

MECHANISMS OF ACTION OF TRADITIONAL HERBAL MEDICINES USED IN THE MANAGEMENT OF DIABETES MELLITUS: A REVIEW OF THE LITERATURE

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Abstract

Background: The prevalence of diabetes mellitus is increasing rapidly in both developed and developing countries. There are various conventional medicines used for the management of the disease, but there is also increased interest in the use of traditional herbal medicines. Although the concepts of illness and diseases in traditional medicine may differ from conventional medicine the outcomes are similar. The antihyperglycemic effects of various herbal medicines prescribed by traditional healers in the management of diabetes mellitus have been proven scientifically using several *in-vitro* and *in-vivo* models as well as clinical studies in humans.

Materials and methods: Literature search was done in several databases. Firstly, the search was conducted using the key terms: diabetes mellitus and traditional medicine, diabetes mellitus and herbs, diabetes mellitus and plants, traditional concepts of health and sickness and diabetes mellitus. After identifying the herbs or plants used in diabetes a search was then conducted by name of herb and efficacy in management of diabetes mellitus.

Results: This review highlights the similarities and differences in mechanisms of action of various traditional herbal medicines and conventional medicines. The major observation is that, herbal medicines often have multiple mechanisms of action ideally making them combination therapies. The review further highlights the need to develop an algorithm of a minimum battery of *in-vitro* and animal studies that can provide solid evidence of the potential of traditional medicines as anti-diabetic treatments.

Conclusion: Traditional herbal medicines often have multiple phytoconstituents and hence multiple mechanisms of action ideally making them combination therapies.

Keywords: traditional herbal medicines, diabetes mellitus, mechanisms of action

Introduction

Normal glucose homeostasis is tightly controlled by three interconnected and interrelated processes: (1) glucose production in the liver through gluconeogenesis and glycogenolysis, (2) glucose uptake and utilization by peripheral tissues mainly skeletal muscle and adipose tissue, and (3) the action of insulin and counter regulatory hormones (including glucagon, somatostatin, growth hormone and corticosteroids) (Kumar et al., 2013). The metabolic effects of insulin can be summarized as anabolic, with increase in glycogenesis, decrease in gluconeogenesis and glycogenolysis, increase in protein synthesis and decrease in degradation of lipids.

Diabetes Mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia as a result of deficiency in insulin secretion, insulin action or often a combination of both. According to the International Diabetes Federation (IDF) in 2015, approximately 415 million people in the world live with DM, the majority of whom are between the age of 40 – 59 years and 80% live in low to middle income countries (International Diabetes Federation, 2015). The prevalence of DM is increasing rapidly in both developed and developing countries. This increase is more pronounced in countries undergoing a transition from traditional to modern lifestyles (International Diabetes Federation, 2015). IDF, in 2015 also reported that approximately 673 billion United States dollars, which is 12% of global health expenditure was spent on management of diabetes and its complications (International Diabetes Federation, 2015).

There are two major types of diabetes mellitus. Type 1 DM is characterized by an absolute deficiency of insulin secretion caused, most commonly, by autoimmune destruction of the pancreatic beta cells that produce the insulin (Kumar et al., 2013). Type 2 DM is usually caused by a combination of peripheral insulin resistance and an inadequate compensatory response of insulin secretion by the pancreatic beta cells (Kumar et al., 2013). Regardless of the type of DM, the clinical presentation and progression are the same. Similarly the complications of uncontrolled disease are the same, affecting the microvascular (kidneys, eyes and nerves) and macrovascular systems (Fowler, 2008).

Diabetes can be diagnosed by any of four criteria. The first criterion is glycated hemoglobin (HbA_{1c}) level $\geq 6.5\%$. This criterion is also considered the gold standard to assess adequacy of therapy and management of diabetes. The second criterion is a fasting blood glucose level $\geq 7\text{mmol/L}$. Fasting is defined as no caloric intake for at least 8 hours. Fasting blood glucose level is the most commonly used in developing countries since HbA_{1c} testing may not be readily available. The third criterion is a 2-hour blood glucose level $\geq 11.1\text{mmol}$ during a 75g oral glucose tolerance test. The last criterion is a random blood glucose $\geq 11.1\text{mmol}$ with classic symptoms of hyperglycemia which are polyuria, polydipsia and polyphagia (Kumar et al., 2013).

