Diabetes Mellitus: Treatment Challenges and the Role of Some Herbal Therapies

[1]Rajalingham Sakthiswary, [2]Zaiton Zakaria and [3]Srijit Das

[1]Department of Medicine, Universiti Kebangsaan Malaysia Medical Centre,
56000, Cheras, Kuala Lumpur, Malaysia
[2]Department of Physiology, Universiti Kebangsaan Malaysia,
50300, Kuala Lumpur, Malaysia
[3]Department of Anatomy, Universiti Kebangsaan Malaysia,
50300, Kuala Lumpur, Malaysia

Abstract: Diabetes mellitus (DM) is a chronic metabolic disorder with devastating complications affecting millions of individuals across the world. Alarmingly, the incidence of DM continues to rise steadily. Hence, it is not surprising that both modern and traditional medicine researchers have been consistently experimenting antidiabetic agents for the treatment of DM and its complications. Despite the promises and convincing scientific evidence that lie beneath the prescription of drugs, a significant number of DM patients opt for herbal preparations. The popularity of herbal supplements for treating DM and its complications is attributed to the cost effectiveness and lesser side effects. The three main domains of complementary and alternative medicine i.e. western herbalism, Chinese and Ayurvedic medicine have been tried for the effective treatment of DM. The main aim of the present review is to highlight the advances of the used herbal antidiabetic preparations. Besides, we have discussed the various macrovascular and microvascular complications occurring in DM with the potential role of herbal supplements in this regard. For the purpose of this review, we have retrieved some related articles from Pubmed, Ebsco and ScienceDirect published between the years 1980 and 2013.

Key words: Diabetes Mellitus · Antidiabetic · Drugs · Treatment · Herbs · Antioxidants

INTRODUCTION

The Global Burden of Diabetes Mellitus: Diabetes mellitus (DM) is an endocrine disorder resulting in hyperglycaemia due to insulin deficiency, insulin resistance or both. This heterogeneous disease which runs an insidious course may result from a complex interplay of metabolism, environmental and genetic factors [1]. DM can be further subdivided into type 1 DM, type 2 DM and gestational DM. Complications of this condition are far too many affecting almost any organ from head to toes. The major macrovascular complications are coronary artery disease, stroke and peripheral vascular disease whereas the microvascular sequela include

diabetic retinopathy, diabetic nephropathy and diabetic neuropathy. The number of diabetics worldwide has steadily grown to an alarming figure of 285 million in 2010 based on the estimation by the World Health Organization (WHO). The number is still expected to increase by almost two fold to over 400 million by 2030 [2].

The vast majority of cases of DM hail from the low to middle income countries. India ranks first in this aspect, accounting with the highest number of DM cases. China is rated as the second nation with regard to the incidence [2, 3]. The rising trend in prevalence of DM over the years are attributable to the modern diet and lifestyle and more effective screening methods. This disease poses an enormous economic burden to many nations in the

Corresponding Author: Rajalingham Sakthiswary,Department of Medicine,Faculty of Medicine Universiti Kebangsaan Malaysia Medical Centre Jalan Yaacob Latif, Bandar Tun Razak 56000, Cheras, Kuala Lumpur, Malaysia.
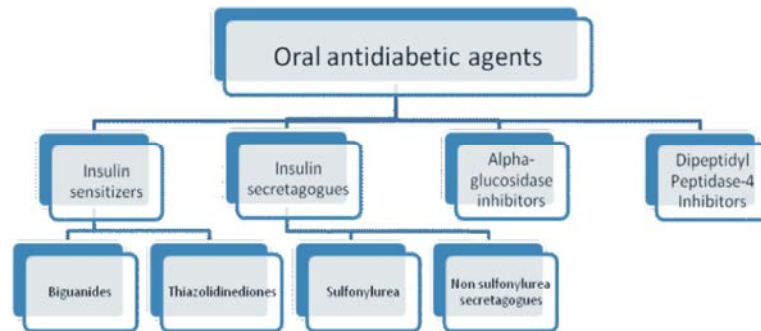Tel: +6-03-91456097.

Fig. 1: Schematic diagram showing the main classes of oral antidiabetic agents used in clinical practice.

east and west [3-9]. In England, it has been reported that the cost of treatment of DM escalated from £458.6 million in 2004/5 to £649.2 million in 2009-2010 [10]. It is reasonable to expect a parallel rise in morbidity and mortality secondary to the cardiovascular disease. The DM epidemic has set off alarms and calls for a global initiative ideally involving practitioners of modern and alternative medicine.

The Evolving Concepts of Pathogenesis of DM: Various complex mechanisms with multifactorial pathways ultimately lead to DM. The pathogenesis of DM has evolved to a great extent ever since it was initially discovered. Although much is known about the mechanisms involved, there are still questions which need to be answered. The severity of the disease and the occurence of complications may vary from one individual to another despite similar levels of endogenous insulin. The interplay of genes, lifestyle, environment and oxidative stress may determine the course of the illness. The key mechanisms involved in DM are insulin resistance and beta-cell dysfunction. Excessive ectopic fat accumulation especially visceral fat increases the risk of insulin resistance. In the recent decades, there has been a paradigm shift in the understanding of DM with newer concepts on insulin resistance which have emerged and been established. It is now believed that it involves cytokine production by activated white blood cells as part of an immune response [11-14]. Besides, oxidative stress, especially involving reactive oxygen species (ROS) can result in auto-oxidation of glucose and impairment of antioxidant defense enzyme activities [15-17]. The incretin hormones secreted by the intestine i.e. glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) enhance insulin production postprandially and accumulating evidence assigns a blunted GLP-1secretion in DM [18].

At a cellular level, more recently, dysfunction of the mitochondria and endoplasmic reticulum (ER) were discovered to be partially responsible for the β-cell dysfunction and insulin resistance. ER stress can trigger mitochondrial dysfunction with subsequent apoptosis signaling via Ca2+- and reactive oxygen species dependent mechanisms. The interaction between mitochondrial dysfunction and ER stress is a rapidly growing area of research interest. Dissection of the processes involved in DM will pave the way for more targeted therapies [19-21].

The Conventional Therapies in DM: The standard international practice now is to adopt an aggressive glucose-lowering approach from the very beginning of the disease process in order to effectively overcome the macrovascular risk. It is strongly recommended to use combination of drugs with a complementary mode of action to achieve an HbA1c level of below 7% [22]. The two broad categories of pharmacological approach to DM are insulin therapy and oral hypoglycaemic agents (OHA). More efficacious therapies are constantly being sought by researchers to achieve optimal glycaemic control and improve outcomes. Today, clinicians have the luxury of an extensive range of OHA. The main classes are heterogeneous in their pharmacodynamics and pharmacokinetics. The older OHAs are sulphonylurea, alpha-glucosidase inhibitors and biguanides while the newer agents are incretin-based therapies, drugs inhibiting kidney glucose reabsorption (SGLT2 inhibitors) and glucokinase activators (Fig. 1). Patients with suboptimal diabetic control while on OHA, severe hyperglycaemia and type 1 DM are some of the candidates for insulin therapy. Oral anti-diabetic agents have variety of ways to exert therapeutic effects. These include stimulation of insulin secretion, reduction of hepatic glucose production, inhibition of absorption of intestinal carbohydrate or enhancement of peripheral insulin sensitivity [23, 24].

