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Recent review of herbal medicine for treatment of diabetes and diabetic vascular complications

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Abstract

In this modern age, Type 2 Diabetes Mellitus (T2DM) has been identified as one of the fast spreading epidemic affecting global population. The epidemic has caused endothelial dysfunction and inflammation; atherosclerosis and vascular complications. Western medications and various treatment approaches lead to serious adverse drug reactions and high costs of treatment with no promising cure. Availability of various herbal medicines need to be explored to be able to provide a holistic approach in treating T2DM. In this review paper, summarize the recent progress and potential herbal treatment in the management of diabetes mellitus. We focus on two medicinal plants, *Gymnema sylvestre* (TIM) and *Panax quinquefolius* (TCM).

Keywords: Traditional Indian Medicine, Traditional Chinese medicine, *Panax quinquefolius*, *Gymnema sylvestre*

1. Introduction

In 2000, it was estimated that adults ≥ 20 years of age with diabetes were around 171 million, worldwide. It has also projected about 221 million people in 2010 and reaching 300 million by 2025. According to International diabetes federation, Malaysia with a population of 31 million has reached 3.3 million numbers of diabetic patients in the year of 2015. The alarming increase in diabetic number maybe due to growing prevalence of obesity, physical inactivity, genetic susceptibility, urbanization and ageing^[1]. As a very common chronic disease, diabetes is becoming the third 'killer' of the health of mankind along with cancer, cardiovascular and cerebrovascular diseases because of its high prevalence, morbidity and mortality^[2]. Glucose is vital to our health because it's an important source of energy for the cells that make up our muscles and tissues. It's also our brain's main source of fuel. Physiologically, the pancreatic β -cells constantly synthesize insulin, regardless of blood glucose levels. Insulin is stored within vacuoles and released once triggered by an elevation of the blood glucose level. Insulin is the principal hormone that regulates uptake of glucose from the blood into most cells, including skeletal muscle cells and adipocytes. Insulin is also the major signal for conversion of glucose to glycogen for internal storage in liver and skeletal muscle cells^[3, 4]. Diabetes mellitus is a systemic metabolic disease characterized by hyperglycemia, hyperlipidemia, hyperaminoacidemia, and hypoinsulinaemia. Generally it affects how the body uses blood sugar (glucose); decrease in insulin secretion and insulin action^[5]. Disordered metabolism in the body with abnormally high blood glucose can lead to either Type 1 diabetes mellitus (T1DM) or Type 2 diabetes mellitus (T2DM)^[6]. Patients with T1DM experience diminishing level of insulin in the body. While T2DM is a complex heterogeneous group of metabolic disorders including hyperglycemia and impaired insulin secretion and/or insulin action. T2DM causes dysfunctions in multiple organs or tissues currently used therapies to treat diabetes are lifestyle-directed interventions, insulin, sulfonylureas, metformin and various other treatment methods in single or combinations with other interventions. In United States, patients are normally treated with diet or sulfonylureas. In 1990's sulfonylureas have been only oral therapy available for patients with non-insulin-dependent Diabetes Mellitus (NIDDM). Initial treatment with sulfonylurea alone gave poor improvements. Metformin was used either alone or in combination with sulfonylurea found to be safe and efficacious in reducing plasma glucose concentrations in patients and inhibiting hepatic glucose production^[8, 9]. Generally, metformin is the only biguanide available. Its major effect is to decrease hepatic glucose output and lower fasting glycemia. Typically, metformin monotherapy will lower A1C levels by ~ 1.5 percentage points^[10-12]. Metformin has been in use for T2DM for more than 40 years. It has also reduced mortality rates (compared with other antihyperglycemic treatments) and is rarely associated with lactic acidosis^[13] although generally well tolerated, Metformin has a common adverse effect, gastrointestinal. Thus, although there are many options available for

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the control of T2DM, various researches will still be launched in future in the search of new therapy or compound to treat the disease while addressing or reducing the side effects.