The pathogenesis of the long term complications of DM are multifactorial but persistent hyperglycemia (glucotoxicity) seems to be the key factor (Kumar et al., 2013). Formation of advanced glycation end products which give rise to release of pro-inflammatory cytokines from macrophages, generation of reactive oxygen species in endothelial cells and increased pro-coagulant activity on endothelial cells is one mechanism that leads to development of both macrovascular and microvascular complications (Kumar et al., 2013). The reactive oxygen species are also implicated in worsening pancreatic beta cell dysfunction in diabetes mellitus (Kumar et al., 2013). Most of the diabetic complications are also related to the presence of glycated products in the blood and generation of free radicals (Kumar et al., 2013). Therefore, use of treatments that have antioxidant properties may delay or stop the development and progression of diabetes complications as well as promote regeneration of pancreatic beta cells.

Management of DM using conventional drugs is achieved through supplementation of insulin, increasing insulin secretion from the pancreas, increasing insulin sensitivity in peripheral tissues especially skeletal muscle, decreasing the rate of glucose absorption in the gut and increasing glucose excretion via the kidney. The drugs can be classified as insulins, insulin secretagogues (sulfonylureas, meglitinides, glucagon like peptide agonists, dipeptidylpeptidase IV inhibitors), insulin sensitizers (metformin, thiazolidinediones), alpha glucosidase inhibitors (acarbose and miglitol) and selective sodium-glucose transporter 2 inhibitors (Inzucchi et al., 2012; Nair & Wilding, 2010).

Despite the availability of the various classes of these conventional medicines the morbidity and mortality due to DM continues to increase globally (International Diabetes Federation, 2015). This is partly because none of the medicines results in cure of the disease. With disease progression, Type 2 DM patients move from single oral drug regimens to oral combination therapy and eventually to combination therapy that includes insulin injections (Inzucchi et al., 2012). The use of the conventional drugs is also often associated with adverse side effects such as severe hypoglycemia (insulin, sulfonylureas), lactic acidosis and vitamin B₁₂ deficiency (biguanides), peripheral edema, bone weakening and hence fractures (thiazolidinediones) and abdominal discomfort (alpha-glucosidase inhibitors) (Lorenzati et al., 2010). Further, the cost of these conventional medicines is beyond the reach of many people who live in low resource settings such as Africa (International Diabetes Federation, 2015). Therefore, the search for more effective, cheaper and safer alternative treatments remains essential.

Herbal medicines are commonly used in traditional medicine (TM) practice for the management of non-communicable diseases including DM (Z. Wang et al., 2013; World Health Organisation, 2012). People use herbal medicines for various reasons. Herbal medicines are perceived to have higher effectiveness, less side effects since they are of natural origin, relatively low cost and more accessible in remote areas (World Health Organisation, 2012). Therefore, research in these perceived benefits has become even more important to promote rational use, improve the action and stability of the herbal medicines by improving the formulations, and identify new chemical entities for management of DM.

Phytochemical screening and isolation has identified various phytoconstituents with antidiabetic effects. Among the phytoconstituents, the main actives are alkaloids, amino acids, glycosides, guanidine, steroids, polysaccharides, proteins, terpenoids, inorganic ions and peptidoglycans. This review article highlights the potential mechanisms of action of various traditional herbal medicines that were shown to be efficacious in various models of diabetes. The review discusses the similarities and differences between the mechanisms of action of the herbal medicines and conventional medicines used in the management of diabetes mellitus. The review also highlights the potential role of herbal medicines in the prevention and/or treatment of diabetes complications. The review then concludes with suggestions of some key parameters that can be used to validate effectiveness of traditional medicines and argues that society may benefit more if science not only emphasized isolation of active chemical entities and drug development, but focuses on improving the action of the traditional herbal medicines in the forms used by traditional healers. This will have far greater efficiency in research as well as impact on morbidity and mortality due to diabetes mellitus.