Insulin sensitizers namely biguanides and thiazolidinediones (TZDs) address the key mechanism involved in Type II diabetes which is insulin resistance. Biguanides reduce hepatic glucose production and increase peripheral utilisation of glucose. This class of OHA has emerged as the most widely prescribed agent in type 2 DM. Metformin has been around since the 1960s and is usually the first line OHA [25, 26]. TZDs, on the other hand, binding to PPARγ, a type of nuclear regulatory protein is involved in transcription of genes involved in glucose homeostasis. These PPARs act on peroxysome proliferator responsive elements (PPRE [1]) to enhance production of mRNAs of insulin-dependent enzyme resulting in improved glucose utilization. Examples of TZDs are rosiglitazone (Avandia), pioglitazone (Actos) and troglitazone (Rezulin). The ADOPT study and DREAM trial had results in favor of TZDs with demonstrable retardation of disease progression among the subjects [27, 28].

Insulin secretagogues can be further subdivided into sulfonylurea and nonsulfonylurea secretagogues. This category of OHAs trigger insulin release by acting on the potassium channels of the pancreatic beta cells. Sulfonylureas were the earliest most widely prescribed OHAs. The first generation of sulphonylureas include tolbutamide, tolazamide, chlorpropamide whereas glipizide, glibenclamide, glimepiride and glyclazide are some of the second generation drugs [29, 30]. Nonsulfonylurea secretagogues refer to meglitinides (repaglinide and nateglinide) which are also known as "short-acting secretagogues [31].

Alpha-glucosidase inhibitors for e.g. acarbose and voglibose act on the small intestine to slow the digestion of starch for a more gradual rise in the plasma glucose levels postprandially. This group of OHA is less popular in the United States but is still widely prescribed in other regions of the world like Asia and Europe [32, 33].

In the recent years, strong emphasis has been placed on GLP-1. It is proven to increase beta-cell mass in murine studies. GLP-1. However, it is rapidly degraded by dipeptidylpeptidase IV (DPPIV) which limits its therapeutic potential. To tackle this problem, GLP-1 analogs (exenatide) which are more resistant to degradation and DPP-IV inhibitors (sitagliptin) were developed [34, 35]. Biological therapies are being increasingly experimented with encouraging results. The pharmacodynamics of these agents are very diverse and consist of insulin sensitization (11beta-HSD-1 inhibitors and antagonists of glucocorticoids receptor), reduction in hepatic glucose output (antagonist of glucagon receptor, inhibitors of glycogen phosphorylase and fructose-1,6-biphosphatase). Glucokinase activators (GKA) lower glucose levels by increasing insulin secretion and hepatic glucose metabolism [36, 37]. A new promising treatment strategy which is awaiting Food and Drug Administration (FDA) approval; targets the sodium-glucose co-transporter 2 (SGLT2). SGLT2 inhibitors regulate glucose through interference of glucose reabsorption in the proximal tubules of the kidneys resulting in increased urinary glucose excretion. Compared to the other antidiabetic agents, SGLT2 inhibitors have a rather unique mode of action which is insulin independent [38] (Fig. 2). Interleukin-1 receptor antagonist (IL-1Ra) is a novel anti-inflammatory therapeutic strategy in DM, which has already been approved by FDA [39].

The Drawbacks of Conventional Therapies and the Unmet Needs in DM: Despite the promises of the wide range of options of prescription medications, these drugs are associated with numerous side effects which are intolerable for many patients. Table 1 summarized the mechanisms of action and the side effects of the main classes of antidiabetic agents. Sulfonylureas are known to cause weight gain and hypoglycemia. Biguanides carry a low risk of lactic acidosis especially among the elderly and in the presence of hepatic, liver or renal failure. The more common side effects of metformin involve the gastrointestinal tract, with nausea, cramps and diarrhea. Up to 30% of patients experience these symptoms while on metformin; the most widely prescribed OHA [40]. Vitamin B_{12} deficiency has been reported in approximately 7% of patients on metformin following 1 year of treatment [41]. Alpha-glucosidase inhibitors, on the other hand, cause flatulence. This is due to gas formation following the digestion of undigested carbohydrate by colonic bacteria in the large bowel. The most feared side effect of this agent is hepatic necrosis high serum a-glucosidase level especially in the presence of renal decompensation [42].

Since 2007, rosiglitazone, a thiazolidinedione, has raised a lot of concerns and controversies pertaining to the increased risk of myocardial infarction and cardiovascular mortality. A meta-analysis published in 2010 concluded that this agent had an unfavorable benefit to risk ratio. The other major problem with this class of drugs is fluid retention due to excess production of vascular endothelial growth factor (VEGF) and overstimulation of the peroxisome proliferator-activated receptor (PPAR) gamma receptors [43].
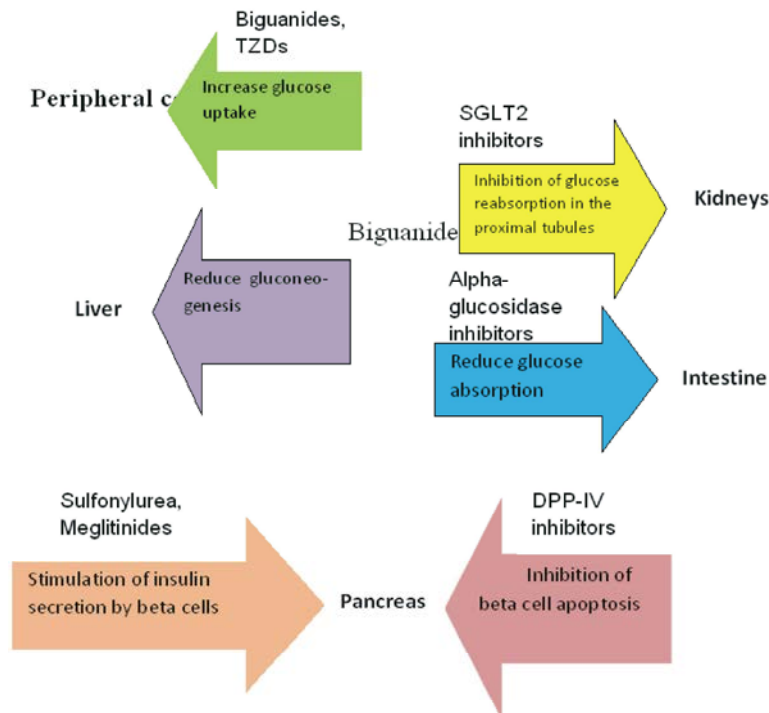
Fig. 2: Schematic diagram of sites and mechanisms of action of oral antidiabetic
SGLT2: Sodium-glucose co-transporter 2, TZD : thiazolidinediones, DPP-IV : dipeptidylpeptidase IV