2. Current Understanding T2DM

Diabetes mellitus is a metabolic disorder in the endocrine system. This dreadful disease is found rapidly increasing in all parts of the world and becoming a serious threat of mankind health [2]. There are lots of chemical agents available to control and to treat diabetic patients, but total recovery from diabetes has not been reported up to this date. In addition to adverse effects, drug treatments are not always satisfactory in maintaining euglycemia and avoiding late stage diabetic complications. Glucose is body's primary source of the energy needed for all bodily functions. Our body uses insulin to convert glucose into energy. Insulin is a hormone produced by the beta cells in the islets of Langerhans in the pancreas. It is a powerful hypoglycemic agent. Insulin facilitates the passage of glucose across cell membranes; inhibits the production of glucose from glycogen (the stored form of glucose); promotes the conversion of fatty acids to fat; inhibits the breakdown of adipose tissue; stimulates the synthesis of protein, and inhibits the production of glucose from protein [14]. Diabetes occur in the absence or reduced function of the hormone, insulin, in the body. This may be because of 1) absence of insulin production, 2) insufficient insulin production, or 3) decreased use of insulin (insulin resistance). Insulin transfers glucose from the blood stream through the cell membrane and into the cell where glucose is made available for energy. In the absence of insulin (such as that which occurs in T1DM), the body cannot use glucose, so it resorts to less effective ways to obtain energy (e.g. the breakdown of fat), which results in toxic by-products called ketones. In T2DM, cells in body resist the incoming of insulin via their cells membranes. Accordingly, the blood glucose rises and stimulates the insulin-producing cells to produce more insulin (hyperinsulinemia). For a time, this satisfies the need, but when insulin resistance persists, the body tries (for as long as it can) to yield more insulin to meet the apparent shortage, but eventually, in spite of the resultant hyperinsulinemia, the blood glucose might increase uncontrollably. Since the fundamental problem is insulin resistance and not an absence of insulin, the body does not produce ketones Diabetes [15]. Type 2 diabetes (DMT2) has typically been a condition of adults who are overweight, and is a consequence of insulin resistance. Increasing rates of obesity among these groups are being blamed, at least in part for this dramatic change (Adams & Lammon, 2007; Soltész, 2006). The cause of DMT2 is believed to be a combination of many metabolic abnormalities. Insulin resistance is typically one of the first abnormalities seen. Others include impairment of insulin secretion and elevated glucose production by the liver. Most persons with DMT2 are overweight. Hence, there is a strong association of DMT2 with overweightness and obesity. In some cases, weight reduction can ameliorate the metabolic problem. (Such an occurrence should not be misconstrued to reflect "cure" of diabetes, but rather, "control" of diabetes via educated changes in the way one eats and the incorporation of regular exercise into one's life. Discontinuation of the control regimen with resultant weight gain will likely result in a return of the clinical signs and symptoms of overt DMT2). In the past, practice guidelines advised a two to three month trial of "lifestyle management" (changes in one's nutritional intake and exercise) when DMT2 was diagnosed, with the

introduction of oral medications if these efforts were unsuccessful in attaining control of the blood glucose after that period of time. Practice guidelines recommended by the American Diabetes Association for the individual with newly diagnosed DMT2 changed within the past several years and now include both lifestyle management (medical nutrition therapy and regular exercise) and oral medication (metformin, unless contraindicated) from the time of diagnosis (American Diabetes Association, 2014-A). Intensive education about diabetes, medical nutrition therapy, and self-monitoring of blood glucose (SMBG) (and documentation of the results!) remains fundamental to success in the treatment of diabetes. "Continuing timely augmentation of therapy with additional agents (including early initiation of insulin therapy) as a means of achieving and maintaining recommended levels of glycemic control (i.e., A1c < (less than) 7% for most [non-pregnant] patients)" (pg. S23) and assuring follow up at regular intervals to verify blood glucose control are critical to reaching established goals (American Diabetes Association, 2014-A).

Diabetes is the leading cause of kidney failure, non-traumatic lower-limb amputations, and new cases of blindness among adults in the United States. It is also a major cause of heart disease and stroke (NDIC 2011).

One emerging treatment for this disease are the utilization of Herbal Medicines, Traditional Chinese Medicine (TCM) and Traditional Indian Medicine (TIM).