Concepts of Health and Sickness in Traditional Medicine and Diabetes Mellitus

The conventional medicine approach is founded on empirical evidence, which has led to the isolation of observable and tangible etiological factors in the understanding and treatment of illness. A similar approach has been

adopted in developing the therapeutic procedures to combat the causes of illness. This approach largely revolves around finding active compounds specific for the desired effect. In the traditional healing context, health is viewed not as an isolated phenomenon but is encompassing and includes other factors that may not be considered in conventional medicine. Good health is therefore defined by means of a harmonious working and co-ordination of this integrated view (Busia, 2005; Okpako, 1999). Therefore it is within this world-view and metaphysics that appropriate and accurate African concepts of health, diseases and treatment can be derived and understood (Dlamini, 2006; Omonzejele, 2008). As the traditional concepts of health and illness are encompassing, the approach to management and treatment of illness is holistic (Omonzejele, 2008). Theoretical assumptions that traditional healers make about the origin of illness are consistent with the methods of treatment of the illness. While medical scientists may regard this approach as unscientific, users and practitioners of TM appreciate its rationality in the context it operates (Okpako, 1999).

Similarly, there are a number of differences between conventional and traditional medicine approaches to the management of diabetes mellitus. Conventional medicines used in DM target specific receptors for them to bring about therapeutic value, and normally one chemical entity has one mechanism of action. Unlike conventional medicines, traditional herbal medicines may contain various active ingredients targeting multiple mechanisms of action, ideally making the traditional herbal medicines combination therapies. In TM practice, the focus is not only on the blood glucose but about the wellness of the human being, hence the multiple phytoconstituents and multiple herbs normally incorporated in traditional herbal mixtures (Baldé et al., 2006; Peltzer et al., 2001; Tong et al., 2012). Whilst the conventional medicine approach defines DM as incurable, in African traditional medicine DM is a temporary condition that can be cured with the help of the ancestors (Awah, 2006).

Efficacy of traditional herbal medicines used to treat diabetes mellitus

The use of TM in the management of DM dates back to many centuries ago especially in Chinese and Indian TM practice. As later discussed, several herbal medicines have been shown to reduce blood glucose levels or reduce progression of diabetes complications. Some of the traditional medicines that have been extensively studied and have shown definitive efficacy as antidiabetic agents are discussed below.

Accumulating pieces of evidence demonstrate that leaves of *Gymnema sylvestre* have antidiabetic properties. In 1990, Shanmugasundaram *et al* evaluated the effectiveness of *G. sylvestre* in 27 Type 1 DM patients in combination with insulin therapy (Shanmugasundaram et al., 1990). The extracts at the dose of 400mg daily for 18 months in combination with insulin therapy, significantly decreased fasting blood glucose, HbA_{1C} and serum lipids of the patients compared to a similar group who received insulin only (Shanmugasundaram et al., 1990). In another study, 200mg of ethanolic extract of *G. sylvestre* significantly reduced fasting blood glucose level and HbA_{1C} in diabetic patients (Nahas & Moher, 2009). In an open-label clinical trial with 58 Type 2 diabetic patients, 500mg *G. sylvestre* leaf extracts taken daily for 3 months (Kumar et al., 2010) induced a significant reduction in polyphagia, blood glucose and HbA_{1C} compared to the control group. Administration of *G. sylvestre* to Type 2 DM patients at a dose of 1g/day for 2 months, also led to significant decreases in fasting blood glucose and early post-prandial blood glucose levels accompanied by increases in insulin and C-peptide in the blood (Al-Romaiyan et al., 2010). In the same study, extracts of *G. sylvestre* stimulated insulin secretion from isolated human islets of Langerhans (Al-Romaiyan et al., 2010).