Table 1: The mechanism of actions and side effects of antidiabetic agents

Antidiabetic agents	Mechanism of action	Adverse effects
Sulfonylurea	-binds to an ATP-dependent potassium channel on the cell membrane of pancreatic beta cells. -sensitizes ?-cells which limits hepatic gluconeogenesis, lipolysis and clearance of insulin by the liver.	Hypoglycaemia,weight gain, abdominal pain, hypersensitivity reactions, teratogenic, increased risk of cardiovascular death (FDA warning)
Metformin	-suppresses hepatic gluconeogenesis -activates AMP-activated protein kinase (AMPK), an enzyme that plays an important role in insulin signaling and glucose metabolism -increases insulin sensitivity, enhances peripheral glucose uptake (by phosphorylating GLUT-4 enhancer factor), increases fatty acid oxidation, and decreases absorption of glucose from the gastrointestinal tract	diarrhea,abdominal cramps, nausea and vomiting increased flatulence lactic acidosis
Alpha-glucosidase inhibitor	- inhibits pancreatic alpha-amylase and reduces glucose absorption from carbohydrates	flatulence, diarrhea, Pneumatosis cystoides intestinalis
Thiazolidinediones	-activates PPARs (peroxisome proliferator-activated receptors leading to decreased insulin resistance, modification of adipocyte differentiation, decreased leptin levels and increased adiponectin levels	Increases cardiovascular risk, Oedema, Weight gain, Worsens congestive cardiac failure
Dipeptidyl Peptidase-4 Inhibitors	-increases blood concentration of the incretin GLP-1 by inhibiting its degradation by dipeptidyl peptidase-4.	Increased risk for infection, headache
Injectable Glucagon-like peptide (GLP) analogs and agonists	-binds to a membrane GLP receptor	decreased gastric motility causing nausea

Antidiabetic agents especially insulin therapy cause fluctuations in the plasma glucose levels. Hypoglycaemic attacks are common and potentially life threatening. Insulin secretagogues are also notorious in this sense. In a recent study in South Central England, 4081 emergency calls over a 1 year period were coded as hypoglycaemia. The vast majority of the patients were diabetics. In the United kingdom, the estimated annual cost for emergency services related to hypoglycaemia was 13.6 million pounds [44].

The safety profile and tolerability of the newer antidiabetic drugs are questionable and require further robust evidence before they are deemed safe. Unfortunately, certain serious side effects are not discovered until years elapse after the drugs official approval. Many antidiabetic agents have been withdrawn from the market due to safety issues. Rezulin, for example, a form of TZD, was banned following reports of serious liver toxicity [45]. Recently, the majority of the FDA panelists voted against the approval of the SGLT2 inhibitor due to the potential hazard of developing bladder and breast cancer [46].

Patients' compliance with medication is strongly affected by the troublesome side effects. On the flip side, compliance is bound to be fair in the setting of a good or tolerable side effect profile. Non compliance accelerates the development of both macro and microvascular complications of DM due to chronic hyperglycaemia. The poor patients are often in a dilemma to choose between the clinical manifestations of DM and the side effects of the medications. Apart from unfavorable patient outcomes, non compliance translates to unproductive public expenditure.

Despite all the elegant clinical studies and trials, there are several unmet needs with the conventional treatment strategies of DM. The earlier discussed medications addressed the effect of the disease which is hyperglycemia rather than tackling the culprit causative processes like declining function of pancreatic beta cells. Antidiabetic agents are not disease-modifying, allowing relentless progression of the disease over years. The ADA/EASD consensus guidelines have clearly highlighted that even among patients who initially succeed in achieving glycemic goals with only metformin monotherapy, may eventually require combination treatment, with or without insulin. Furthermore, the results of the U.K.'s Prospective Diabetes study showed that despite successful initial lowering of fasting blood glucose and HbA1c with intensive monotherapy, these parameters steadily increased with time due to the progressive nature of DM [47]. Regardless of the initial choice of OHA, the good glycaemic control achieved is not sustained over a prolonged period requiring either combination therapy or switches between drug classes.

Besides, the currently available drugs, with the exception of insulin, only result in modest lowering of glycated hemoglobin (HbA1c) by approximately 1%-2%. This response is inadequate for the long-standing diabetics and for those with HbA1c which is way above the recommended targets.

Patients on antidiabetic agents are required to have a battery of regular blood tests to screen for complications related to the disease and the medications. For instance, following the commencement of TZDs, the liver function test has to be checked every few months. It is most inconvenient for patients on insulin therapy who may have to self-monitor their glucose levels by performing the fingertip glucose measurements on a daily basis. Routine blood check while incurring extra costs are often troublesome and a problem for many patients.

Evidence Based Herbal Therapies for DM and its Complications: We have performed a random search of the Pubmed, Scopus and Science Direct databases for the herbal extracts which were reported to possess antidiabetic properties. A selected number of the aforementioned agents are described in this review.

Gingko: Ginkgo belongs to the *Gingko Biloba* species, also known as EGb 761 in the scientific literature; was coined by W. Schwabe Company, Karlsruhe, Germany and it is one of the most popular over-the-counter herbal dietary supplement in the United States and Europe [48]. This herb has been used mainly to treat age-associated memory impairments and cerebral insufficiency [49]. Researches have revealed that ingestion of 120 mg of EGb 761 as a single dose for 3 months, produced an increase in pancreatic beta cell function and reduction in collagen and arachidonic mediated platelet aggregation [50]. It is reasonable to assume that any agent which enhances beta cell function will be beneficial in type 2 DM. The popular consumption of EGb 761 in the United States of America proves its role as an effective supplement.

Momordica Charantia: Momordica charantia (MC) or bitter gourd which belongs to the Cucurbitaceae family has been proven to be an effective antihyperglycemic vegetable. Experiments conducted on animals as well as in humans showed the potential hypoglycaemic action of MC in DM [51, 52]. In our earlier experiments, we

observed the potential therapeutic effects of MC in DM wound healing [53]. Moreover, administration of MC extract reversed the damages caused in the liver and kidneys of experimental Sprague-Dawley rats induced with diabetes [54, 55].

MC has been reported to reduce the fructosamine level [56]. Research studies have shown that hypoglycaemic properties of MC are attributed to its insulin-like properties [57], increased insulin secretion [58], peripheral tissue uptake of glucose [59], liver and muscle glycogen storage [60] and suppression of hepatic gluconeogenesis [61].