3. Hyperglycemia, insulin resistance, Inflammation and vascular complications

Diabetes mellitus is a systemic metabolic disease characterized by hyperglycemia, hyperlipidemia, hyperaminoacidemia, and hypoinsulinaemia. It is frequently associated with the development of micro and macro vascular diseases which include neuropathy, nephropathy, cardiovascular and cerebrovascular diseases [5, 16]. The disease is associated with reduced quality of life and increased risk factors for mortality and morbidity. The long-term hyperglycemia is an important factor in the development and progression of micro- and macrovascular complications [16, 17]. Thus the underlying goal of all diabetes treatment and management is to maintain an adequate blood glucose concentration (Arallelimath, 2012) in order to withhold other complications. Besides that, accretion of free radicals in the vasculature of diabetic patients is found to be accountable for the activation of detrimental biochemical pathways, miRs deregulation, release of MPs, and epigenetic variations contributing to vascular inflammation and ROS generation. Oxidative stress plays a major role in the expansion of micro- and macrovascular complications. Since cardiovascular risk burden is not eliminated by intensive glycemic control associated with optimal multifactorial treatment, mechanism-based therapeutic strategies are in highly demand [18-20]. Specifically, inhibition of key enzymes involved in hyperglycemia-induced vascular damage or activation of pathways refining insulin sensitivity may represent promising approaches. Modulation of specific miRs might contribute to improve EPC-driven vascular repair. Moreover, the progressive identification of a complex scenario driven by epigenetic changes that modulate transcription of ROS-generating and pro-inflammatory genes may represent an attractive opportunity to dampen oxidative stress, vascular inflammation, and hence to prevent cardiovascular complications in patients with diabetes [19, 21]. Generally good treatment and management of hyperglycemia will help to

prevent other complications such as inflammation and vascular complications.

4. Chinese and Indian Herbal Medicines

Advancement in recent health care system have created more western treatment options for T2DM. Western or conventional therapies for diabetes have been geared toward regulating blood glucose with a combination of diet modification, insulin and/or oral pharmacological agents, weight loss when appropriate, and exercise (Maggie B. Covington, 2001)

Unfortunately it comes as package with various side effects and high medication and treatment cost. The treatments often have side effects such as weight gain/lose, bone lose and increased risk of cardiovascular complications (AHFS). These side effects could become more prevalent due to continuous use. Moreover, treatment is very expensive as well, since T2DM is a chronic disease, long-term medications are necessary. Herbal medications can be a good alternative to replace or at least supplement to Western medications [2, 22, 23]. Herbal medicines from China and India have been used to hinder and manage T2DM since several thousand years ago. Traditional Chinese Medicines (TCM) and Traditional Indian Medicines (TIM) have been used widely in China, India and many other countries for the treatment of diabetes

and its complications (Tong *et al.*, 2012)

Herbal medicines are usually derived from natural plants, they are considered to be relatively safe and have few side effects compared to the conventional drugs, and this has been proven with clinical studies too. Approximately 800 plants have been identified in the treatment or prevention of T2DM. According to Ray *et al.* (2010), herbal medicines can treat T2DM via multiple mechanisms such as boosting insulin sensitivity, prompting insulin secretion and reduction of carbohydrate absorption, increasing peripheral glucose uptake, potentiating endogenous incretins, increasing the glycogenesis or inhibiting hepatic glycogenolysis [22, 24-26]. In contrast Western medicine generally contains a single active ingredient targeting a specific mechanism. It is also found to be more potent in lowering blood glucose. However, herbal supplements have shown to be able to treat diabetic complications based on the holistic theory, which plays important concentration on the integrated body [27].

Herbal extracts are available in single formulation or complex formulas. There are over 400 extracts found to be effective in vitro or in vivo [24]

Common Herb in Both TCM and TIM

Table 1: Important anti-diabetic potential herbal plants source and their active principles

Botanical Name	Category	Family	Part Used	Main Active Components
<i>Gymnema sylvestre</i>	TIM	Asclepiadaceae	Leaf	Dihydroxygymnemic triacetate [16]
<i>Panax quinquefolius</i>	TCM	Araliaceae	Root	Ginsenosides, protopanaxadiol and Protopanaxatriol [16, 28, 29]

5. *Gymnema sylvestre*

Gymnema is a perennial plant which has climbing characteristics. It grows in Malaysia, Srilanka, Australia, Indonesia, Japan, Vietnam, tropical forests of central and southern India and China. It grows up to 600m. In India, it is found in tropical forest of Andrapradesh, Bihar, Chhattisgarh, Tamilnadu, Uttar Pradesh and West Bengal. It is also found in Banda, Konkan, Western Ghats, and Deccan extending to the parts of western and northern India [16, 30, 31]

