commonly used in cooking especially for curry [17]. TFG seeds or its extracts can be used for their nutritive and therapeutic values in many parts of the world, especially in China, Egypt, India and Middle Eastern countries [17]. The present study has found TFG seeds can be used for diet supplementation on blood glucose and lipid profile in T2DM patients. Active compounds of fenugreek included soluble fiber, saponins, trigonell, diosgenin, and 4-hydroxyisoleucine. Marker compound for hypoglycemic activities have mainly been attributed to dietary fiber and saponin, alkaloids, amino acids, galactomannan, nicotinicacid, vitamins and minerals [17]. Soluble fibers like galactomannan help in slowing down digestion affect blood sugar reduction and absorption of carbohydrates [19]. Saponins form large mixed micelles with bile salts and significantly reduce cholesterol by increasing fecal excretion of bile salts, thereby inhibiting cholesterol absorption [19]. 4-Hydroxy leucine found in these seeds stimulates insulin secretion in pancreas and lowers absorption of glucose [19].

Shakour et al (2003) reported that fenugreek seed dietary supplements may be beneficial to T2DM patients and its compliance to reduce blood glucose [18]. The subjects divided to 5 groups, 25 patients included control group receiving diets recommended by the diabetes institute with no other diet supplementation, group received boiled fenugreek seeds as diet supplementation, group received germinated fenugreek seeds as diet supplementation, group received defatted fenugreek seeds as diet supplementation, and group received defatted fenugreek seeds for diet supplementation. All fenugreek was given in a daily dose of 15 g. The results told that there was no significant change in blood glucose, fructosamine and lipid profile. But, there was a significant change in improved serum cholesterol, serum TG, Low Density Lipoprotein (LDL) and Very Low Density Lipoprotein (VLDL). And also there was a significant change that reduced
significant (p=0.000) reduction in the levels of FBG, recruited have given oral administration of ginger blind, placebo daily i.

In another randomized, double blind, placebo controlled conducted by Azimi et al., [23] the CRP decrease significantly (p<0.05) within group (5.65 ± 0.1 to 5.55 ± 0.1).

D. Tinospora cordifolia

*Tinospora cordifolia* (Willd.) Hook.f. & Thomson (TC) is a medicinal plant which has the potential for anti-diabetic and anti-dyslipidemic because of its high alkaloid and terpenes content. Its stem contains some medicinal substances berberine, palmatine, tembetarine, magnoflorine, tinosporin, tinosordifolin [24]. The alcoholic extract of stem has anti diabetic and antihyperlipidemic effect and it has been demonstrated in Wistar rats for its effect. The potential effect of TC extract is better to reduce diabetic-dyslipidemia and extrapancreatic and intrapancreatic activities are known to take part in the anti-diabetic effect. There is no available study on humans after knowing its great potential on the glycemic and lipemic profile in animal models. The stem of TC has great potential to control dyslipidemia and T2DM [24]. The study from this article recruited 100 patients T2DM from the Medicine and Diabetic OPD of King George Medical University who met the inclusion criteria (age of patients between 30-60 years and a known case type 2 diabetes mellitus with taking oral antidiabetic drugs). The exclusion criteria for the patients were type 2 diabetes patients with insulin, type 1 diabetes and gestational diabetic patients, patients above 60 years, patients with nephropathy, neuropathy, retinopathy, and any other chronic complication. 100 patients who met the inclusion criteria were randomly divided into two groups, group A and B. Patients in group A were treated as control (continued to take oral antidiabetic drugs) and patients in group B were given extract of TC in tablet form as add-on therapy alongside the oral antidiabetic drugs. A TC tablet contained 500 mg extract was given three times a day with meals for 6 months. Each patient body mass index (BMI), blood pressure, age, weight, weight was recorded for baseline characteristics [24]. The results of this study after 6 months: the baseline parameters were not statistically significant
(similar from the beginning of this study); the reduction of FBG levels was statistically significant in group A ($p \leq 0.05$) and highly significant in group B ($p \leq 0.005$); the reduction of post prandial blood glucose levels was statistically significant in group A and B ($p \leq 0.05$); the reduction A1C of group B was more statistically significant than group A [24].

59 patients who met the inclusion criteria (T2DM and dyslipidemia and were taking oral antidiabetic drugs and statins) were recruited. The exclusion criteria of this study were patients with secondary complication, gestational diabetes, and type 1 diabetes. The patients divided into 2 groups, intervention group (n=29) and control group (n=30). The intervention group accepted 250 mg of encapsulated mature stem of TC and took it before meals twice daily alongside the dyslipidemia and antidiabetic drugs, but the control group only took the oral dyslipidemia and antidiabetic drugs for 2 months. All parameters were checked before and after 2 months of study to evaluate the effect of the intervention. The results of this study after 2 months: the reduction of CRP was statistically significant; the A1C was similar with the beginning of this study; the reduction of FBG levels was statistically significant in group A and B ($p \leq 0.05$) and highly significant in group B ($p \leq 0.005$); the reduction in HDL and LDL showed statistically significant reduction in FBG, mean total cholesterol, HDL-C, TG, and improvement in High Density Lipoprotein cholesterol (HDL-C) after 24 weeks of treatment [29]. In this study, garlic combined with typical antidiabetic agent. The meta-analysis showed that the administration of garlic resulted in a significant reduction in FBG concentrations [28]. Few adverse effects had reported in clinical studies using AS consist of gastrointestinal discomfort and nausea, allergic contact dermatitis, rhinitis, bloating, headache, dizziness [29,30].

Overall, garlic showed significant effect on prevention diabetes mellitus and its complication as single treatment and with combination with antidiabetic agent, and may be a potential addition in the treatment of patients with T2DM and hyperlipidemia.

IV. CONCLUSION

Indonesian scientifically proven traditional herbs have potentials to be used as dietary supplementation to reduce the development of diabetes and its complication. Indonesian traditional herbs such as Momordica chataurantia called bitter melon; seeds of Trigonella foenum graecum, rhizome of Zingiber officinale; stems of Tinospora cordifolia; roots of Allium sativum were represent the herbs which are most frequently used as herbal medicine. These plants have been studied intensively up to clinical trial stage for their activity in reducing diabetic development and its secondary complications. The mechanisms of action of these plants in reducing diabetic factors have been
studied in molecular level lately. Therefore, it can be the investment to tackle the global challenge for reducing deaths caused by diabetes and its cardiovascular complication.

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