Cuminum Cyminum L: The English name *Cumin* is derived from the Latin name *Cuminum*. It belongs to the family *Cuminum Cyminum. Cuminum cyminum* L is used to improve the taste and flavour of various food preparations. Earlier research reports have shown that the *Cuminum cyminum* L which belongs to the family of Apiaceae exhibited potential hypoglycaemic effects in experimental animals [62]. The authors explained that the hypoglycaemic effects of *Cuminum cyminum* L was probably due to insulin-like action or increased production of insulin by the pancreatic islets [62]. Interestingly, it was shown that *C. cyminum* normalised the total haemoglobin and HbA1C in the experimental diabetic rats, by reducing the plasma glucose levels [61].
5.4 Fruits of *Emblica officinalis* and *Terminalia bellerica*

The fruits of *Phyllanthus emblica* also known as Emblica officinalis (EB) or Indian gooseberry and Terminalia bellerica (TB) or also known as Gaertn, possess potent antibacterial, antiviral and anti-inflammatory activity. EB and TB have been reported to possess good antioxidant and free radical scavenging activity [62]. It cannot be refuted that DM is a disease that involves oxidative stress and production of reactive oxygen species (ROS) is responsible for multiorgan damage. The EB and TB extract have also been reported to show α-amylase and α-glucosidase inhibitory potential along with antiglycation activity which may be helpful in treatment of DM [63]. Interestingly, past researchers reported that EB extract reduced the lipid profile in experimental diabetic animals [64]. There are reports of TB suppressing the absorption of triacylglycerol and exhibiting a strong inhibitory effect on pancreatic lipase activity [65]. The authors of the same study [65] had the opinion that gallic acid was the component which was responsible for the inhibition of the pancreatic lipase activity.

Cordyceps: A parasitic fungus i.e. *Cordyceps sp*, also known as ''winter-worm and summer-grass'' is a popular Chinese herb which has been used effectively for the treatment of various household disorders. Researches have showed that polysaccharides extracted from cultured mycelium of Cordyceps, when administered intraperitoneally exhibited potent hypoglycemic activity in diabetic mice [66]. The plausible mechanism involved the presence of the high content of the fibres. It cannot be forgotten that a delay in glucose absorption or reduction in glucose absorption may help stabilise plasma glucose levels in DM. The fibres have an effect on glucose absorption [66].

Eggplant (*Solanum melongena*): Eggplant (*Solanum melongena*), a type of tropane alkaloids, is also known to possess glycosidase inhibitory activity [67]. Phenolic phytochemicals present in this plant can help in scavenging the free radicals and combat oxidative damage to the organs in DM. It was shown that the phenolic ingredients of eggplant could cause intestinal α-glucosidase inhibition [67] which reduces hyperglycaemia.

Enicostemma Littorale Blume: *Enicostemma littorale* Blume, is a small herb which hails from the family Gentianaceae and it has been widely used in India. The herb has shown hypoglycaemic effect on alloxan treated rats [68]. It was found experimentally that the herb possessed insulinotropic effect at 10 mins and 60 mins, thereby suggesting that the extract caused the release of insulin from the secretory as well as the reserve pool [68]. Interestingly, the *Enicostemma littorale* Blume possibly works through activating another secondary messenger, which may be responsible for increasing the intracellular Ca^{2+} ions from another source and cause insulin exocytosis [69].

Ginseng: Ginseng (Panax) is a plant from the Araliaceae family and it is widely used in Chinese medicine. The usage of the herb is also gaining popularity all over the world. The active constituent of the herbs is ginsenocide, a group of steroidal saponins. The extract of the herb acts on the intestinal absorption of glucose and regulates the secretion of insulin [70].

Panax ginseng CA Meyer has been used effectively as a supplement in many parts of Asia, over the last 2000 years [71]. Fresh Ginseng is steamed and dried to yield the red ginseng. During such process, the ginsenocide is subjected to various chemical changes which result in important physiological properties [71]. Clinical trials have

shown that ginseng induces a reduction in plasma glucose as well as HbA1c levels in T2DM patients [72]. Treatment with red ginseng improves insulin sensitivity [71]. Research reports reveal that activation of adenosine monophosphate–activated protein kinase (AMPK) increases fatty acid oxidation and glucose uptake by the skeletal muscles of the body [73]. The herb regulates the glucose metabolism by the above mentioned pathway.

Piper Sarmentosum (PS) and Piper Betle (PB): PS and PB belong to the Piperaceae family. The leaves are chewed in many parts of Asia. Researches have shown that oral administration of PB for 30 days reduced the blood glucose level, glycosylated haemoglobin and decreased the activities of liver glucose-6-phosphatase and fructose-1,6-bisphosphatase [74]. The results of previous studies showed that PB is effective in influencing the glucose metabolism.

In our earlier studies, we documented the protective effect of PB on DM. The damage to the cardiac muscle and proximal aorta was reversed when the experimental diabetic animals were treated with PS extract [75].

Goshajinkigan: Goshajinkigan (GJG) is a traditional herb that has been widely used to treat diabetic neuropathy. Interestingly, research studies found that GJG was better than mecobalamin in the treatment of diabetic neuropathy [76]. The GJG had a remarkable effect on the vibratory threshold. Thus, GJG improved the sense of vibration in diabetics. Few authors have opined that the GJG may act to correct the abnormal steps of the insulin signal pathway in the skeletal muscle [77]. The same study showed that decreased insulin receptor substrate-1 (IRS-1) protein content was significantly improved by treatment with GJG [77].

Soybeans (Glycine Max (L.) Merrill): Soybeans (Glycine max (L.) Merrill) is one of the dietary legumes and forms the major source of protein in the food. Soybean has been reported to act against cancer, osteoporosis and coronary heart disease [78]. Experiments showed that bound phenolic extract caused higher α-amylase and ACE inhibition than the free phenolic extract [79]. It was reported that inhibition of amylase by the soybean bound phenolic extract involves direct interaction with the antioxidants with the disulfide bridges [79]. It was also found that free phenolic extract had a higher

α-glucosidase inhibitory activity compared to that of α-amylase and this is the reason why the soyabean phenolic extracts are considered to be better than other anti-diabetic drugs available in the market with little or no side effects [79].

Kudzu Root: Kudzu root (*Pueraria lobata*) belonging to the family Fabaceae, has been traditionally used by Chinese population in Asia. It is also used in the United States of America and Australia. Interestingly, the Kudzu root was included in the Japanese pharmacopoeia [80]. Puerarin, the major isoflavone isolated from kudzu root, has been reported to possess anti-hypercholesterolaemic, anti-platelet, anti-inflammatory, anti-arrhythmic, anti-oxidant, anti-ischaemic, anti-apoptotic, hypoglycaemic and neuro-protective properties [81]. Puerarin can induce adipogenesis through PPARr pathway [81]. The pathological changes occurring as a result of DM was reversed by Kudzu root. Peroxisome proliferator-activated receptor gamma (PPARγ) is responsible for regulating glucose homeostasis, adipocyte differentiation, lipid metabolism and inflammation [82]. PPARγ is a regulator of lipid metabolism and it can reduce lipid accumulation in various insulin sensitive tissues [83].

Salacia: The *Salacia* (S) species which belongs to the family Celastraceae and it is found in many parts of India, Sri Lanka and South-East Asia. The plant extract has been used traditionally to treat gonnorhea, pruritus, rheumatism and asthma [84]. The extract was reported to enhance PPAR-α-mediated lipogenic gene expression [PPAR- α mRNA and protein, carnitine palmitoyltransferase-1 (CPT-1) [85]. According to previous research, *Salacia* has PPAR-alpha activator, which provides a potential mechanism for checking the postprandial hyperlipidemic state and hepatic steatosis, in conditions such as diabetes and obesity [86].