Gymnema sylvestre (Asclepiadaceae) is stepping up as a potential treatment for the management of diabetes in India and parts of Asia where diabetes is referred as "sweet urine". Herbal medicine preparation is made using the leaves of the plant and the action (blood sugar lowering) of *Gymnema* leaves was preliminarily documented in the late 1920s [32]. The crude extracts and its isolated compound dihydroxygymnemic triacetate shows hypoglycemic effect against streptozotocin induced diabetic rats in dose and time dependent pattern [33]. This hypoglycemic effect was due to the ability of gymnemic acids to delay the glucose absorption in the blood. Because gymnemic acid molecules prevent sugar molecules absorption by binding to the receptor in absorptive external layers of the intestines [34]. Besides that, dihydroxygymnemic triacetate stimulated the regeneration and revitalization process of remaining beta cells and thus increasing insulin release to regulate glucose levels [16, 35, 36]. Reports from a study also show that *Gymnema sylvestre* extract is capable of regenerating β -cells and portrayed hypoglycemic and hypolipidemic activity in long-term treatment [37]. The same report states people in the early stages of diabetes could be treated to prolong or prevent full-blown clinical effects of diabetes with *Gymnema sylvestre*'s ability to restore of β -cells. According to another study morphological examinations indicate that the damage caused

to the sciatic nerve by STZ was markedly reduced following the administration of *Gymnema sylvestre* [38]. Therefore, *Gymnema sylvestre* extract application may be useful for the treatment of neuropathy in patients with chronic diabetes. By reviewing all the literature we conclusively affirm that the novel compound dihydroxygymnemic triacetate which was isolated from the leaves of *Gymnema sylvestre* represent a good candidate for alternative and/or complementary medicine in the management of diabetes mellitus, since they exhibited beneficial effects on the blood glucose levels and associated biochemical parameters of STZ induced diabetic animals. Adding to that *Gymnema* too found to be useful for the treatment of neuropathy in patients with chronic diabetes. Further clinical trials with the compound as drug are recommended to be performed on human subjects to widen the prospects of the compound.

6. *Panax quinquefolius*

Various herbal compounds are used for reduction of postprandial glycemia (PPG). Main bioactive component with this important capacity would be Ginsenosides from ginseng. The exact effective proportions of total and specific ginsenosides are still not known though. The study by Lee *et al.* (2010) has compared acute efficacy of different ethanol-extraction preparations of American ginseng (AG) and Korean red ginseng (KRG), with their whole-root origins, on PPG and insulin parameters in healthy adults. It was reported that alcohol extraction of whole ginseng root can be used to selectively handle the ginsenoside profile with increasing alcohol concentrations producing high yields of total ginsenosides and varying their individual proportions. This paper concluded that the insulin sensitizing effects of KRG-30% and AG-50% extracts suggest that other root parts, including other ginsenosides not typically measured, may

influence PPG and insulin parameters. There is potential for AG and KRG extracts to modulate IS, an independent predictor of type 2 diabetes (Lee *et al.*, 2010) While data from a study demonstrated that oral administration of American Ginseng berry juice (AGBJ) significantly reduced high blood glucose levels and body weight in *ob/ob* mice. Their conclusion suggests that the hypoglycemic activity of the berry juice may be beneficial in the prevention and management of type 2 diabetes [39].

7. Phytochemical and Pharmacological Properties

7.1 *Gymnema sylvestri*

Gymnema sylvestri leaves contain triterpene saponins that belongs to oleanane and dammarane classes. Key elements like gymnemic acids and gymnemasaponins are members of oleanane group of saponins while gymnemasides are dammaranesaponins [40,41]. Other phytoconstituents include anthraquinones, flavones, hentriacontane, pentatriacontane, phytin, resins, tartaric acid, formic acid, butyric acid, lupeol, β -amyrin related glycosides, stigmasterol, and calcium oxalate [42]. Plant extracts too had alkaloid contents [43]. The major secondary metabolites in *Gymnema* includes a set of nine closely related acidic glycosides. The main are gymnemic acid A–D and found in all parts of the plant. Gymnemagenin is acylated aglycone of gymnemic acid, a glycoside in the leaves of *Gymnema sylvestri*, known for its antisweet principle [44, 45]. Another isolate of *Gymnema sylvestri* is Gurmarin, an important 35 amino-acid peptide having a molecular weight of 4209 [46]. The sugar suppression activity of this compound was determined electrophysiologically on the taste responses of rat. The antisweet effect of this polypeptide is very specific to sweet taste on tongue, affected by the pH change. It has been reported that the polypeptide exhibited maximum anti-sweetener property near its isoelectric point. The hydrophobic, rather than the ionic, interaction plays a significant role in proper binding of gurmarin to the target molecules [46]. Numerous studies have been conducted on using *Gymnema sylvestri* as anti-diabetic treatment or to ease diabetic vascular complications. For example scientific evidences have been proved in animal studies [46]. According to this study, a new substance called 'Gurmarin' suppressed strongly the sweet taste responses of the rat chorda tympani was purified from the leaves of *Gymnema sylvestri*. Chemical analysis and ¹H-NMR spectroscopy have revealed that the substance was a peptide consisting of 35 amino acids and having molecular weight of about 4000. The inhibitory effect was quite specific to the sweet taste responses such as to sucrose, glucose, glycine and saccharin, reduced by more or less the same extent. While similar study have been carried out among human using *Gymnema sylvestri*.