Trigonella foenum-graecum seed was used in ancient Egypt as a remedy for DM and spread to Asian countries such as China and India (Bawadi et al., 2009). *T. foenum-graeceum* was reported to have hypoglycemic effects in rats as early as 1974 (Mishkinsky et al., 1974). In a study in diabetic patients, insulin levels were significantly higher in the *T. foenum-graecum* treatment group compared to the placebo treatment group (Mathern et al., 2009). Sharma *et al*, 1990, showed that the defatted seeds of *T. foenum-graecum* administered to Type 1 DM patients at a dose of 100g daily for 10 days significantly lowered fasting blood glucose, total cholesterol, low-density lipoproteins and tryglycerides (Sharma et al., 1990). A meta-analysis on the effect of herbal supplement in Type 2 DM patients showed that *T. foenum-graecum* reduced HbA_{1C} by 1.13% (P=0.03) (Suksomboon et al., 2011). In a double blind placebo controlled study, *T. foenum-graecum* was shown to improve glycemic control and insulin resistance in mild Type 2 diabetic patients (Gupta et al., 2001).

Momordica charantia is one of the most extensively studied herbal medicines that is used in the management of DM. The extracts of *M. charantia* reduced blood glucose levels and improved glucose tolerance comparable to conventional medicines in diabetic rat models (Ahmed et al., 2004; Ahmed et al., 2001; Sarkar et al., 1996; Viridi et al., 2003; Welihinda et al., 1986). The efficacy of *M. charantia* in humans has also been documented (Welihinda et al., 1986). Malik *et al*. 2009, compared the effects of *M. charantia* to rosiglitazone (thiazolidinedione which has since been banned because of cardiovascular side effects) in 25 Type 2 DM patients (Malik et al., 2009). Administration of 55ml/day of *M. charantia* juice for 5 months resulted in better control of diabetes and its related complications especially diabetes retinopathy and myocardial infarction compared to rosiglitazone (Malik et al., 2009). Ahmad et al. (1999) reported that drinking an aqueous suspension of the vegetable pulp of *M. charantia* resulted in a significant reduction in fasting blood glucose and post-prandial blood glucose levels in 86 out of 100 patients with Type 2 DM (Ahmad et al., 1999).

One of the most successful stories of TM research in DM was the discovery of metformin, a biguanide which is currently the backbone of Type 2 DM treatment. Metformin was developed based on the findings that guanidine like

compounds isolated from *Galega officinalis* significantly reduced blood glucose levels (Bailey & Day, 2004). Guanidine compounds however, were too toxic for clinical use (Muller & Rheinwein, 1927). Through a series of testing and research, biguanides were then developed and shown to retain the antidiabetic effects of the guanidine like compounds yet safer to use clinically (Hesse & Taubmann, 1929; Mehnert & Seitz, 1958; Slotta & Tsesche, 1929; Sterne, 1957; Ungar et al., 1957).

The success of metformin discovery has not been emulated with any other herbal medicine. This is possibly because other herbal medicines do not have one single chemical entity that is as highly active in the management of DM. Rather, a synergistic combination of effects and mechanisms by various phytoconstituents is responsible for the blood glucose lowering properties. This can be a lesson to the scientific community to not only look to the road of drug discovery but to try and improve the action of these herbal medicines as close to their traditional use as possible. Investing into research on the formulations of these raw herbal medicines may help in improving their stability and safety, which may reduce the marginalization of traditional herbal medicine use in DM.

Mechanisms of action of traditional herbal medicines in DM management

Antioxidant properties

Free radicals may be responsible for development and progression of DM as well as development and progression of DM complications (Baynes & Thorpe, 1999). The free radicals that are most implicated in DM and its complications are the superoxides, hydroxyl and lipid peroxides (Oberley, 1988). Therefore, antioxidants could potentially slow down, prevent and treat some of the complications. A number of herbal medicines have been proven to have antioxidant properties. These properties are suggested to be partly responsible for the antidiabetic effects.