Green Tea: Green tea is made from the leaves of *Camellia sinensis*. Green tea is a popular drink consumed worldwide. Research studies have shown that green tea reduces the level of the blood glucose, improves sensitivity to insulin and enhances antioxidant defences [87]. It was found that green tea reduced the collagen content in the tendon of the rat tail and also reduced the extent of advanced glycation and its end products (AGE) [87].

Gynura Procumbens: Gynura procumbens is a herb which contains flavonoids and alkaloids. Specifically, flavanoids and alkaloids are responsible for inhibition of the α-amylase and α-glucosidase [88]. Synergistic effect by all active constituents in the herb extracts is responsible for ACE inhibition [88].

Aloe Arborescens: Aloe *arborescens* has been reported to exhibit hypoglycaemic action. Aloe as dietary supplements have been tried to treat DM [89]. Histological findings also revealed that the extract was able to combat the pancreatic cell damage and inhibit intestinal glucose absorption [89].

Ginger: Ginger (*Zingiber officinale* Roscoe Zingiberaceae) is commonly used as a spice all over the world. It is known for its anti-inflammatory and antioxidant properties. Recent research studies had shown that ginger extract at a dose of 100- 800 mg/Kg, was able to reduce 24-53% of blood glucose in STZ-type 1 diabetic rat models [90]. Another research study showed that ginger was able to prevent the 5-Hydroxytryptamine (5 HT) induced acute hyperglycemia by acting on the 5 HT receptors [91]. Besides, there is evidence that ginger could influence the key enzymes which control the carbohydrate metabolism and also increase insulin release/sensitivity which lead to the increase in glucose uptake by the peripheral fat tissues and skeletal muscles [92]. In fact, the lipid lowering property of ginger overall improves insulin resistance [92].

F. Japonica: F. japonica (syn: Polygonum cuspidatum Sieb. et Zucc. or Reynoutria japonica Houtt.) is a Polygonaceae plant, found in different regions of Asia and North America [93]. In Chinese medicine, this herb has been successfully tried for treatment of inflammation, hepatitis, infection, tumors, hypertension, bleeding and hyperlipidemia [94, 95]. Earlier researches have shown the active anthranoids from *F.Japonica* could could inhibit CXCR4-mediated chemotaxis in a MEK/MAPK-dependent fashion [93]. It was shown that anthranoids usually target the intraceullar proteins downstream of the chemokine receptors, hence they may be used as alternative inhibitors of chemokine signaling [93]. The same study showed that the inflammatory process involved in DM may be arrested by treatment with F. japonica extract in an animal model [93].

Poria Cocos (Polyporaceae): *P.cocos,* a rotten tree fungus has been commonly used in Chinese medicine. According to research reports, dehydrotrametenolic acid, one triterpene constituent of P. cocos, was reported to exhibit hyperglycemic effects in db/db mice [96]. Interestingly, researches also showed that dehydrotumulosic acid was one of the most effective constituents present in the crude extract of *P.cocos* but the glucose lowering effect of dehydrotrametenolic acid and pachymic acid was more pronounced than the dehydrotumulosic acid [97].

CONCLUSION

Type 1 DM is known to affect at least 10 million individuals worldwide. Insulin is the only reported medication and the side effects are many. Over the years the incidence of DM and its complications has been on the rise. Many herbal and vegetable products have been tried as effective supplements. All the actions of the herbal supplements can be better understood if the possible mechanisms are defined clearly. There are not many documented side effects for the majority of the herbal extracts consumed. This is because of less side effects, easy availability, cost effectiveness and patient compliance factors. Further research is advised to gain new insights into the herbal alternatives for DM. This would reduce the sufferings of patients and ease the world economic burden caused by DM; one of the world's most deadly diseases.

REFERENCES

1. Park, K., 2009. Epidemiology of chronic non-communicable diseases and condition,20th ed., Park's textbook of preventive and social medicine Jabalpur, India: Banarsidas Bhanot., 6: 341.
2. Guariguata L., D. Whiting, C. Weil and N. Unwin, 2011. The International Diabetes Federation diabetes atlas methodology for estimating global and national prevalence of diabetes in adults, Diabetes Research and Clinical Practice, 94(3): 322-32.
3. Wild S., G. Roglic, A. Green, R. Sicree and H. King, 2004.Global prevalence of diabetes: estimates for the year 2000 and projections for 2030, Diabetes Care, 27(5): 1047-53.

4. De Berardis, G., A. D'Ettorre, G. Graziano, G. Lucisano, F. Pellegrini, S. Cammarota, A. Citarella, C. A. Germinario, V. Lepore, E. Menditto, A. Nicolosi, F. Vitullo and A. Nicolucci, 2011. The burden of hospitalization related to diabetes mellitus: A population-based study, Nutrition, Metabolism and Cardiovascular Diseases, Feb 16.

5. Skordis N., E. Efstathiou, T.C. Kyriakides, A. Savvidou, S.C. Savva, L.A. Phylactou, C. Shammas and V. Neocleous, 2012. Epidemiology of Type 1 diabetes mellitus in Cyprus: rising incidence at the dawn of the 21st century, Hormones (Athens), 11(1): 86-93.

6. Mukai, N. and Y. Kiyohara, 2011. [The epidemiology of diabetes mellitus: the Hisayama study], Fukuoka Igaku Zasshi, 102(5): 175-84.

7. Cinek, O., 2011. Epidemiology of childhood type 1 diabetes mellitus: lessons from Central and Eastern European data, Hormone Research in Paediatrics, 76(1): 52-6.

8. Yang Y., S. Y. Goh, S. B. Tan, H. J. Ho, S. Emmanuel, P. Wang and H. S. Ng, 2012.The burden of diabetes mellitus in elderly patients from an Asian tertiary hospital, European Journal of Internal Medicine, 23(1): e1-4.

9. Bharati, D.R., R. Pal, R. Rekha and T.V. Yamuna, 2011. Evaluation of the burden of type 2 diabetes mellitus in population of Puducherry, South India, Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 5(1): 12-16.

10. http://www.diabetes.co.uk/cost-of-diabetes.html

11. Lee, D.H., R. Blomhoff and D.R. Jacobs, 2004. Jr, Is Serum Gamma Glutamyltransferase a Marker of Oxidative Stress?, Free Radical Research, 38(6): 535-9.

12. Pickup, J.C. and M.A. Crook, 1986. Is Type II Diabetes Mellitus a Disease of the Innate Immune System?, Diabetologia, 41(10): 1241-8.

13. Pickup, J.C., M.B. Mattock, G.D. Chusney and D. Burt, 1997. Niddm as a Disease of the Innate Immune System: Association of Acute-Phase Reactants and Interleukin-6 with Metabolic Syndrome X, Diabetologia, 40(11): 1286-92.

14. Fukui, M., M. Tanaka, H. Toda, T. Senmaru, K. Sakabe, E. Ushigome, M. Asano, M. Yamazaki, G. Hasegawa, S. Imai and N. Nakamura, 2011. Risk Factors for Development of Diabetes Mellitus, Hypertension and Dyslipidemia, Diabetes Research Clinical Practice; 94(1): e15-8.