7.2 *Panax quinquefolius*

Over 90% of diabetic cases are Type 2 diabetes mellitus, a syndrome with disordered metabolism of carbohydrates and lipids because of resistance to insulin action and impaired insulin secretion [47].

Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*) root have showed hypoglycemic effects in diabetic mice models [48-50]. Using the *ob/ob* mouse model, it was demonstrated that a 12-day treatment of American ginseng leaf and berry extracts decreased fasting blood glucose, improved glucosedisposal, and reduced body weight [48].

Generally active or inactive chemical entities obtained from

ginseng species can be classified into five categories mentioned in the order of their bioactivities: saponins polysaccharides, polyynes, flavonoids, and volatile oils. Most of the biological activities of ginseng are derived from its main constituents, ginsenosides [51, 52].

Ginsenosides have been portrayed with antidiabetic effects in animal models by Rb1 [53]. Oxidative stress too were reduced [54], activated peroxisome proliferator-activated receptor γ , increased GLUT expression, and enhanced PKA-dependent pathways [55, 56]. A series of randomized, placebo-controlled acute clinical studies were conducted to evaluate the efficacy of American ginseng in lowering postprandial glycemia in subjects with and without diabetes [57]. American ginseng demonstrated a good acute safety profile. Escalation of dose and time of administration offered no added benefit in people with diabetes. A time, but not dose-dependent effect was observed in healthy individuals, suggesting that people without diabetes are sensitive to the time of ginseng administration. Evidence indicates that the glycemia-lowering effect of ginseng root may be species dependent. Some clinical evidence suggested that the ratio of protopanaxadiols to protopanaxatriols is inversely correlated with the glycemia-lowering efficacy of ginseng root. American ginseng with a relatively high ratio has a better effect on acute postprandial glycemic indices in healthy humans than dose of Asian ginseng [58].

Besides diabetes, various pharmacological actions of American ginseng have been observed on the central nervous, cardiovascular, endocrine, and immune systems. Their neuroprotective, cardioprotective, antioxidant and anticancer properties have been reviewed by Qi [28]. Reports of the effectiveness of ginseng are sometimes contradictory, perhaps as chemical content of ginseng root or root extract differs, depending on the method of extraction, subsequent handling, or even the season of its collection. The high variability in ginsenoside composition of ginseng among different species and batches may contribute to similar high variability in efficacy [59].

8. Summary

T2DM is a multifaceted metabolic disorders characterized by hyperglycemia and insufficient insulin secretion and/or impaired insulin action. The complex nature of T2DM reflects the complicated genetic background and the varied genetic-environmental interaction. The current theories of T2DM include a defect in insulin-mediated glucose uptake, a dysfunction of the pancreatic β -cell, a dysregulation of the adipocyte as a secretory organ, and adysfunction of the liver. Dysregulation of metabolism in diabetes also causes extensive complications in nearly all organs or tissues such as inflammation and vascular complications. Recent advances in animal models of T2DM make it possible to explore the previously unidentified pathogenesis of the disease. Besides of a whole range of Western medicines available for the treatment of T2DM, a few herbal medicines could be options of treatment for diabetic patients which are more economic to obtain and consume. These herbal medicines are found to be able to treat diabetic complications based on the holistic theory, which plays important concentration on the integrated body without emitting side effects. Herbal medicines could manage T2DM via multiple mechanisms such as boosting insulin sensitivity, prompting insulin secretion and reduction of carbohydrate absorption, increasing peripheral glucose uptake, potentiating endogenous incretins, increasing the glycogenesis or inhibiting hepatic glycogenolysis. Therefore

herbal medicine can also be used as supplementation or in combination with the Western medicine to improve better therapeutic outcomes for diabetic patients. Further animal and clinical studies using herbal medicines could generate numerous treatments and prevention of T2DM in the worlds' population.

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