In one study, extracts of *Embllica officinalis*, *Terminalia bellerica*, *Terminalia chebula* and a combination of all the 3 extracts were shown to scavenge free radicals in-vitro (Sabu & Kuttan, 2002). Green tea polyphenols (GTP) from *Camellia sinensis* were shown to have free radical scavenging properties both *in vitro* and *in vivo* studies (Sabu et al., 2002). Administration of GTP for 18 days resulted in significantly lower blood glucose levels in alloxan induced diabetic rats. Administration of GTP (100mg/kg) was also shown to considerably reverse alloxan-induced pancreatic cell damage (Sabu et al., 2002). *T. foenum-graecum* extracts reduced oxidative stress, lowered lipid peroxidation and significantly increased antioxidant systems in animal models of DM (Annida et al., 2005).

Berberine, an isoquinoline alkaloid from *Coptis sinensis* was shown to reverse renal dysfunction in rats with diabetic nephropathy by decreasing blood glucose levels, reduction of the oxidative stress and suppressing the polyol pathway (sorbitol-aldose reduction) which is implicated in development of diabetic complications (Liu et al., 2008). *Rhus hirta* fruit extracts, *Solidago Canadensis* root extracts, *Amarantus hypochondriacus* seed extracts have higher free radical scavenging properties than ascorbic acid hence maybe utilized in preventing, reducing or stopping the progression of pancreatic beta cell destruction caused by free radicals as well as halting the progression of diabetes complications (McCune & Johns, 2002; Nsimba et al., 2008). The antioxidant properties of *M. charantia* have also been associated with the antidiabetic activity of the plant extracts (Kubola & Siriamornpun, 2008; Park et al., 2007; Sen et al., 2014).

The anti-oxidant properties of traditional herbal medicines make them potential supplements to conventional medicines to reduce and/or reverse pancreatic beta cell damage and hence development and progression of the complications of DM.

Increase in insulin secretion

In advanced type 2 DM there is reduced insulin secretion making insulin secretagogues logical options for management of the disease. Some herbal extracts were shown to increase insulin secretion though the mechanisms have not been clearly elucidated. *G. sylvestre* leaf extracts were shown to stimulate insulin secretion in-vitro by increasing membrane permeability of pancreatic beta cells resulting in influx of calcium which then leads to insulin secretion (Persaud et al., 1999). Slow acting protein extract from fruit pulp of *M. charantia* increased insulin secretion in Streptozotocin-induced diabetic rats as evidenced by increased plasma insulin concentrations in treated compared to control animals (Yibchok-anun et al., 2006). The increase was attributed to activation of glucokinase hence lowering the glucose threshold for insulin secretion in the pancreas (Rathi et al., 2002). Similarly, *T. foenum-graecum* extracts increased insulin secretion in animal studies; the increase being attributed to 4-hydroxyleucine, an amino acid mimicking the insulin secreting properties of the gluconeogenic amino acids arginine and leucine (Broca et al., 2000).

Regeneration of the pancreatic beta cells

Destruction of the pancreatic beta cells is responsible for the onset of Type 1 DM and may also occur in late stage Type 2 DM especially when the patients are taking insulin secretagogues particularly the sulfonylureas (Del Guerra et al., 2005; Maedler et al., 2005). Currently, there is no conventional medicine that works by promoting the regeneration of pancreatic beta cells. A formulation that has such properties would be novel and potentially could cure both type 1 and type 2 DM.

Leaf extracts of *G. sylvestre* were shown to promote pancreatic beta cell regeneration in alloxan-induced diabetic Wistar rats (AHMED et al., 2010). Extracts of *G. sylvestre* increased both the pancreas mass and the liver glycogen content levels (AHMED et al., 2010). Berberine, from *Coptis sinensis* restored damaged pancreatic tissues in alloxan induced diabetic rats (Liu et al., 2008; Zhou et al., 2009). Pancreatic beta cell regeneration was also demonstrated with *Momordica charantia* (Hafizur et al., 2011; Singh & Gupta, 2007b), *Cantaranthus roseus* (Ahmed et al., 2010), *Nigella sativa* (Abdelmeguid et al., 2010; Kanter et al., 2009), *Allium sativum* (Albajali et al., 2011) and *Syzygium cumini* (Singh & Gupta, 2007a). These findings suggest that these extracts can potentially cure Type 1 DM as well as play an important role in management of Type 2 DM.