15. Ceriello, A., K. Esposito, L. Piconi, M.A. Ihnat, J.E. Thorpe, R. Testa, M. Boemi and D. Giugliano, 2008.Oscillating Glucose Is More Deleterious to Endothelial Function and Oxidative Stress Than Mean Glucose in Normal and Type 2 Diabetic Patients, Diabetes, 57(50): 1349-54.

16. Fearon, I.M. and S.P. Faux, 2009. Oxidative Stress and Cardiovascular Disease: Novel Tools Give (Free) Radical Insight, Journal of Molecular and Cellular Cardiology, 47(3): 372-81.

17. Lhommeau, I., S. Douillard, E. Bigot, I. Benoit, M. Krempf and T. Patrice, 2011. Serum Resistance to Singlet Oxygen in Patients with Diabetes Mellitus in Comparison to Healthy Donors, Metabolism, 60(9): 1340-8.

18. Cersosimo, E., A. Gastaldelli, A. Cervera, E. Wajcberg, A. Sriwijilkamol, M. Fernandez, P. Zuo, R. Petz, C. Triplitt, N. Musi and R.A. DeFronzo, 2011. Effect of Exenatide on Splanchnic and Peripheral Glucose Metabolism in Type 2 Diabetic Subjects, The Journal of Clinical Endocrinology and Metabolism, 96(6): 1763-70.

19. Leem, J. and E.H. Koh, 2012. Interaction between Mitochondria and the Endoplasmic Reticulum: Implications for the Pathogenesis of Type 2 Diabetes Mellitus, Experimental Diabetes Research, doi:10.1155/2012/242984.

20. Lowell, B.B. and G.I. Shulman, 2005. Mitochondrial dysfunction and type 2 diabetes, Science, 307(5708): 384-387.

21. Patti, M.E. and S. Corvera, 2010. The role of mitochondria in the pathogenesis of type 2 diabetes, Endocrine Reviews, 31(3): 364-395.

22. Krentz, A.J. and C.J. Bailey, 2005. Oral Antidiabetic Agents: Current Role in Type 2 Diabetes Mellitus, Drugs, 65(3): 385-411.

23. Cavallo Perin, P. and P. Fornengo, 2011. New Oral Antidiabetic Agents, Internal and Emergency Medicine, 6(1): 135-8.

24. Combettes M. and C. Kargar, 2007. Newly Approved and Promising Antidiabetic Agents, Therapie, 62(4): 293-310.

25. Fantus, I.G. and R. Brosseau, 1986. Mechanism of Action of Metformin: Insulin Receptor and Postreceptor Effects *in Vitro* and *in Vivo*, The Journal of Clinical Endocrinology and Metabolism, 63(4): 898-905.

26. Jackson, R.A., M.I. Hawa, J.B. Jaspan, B.M. Sim, L. Disilvio, D. Featherbe and A.B. Kurtz, 1987. Mechanism of Metformin Action in Non-Insulin-Dependent Diabetes, Diabetes, 36(5): 632-40.

27. Flemmer, M. and J. Scott, 2001. Mechanism of Action of Thiazolidinediones, Current Opinion in Investigational Drugs, 2(11): 1564-7.

28. Bilous, R., 2007. Dream and Adopt: Rosiglitazone Does What It Says on the Packet. Diabetic Medicine : A Journal of the British Diabetic Association, 24(2): 107-9.

29. Panten, U., M. Schwanstecher and C. Schwanstecher, 1996. Sulfonylurea Receptors and Mechanism of Sulfonylurea Action, Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association, 104(1): 1-9.

30. Lebovitz, H.E. and M.N. Feinglos, 1983. Mechanism of Action of the Second-Generation Sulfonylurea Glipizide, The American Journal of Medicine, 75(5B): 46-54.

31. Rudovich, N.M., M. Mohlig, B. Otto, O. Pivovarova, J. Spranger, M.O. Weickert and A.F. Pfeiffer, 2010. Effect of Meglitinides on Postprandial Ghrelin Secretion Pattern in Type 2 Diabetes Mellitus, Diabetes Technology & Therapeutics, 12(1): 57-64.

32. Hirsh, A.J., S.Y. Yao, J.D. Young and C.I. Cheeseman, 1997. Inhibition of Glucose Absorption in the Rat Jejunum: A Novel Action of Alpha-D-Glucosidase Inhibitors, Gastroenterology, 113(1): 205-11.

33. Odaka, H., 2002. [Alpha-Glucosidase Inhibitor, Its Structure and Mechanism of Antidiabetic Action], Nihon Rinsho. Japanese Journal of Clinical Medicine, 60(suppl. 9): 393-8.

34. Sulistio, M., C. Carothers, M. Mangat, M. Lujan, R. Oliveros and R. Chilton, 2009. Glp-1 Agonist-Based Therapies: An Emerging New Class of Antidiabetic Drug with Potential Cardioprotective Effects, Current Atherosclerosis Reports, 11(2):93-9.

35. Freeman, J.S., 2010. Managing Hyperglycemia in Patients with Type 2 Diabetes Mellitus: Rationale for the Use of Dipeptidyl Peptidase-4 Inhibitors in Combination with Other Oral Antidiabetic Drugs, The Journal of the American Osteopathic Association, 110(9): 528-37.

36. Tahrani, A.A., C.J. Bailey, S. Del Prato and A.H. Barnett, 2011. Management of Type 2 Diabetes: New and Future Developments in Treatment, Lancet, 378(9786): 182-97.

37. Ho, J., A.K. Leung and D. Rabi, 2011. Hypoglycemic Agents in the Management of Type 2 Diabetes Mellitus, Recent patents on Endocrine, Metabolic & Immune Drug Discovery, 5(1): 66-73.

38. Basile, J., 2011. A New Approach to Glucose Control in Type 2 Diabetes: The Role of Kidney Sodium-Glucose Co-Transporter 2 Inhibition, Postgraduate Medicine, 123(4): 38-45.

39. Akash, M.S., Q. Shen, K. Rehman and S. Chen, 2012. Interleukin-1 Receptor Antagonist: A New Therapy for Type 2 Diabetes Mellitus. Journal of Pharmaceutical Sciences, 101(5): 1647-58.

40. Cubeddu, L.X., H. Bonisch, M. Gothert, G. Molderings, K. Racke, G. Ramadori, K.J. Miller and H. Schworer, 2000. Effects of Metformin on Intestinal 5-Hydroxytryptamine (5-Ht) Release and on 5-Ht3 Receptors, Naunyn-Schmiedeberg's Archives of Pharmacology, 361(1): 85-91.

41. Vidal-Alaball, J. and C.C. Butler, 2010. Reduced Serum Vitamin B-12 in Patients Taking Metformin, British Medical Journal, 340: c2198.

42. Lieber, C.S., M.A. Leo, K.M. Mak, Y. Xu, Q. Cao, C. Ren, A. Ponomarenko and L.M. DeCarli, 2004. Acarbose Attenuates Experimental Non-Alcoholic Steatohepatitis. Biochemical and Biophysical Research Communications, 315(3): 699-703.

43. Nissen, S.E. and K. Wolski, 2010. Rosiglitazone Revisited: An Updated Meta-Analysis of Risk for Myocardial Infarction and Cardiovascular Mortality. Archives of Internal Medicine, 170(14): 1191-1201.

44. Farmer, A.J.K., J. Brockbank, M.L. Keech, E.J. England and C.D. Deaki, 2012. Incidence and Costs of Severe Hypoglycaemia Requiring Attendance by the Emergency Medical Services in South Central England, Diabetic Medicine : A Journal of the British Diabetic Association.

45. Saha, S., L.S. New, H.K. Ho, W.K. Chui and E.C. Chan, 2010. Direct Toxicity Effects of Sulfo-Conjugated Troglitazone on Human Hepatocytes, Toxicology Letters, 195(2-3): 135-41.

46. Jones, D., 2011. Diabetes Field Cautiously Upbeat Despite Possible Setback for Leading Sglt2 Inhibitor, Nature reviews. Drug discovery, 10(9): 645-6.

47. Home, P.D., 2008. Impact of the Ukpds--an Overview. Diabetic Medicine : A Journal of the British Diabetic Association, 25(Suppl 2): 2-8.

48. Kudolo, G.B., W. Wang, M. Javors and J. Blodgett, 2006. The effect of the ingestion of Ginkgo biloba extract (EGb 761) on the pharmacokinetics of metformin in non-diabetic and type 2 diabetic subjects--a double blind placebo-controlled, crossover study, Clinical Nutrition, 25: no.4.

49. Oken, B.S., D.M. Storzbach and J.A. Kaye, 1998. The efficacy of Ginkgo biloba on cognitive function in Alzheimer disease, Archives of Neurology, 55(11): 1409-1415.

50. Kudolo, G.B., W. Wang, J. Barrientos, R. Elrod and J. Blodgett, 2004. Ginkgo biloba extract inhibits arachidonic acid-mediated platelet aggregation and thromboxane B2 production in healthy subjects, Journal of Herbal Pharmacotherapy, 4: 13-26.

51. Karunanayake, E.H., S. Jeevathayaparan and K.H. Tennekoon, 1990. Effect of Momordica charantia fruit juice on streptozotocin-induced diabetes in rats, Journal of Ethnopharmacology, 30(2): 199-204.

52. Higashino, H., A. Suzuki, Y. Tanaka and K. Pootakham, 1992. [Hypoglycemic effects of Siamese Momordica charantia and Phyllanthus urinaria extracts in streptozotocin-induced diabetic rats (the 1st report)], Nihon Yakurigaku Zasshi, 100(5): 415-221.

53. Teoh, S.L., A.A. Latiff and S. Das, 2009. The effect of topical extract of Momordica charantia (bitter gourd) on wound healing in nondiabetic rats and in rats with diabetes induced by streptozotocin, Clinical and Experimental Dermatology, 34(7): 815-22.

54. Teoh, S.L., A.A. Latiff and S. Das, 2010. Histological changes in the kidneys of experimental diabetic rats fed with Momordica charantia (bitter gourd) extract, Romanian Journal of Morphology and Embryology, 51(1): 91-5.

55. Teoh, S.L., A.A. Latiff and S. Das, 2009. A histological study of the structural changes in the liver of streptozotocin-induced diabetic rats treated with or without Momordica charantia (bitter gourd)," La Clinica Terapeutica, 160(4): 283-6.

56. Fuangchan, A., P. Sonthisombat, T. Seubnukarn, R. Chanouan, P. Chotchaisuwat, V. Sirigulsatien, K. Ingkaninan, P. Plianbangchang and S.T. Haines, 2011. Hypoglycemic effect of bitter melon compared with metformin in newly diagnosed type 2 diabetes patients, Journal of Ethnopharmacology, 134(2): 422-8.

57. Khanna P., S.C. Jain, A. Panagariya and V.P. Dixit, 1981. Hypoglycemic activity of polypeptide-p from a plant source, Journal of Natural Products, 44(6): 648-55.

58. Yibchok-anun, S., S. Adisakwattana, C.Y. Yao, P. Sangvanich, S. Roengsumran and W.H. Hsu, 2006. Slow acting protein extract from fruit pulp of Momordica charantia with insulin secretagogue and insulinomimetic activities, Biological and Pharmaceutical Bulletin, 29(6): 1126-31.

59. Welihinda, J., E.H. Karunanayake, M.H. Sheriff and K.S. Jayasinghe, 1986. Effect of Momordica charantia on the glucose tolerance in maturity onset diabetes, Journal of Ethnopharmacology, 17(3): 277-82.

60. Sarkar, S., M. Pranava and R. Marita, 1996. Demonstration of the hypoglycemic action of Momordica charantia in a validated animal model of diabetes, Pharmaceutical Research, 33(1): 1-4.

61. Shibib, B.A., L.A. Khan and R. Rahman, 1993. Hypoglycaemic activity of Coccinia indica and Momordica charantia in diabetic rats: depression of the hepatic gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-bisphosphatase and elevation of both liver and red-cell shunt enzyme glucose-6-phosphate dehydrogenase, Biochemistry Journal, 292(1): 267-70.

62. Dhandapani, S., V.R. Subramanian, S. Rajagopal and N. Namasivayam, 2002. Hypolipidemic effect of Cuminum cyminum L. on alloxan-induced diabetic rats, Pharmaceutical Research, 46(3): 251-5.

63. Nampoothiri, S.V., A. Prathapan, O.L. Cherian, K.G. Raghu, V.V. Venugopalan and A. Sundaresan, 2011. *in Vitro* antioxidant and inhibitory potential of Terminalia bellerica and Emblica officinalis fruits against LDL oxidation and key enzymes linked to type 2 diabetes, Food and Chemical Toxicology, 49(1): 125-31.

64. Nain, P., V. Saini, S. Sharma and J. Nain, 2012. Antidiabetic and antioxidant potential of Emblica officinalis Gaertn. leaves extract in streptozotocin-induced type-2 diabetes mellitus (T2DM) rats, J. Ethnopharmacol, 26(142): 65-71.

65. Makihara, H., T. Shimada, E. Machida, M. Oota, R. Nagamine, M. Tsubata, K. Kinoshita, K. Takahashi and M. Aburada, 2012. Preventive effect of Terminalia bellirica on obesity and metabolic disorders in spontaneously obese type 2 diabetic model mice, J. Nat Med, 66(3): 459-67.

66. Lo, H.C., S.T. Tu, K.C. Lin and S.C. Lin, 2004. The anti-hyperglycemic activity of the fruiting body of Cordyceps in diabetic rats induced by nicotinamide and streptozotocin, Life Science, 74(23): 2897-908.

67. Kwon, Y.I., E. Apostolidis and K. Shetty, 2008. *in Vitro* studies of eggplant (Solanum melongena) phenolics as inhibitors of key enzymes relevant for type 2 diabetes and hypertension, Bioresource Technology, 99(8): 2981-8.