Increase in insulin sensitivity and glucose uptake

One of the most prominent features of Type 2 DM is insulin resistance often times as a result of obesity (Boden & Shulman, 2002; Inzucchi et al., 2012). Several studies assessing the effects of traditional herbal medicines on insulin sensitivity and glucose uptake have been conducted. A protein from fresh fruit pulp of *M. charantia* increased the uptake of 2-deoxyglucose in C2C12 cells (from the myocyte) in-vitro by 28% comparable to 37% increase in uptake induced by insulin (Yibchok-anun et al., 2006). This could be due to a direct effect of the extract on GLUT-4 transporters in the muscle cells or promotion of the translocation of these transporters resulting in the increase in glucose uptake. In the same study, *M. charantia* protein extract and insulin also increased 2-deoxyglucose uptake in 3T3-L1 adipocytes by 2.4 fold and 6.3 fold respectively, compared to the basal control group (Yibchok-anun et al., 2006). The ethyl acetate extract from *M. charantia* was also shown to activate both PPAR γ and α receptors leading to the modulation of insulin receptors. This could explain the increase in insulin sensitivity and glucose utilization in muscle cells and adipocytes (Chao & Huang, 2003; Chuang et al., 2006).

The effect of *Coptis sinensis* extracts on glucose homeostasis has been attributed to berberine, commonly present in the plant rhizomes, bark, roots and stems of the plant. Administration of berberine (200mg daily), via oral gavage in diabetic rats decreased fasting blood glucose levels, triglycerides, low density lipoproteins and total cholesterol and increased high density lipoprotein levels (Yu et al., 2005). Berberine increases GLUT 4 translocation in both myotubes and adipocytes (Kaleem et al., 2006), increases the expression of PPAR γ and α proteins in the liver (Zhou & Zhou, 2010; Zhou et al., 2008), increases the expression of insulin receptors in both the skeletal muscles and liver; and increases glucose uptake by glucose utilizing tissues in the presence of insulin (Kong et al., 2009).

Alpha glucosidase and alpha amylase inhibition

Alpha amylases and alpha glucosidases are responsible for breakdown of complex polysaccharides to oligosaccharides, disaccharides, and glucose. Inhibition of these enzymes decreases the rate of glucose absorption resulting in a decrease in post prandial blood glucose levels. Several herbal medicines have been shown to inhibit alpha glucosidase and amylase enzymes. The plants include, guava leaves (Wang et al., 2010), *Adhatoda vasica* (Gao et al., 2008), *Baccharis trimera* (Oliveira et al., 2005), *Bergenia ciliate* (Bhandari et al., 2008), *Brachylaena discolor* (Mellem et al., 2015), *G. sylvestre* (Luo et al., 2001), *M. charantia* (Uebanso et al., 2007), *Phyllanthus amarus* (Ali et al., 2006), *Pinus densiflora* (Kim et al., 2005; Schäfer & Högger, 2007), and *Tournefortia hartwegiana* (Ortiz-Andrade et al., 2007).

Dipeptidyl peptidase IV (DPP-IV) inhibition

The DPP-IV enzyme is responsible for the breakdown of incretin hormones (GLP-1 and Glucose-dependent insulinotropic polypeptide). Incretin hormones increase insulin synthesis and release from pancreatic beta cells and reduce glucagon secretion from pancreatic alpha cells. Therefore, the inhibition of DPP-IV results in increased insulin synthesis and release and reduce glucagon secretion. Protein hydrolyzates from *Amarantus hypochondriacus* reduced postprandial glycemia in streptozotocin-induced diabetic mice, possibly through inhibition of DPP-IV as observed in an in-vitro study (Soriano-Santos et al., 2015).