68. Vijayvargia, R., M. Kumar and S. Gupta, 2000. Hypoglycemic effect of aqueous extract of Enicostemma littorale Blume (chhota chirayata) on alloxan induced diabetes mellitus in rats, Indian Journal of Experimental Biology, 38(8): 781-4.

69. Komatsu, M., M. Noda and G.W. Sharp, 1998. Nutrient augmentation of Ca2+-dependent and Ca2+-independent pathways in stimulus-coupling to insulin secretion can be distinguished by their guanosine triphosphate requirements: studies on rat pancreatic islets, Endocrinology, 139(3): 1172-83.

70. Kimura, M. and J. Suzuki, 1981. The pattern of action of blended Chinese traditional medicines to glucose tolerance curves in genetically diabetic KK-CAy mice, Journal of Pharmacobiodynamics, 4(12): 907-15.

71. Lee, H.J., Y.H. Lee, S.K. Park, E.S. Kang, H.J. Kim, Y.C. Lee YC, *et al.*, 2009. Korean red ginseng (Panax ginseng) improves insulin sensitivity and attenuates the development of diabetes in Otsuka Long-Evans Tokushima fatty rats. Metabolism, 58(8): 1170-7.

72. Sotaniemi, E.A. and E. Haapakoski, 1995. A. Rautio, Ginseng therapy in non-insulin-dependent diabetic patients, Diabetes Care, 18: 1373-5.

73. Bonen, A., M.L. Parolin, G.R. Steinberg, J. Calles-Escandon, J.F. Glatz, J.J. Luiken, G.J. Heigenhauser and D.J. Dyck, 2004. Triacylglycerol accumulation in human obesity and type 2 diabetes is associated with increased rates of skeletal muscle fatty acid transport and increased sarcolemmal FAT/CD36, Faseb Journal, 18: 1144-6.

74. Santhakumari, P., A. Prakasam and K.V. Pugalendi, 2006. Antihyperglycemic activity of Piper betle leaf on streptozotocin-induced diabetic rats, Journal of Medical Food, 9(1): 108-12.

75. Thent, Z.C., T.S. Lin, Z. Zakaria and S. Das, 2012. Histological changes in the heart and the proximal aorta in Streptozotocin-induced diabetic rats following Piper Sarmentosum administration, African Journal of Traditional, Complementary and Alternative Medicine, 9(3): 396-40.

76. Tawata, M., K. Kurihara, K. Nitta, E. Iwase, N. Gan and T. Onaya, 1994. The effects of goshajinkigan, a herbal medicine, on subjective symptoms and vibratory threshold in patients with diabetic neuropathy, Diabetes Research in Clinical Practice, 26(2): 121-8.

77. Qin, B., M. Nagasaki, M. Ren, G. Bajotto, Y. Oshida and Y. Sato, 2004. Gosha-jinki-gan (a Herbal Complex) Corrects Abnormal Insulin Signaling, Evidence Based Complementary and Alternative Medicine, 1(3): 269-276.

78. Mesa, M.D., J.M. Silvαn, J. Olza, Α Gil and M.D. del Castillo, XXXX. Antioxidant properties of soy protein - fructooligosaccharide glycation systems and its hydrolyzates, Food Research International, 41: 606-15.

79. Ademiluyi, A.O., G. Oboh and G. Soybean, 2011. Phenolic-rich extracts inhibit key-enzymes linked to type 2 diabetes (α-amylase and α-glucosidase) and hypertension (angiotensin I converting enzyme) *in Vitro*, Experimental and Toxicology Pathology: Oct 15.

80. Bodner, C.C., T. Hymowitz and T. Ethnobotany, 2002. of Pueraria species Pueraria: The Genus Pueraria, CRC Press, USA, 13.

81. Wong, K.H., G.Q. Li, K.M. Li, V. Razmovski-Naumovski and K. Chan, 2011. Kudzu root: traditional uses and potential medicinal benefits in diabetes and cardiovascular diseases, Journal of Ethnopharmacology, 134(3): 584-607.

82. Semple, R.K., A. Meirhaeghe, A.J. Vidal-Puig, J.W. Schwabe, D. Wiggins, G.F. Gibbons, M. Gurnell, V.K. Chatterjee and S.A. O'Rahilly, 2005. A dominant negative human peroxisome proliferator-activated receptor (PPAR){alpha} is a constitutive transcriptional corepressor and inhibits signaling through all PPAR isoforms Endocrinology, 146: 1871-82.

83. Chiarelli, F. and D. Di Marzio, 2008. Peroxisome proliferator-activated receptor-gamma agonists and diabetes: current evidence and future perspectives. Vascular Health & Risk Management, 4: 297-304.

84. Vaidyaratnam, P.S., 1996. Indian medicinal plants: a compendium of 500 species, pp: 47-48.

85. Li, Y., T.H. Huang and J. Yamahara, 2008. Salacia root, a unique Ayurvedic medicine, meets multiple targets in diabetes and obesity. Life Sciences, 82(21-22): 1045-9.

86. Huang, T.H., G. Peng, G.Q. Li, J. Yamahara, B.D. Roufogalis and Y. Li., 2006. Salacia oblonga root improves postprandial hyperlipidemia and hepatic steatosis in Zucker diabetic fatty rats: activation of PPAR-alpha.Toxicology and Applied Pharmacology, 210: 225-235.

87. Babu, P.V., K.E. Sabitha and C.S. Shyamaladevi, 2008. Effect of green tea extract on advanced glycation and cross-linking of tail tendon collagen in streptozotocin induced diabetic rats.Food and Chemical Toxicology, 46(1): 280-5.

88. Wu, T., X. Zhou, Y. Deng, Q. Jing, M. Li and L. Yuan, 2011. *in Vitro* studies of *Gynura divaricata* (L.) DC extracts as inhibitors of key enzymes relevant for type 2 diabetes and hypertension. Journal of Ethnopharmacology; 136(2): 305-8.

89. Yeh, G.Y., D.M. Eisenberg, T.J. Kaptchuk and R.S. Phillips, 2003. Systematic review of herbs and dietary supplements for glycemic control in diabetes. Diabetes Care, 26: 1277-94.

90. Ojewole, J.A., 2006. Analgesic, antiinflammatory and hypoglycaemic effects of ethanol extract of Zingiber officinale (Roscoe) rhizomes (Zingiberaceae) in mice and rats. Phytotherapy Research, 20(9): 764-72.

91. Akhani, S.P., S.L. Vishwakarma and R.K. Goyal, 2004. Anti-diabetic activity of Zingiber officinale in streptozotocin-induced type I diabetic rats. Journal of Pharmacy and Pharmacology, 56(1): 101-5.

92. Li, Y., V.H. Tran, C.C. Duke and B.D. Roufogalis, 2012. Preventive and Protective Properties of Zingiber officinale (Ginger) in Diabetes Mellitus, Diabetic Complications and Associated Lipid and Other Metabolic Disorders: A Brief Review, Evidence Based Complementary and Alternative Med icine; 2012:516870. doi: 10.1155/2012/516870.