Sodium-glucose transporter - 1 (SGLT-1) inhibition

SGLT-1 is a transporter that is found in the brush border of the small intestines which is responsible for absorption of glucose. Therefore, inhibition of SGLT-1, just like alpha glucosidase inhibitors, results in decreased absorption of glucose in the small intestines. The models to study inhibition of SGLT-1 include brush border membrane vesicles (BBMV) prepared from apical membrane and vesicles prepared from basolateral membrane (BLMV) of the small intestines (Soumyanath, 2005). Extracts of *G. sylvestre* were shown to inhibit intestinal SGLT-1 and hence reduce absorption of glucose from the small intestines (Y. Wang et al., 2014). Extracts of *T. foenum-graecum*, *Camellia sinensis* and Green Tea Polyphenols inhibited glucose absorption in BBMV models (Al-Habori et al., 2001) (Kobayashi et al., 2000). Since there is no SGLT-1 inhibitor among the conventional anti-diabetic medicines, this is an important area of future research.

A comparison of the mechanisms of action of conventional and some herbal medicines is summarized in the table below.

Table: Comparison of mechanisms of action of conventional medicines with TM

	Decreased rate of carbohydrate absorption	Stimulation of insulin secretion	Activation of PPAR	Increase in insulin receptor sensitivity	Regeneration or decrease in apoptosis of B-cells	Antioxidant activity	Increase in glucose excretion
Conventional Medicines							
Alpha glucosidase inhibitors	*						
Amylinomimetics	*	*					
Biguanides				*			
DPP-IV inhibitors		*					
GLP-1 agonists		*					
Meglitinides		*					
SGLT-2 inhibitors							*
Sulfonylureas		*					
Thiazolidinediones			*				
Herbal medicines							
<i>Adhatoda vasica</i>	*						
<i>Allium sativum</i>					*	*	
<i>Brachylaena discolor</i>	*						
<i>Camelia sinensis</i>	*					*	*
<i>Catharanthus roseus</i>					*	*	
<i>Coptis sinensis</i>			*	*	*	*	
<i>G.sylvestre</i>	*	*		*	*	*	
<i>M. charantia</i>	*	*	*	*	*	*	
<i>Nigella sativa</i>					*	*	
<i>Panax ginseng</i>				*		*	
<i>Phyllanthus amarus</i>	*						
<i>Rhus hirta</i>						*	
<i>Solidago Canadensis</i>						*	
<i>Syzygium cumini</i>					*	*	
<i>T. foenum-graecum</i>	*	*			*	*	
<i>Tourbfortia hartwegiana</i>	*					*	

Conclusion

Clearly, herbal medicines have multiple mechanisms possibly because of the multiple phytoconstituents, which effectively make them combination therapies. In addition, the multiple phytoconstituents may make traditional herbal medicines effective for the whole metabolic syndrome compared to conventional medicines that mainly focus on diabetes with limited or no effect on the other pathophysiological pathways of the metabolic syndrome.

The review has discussed several in-vitro and in-vivo models that have been used to evaluate efficacy and study possible mechanisms of action of herbal medicines used to treat diabetes. Clearly, there is need for consensus on the minimum evidence that is required to conclude that a particular traditional medicine is truly anti-diabetic, and build the necessary evidence towards human studies. This means that a minimum algorithm of in-vitro and in-vivo models to assess the anti-diabetic effects of herbal medicines is therefore required.

Amongst the in-vitro models, alpha glucosidase inhibition and antioxidant activity have been extensively used in evaluating anti-diabetic potential of traditional herbal medicines. Models that assess the other potential mechanisms of action need to be developed, optimized and utilized in diabetes research. Research should also focus on improving the action of traditional herbal medicines in the forms used by the traditional healers as much as it focuses on isolation of active chemical entities.

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