HERBAL MEDICINE AND DIABETES MELLITUS MANAGEMENT

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Summary

In view of the increasing demand by patients to use herbal preparations with antidiabetic effects in the management of diabetes mellitus worldwide especially in developing countries. Also considering the economic resource constraints of diabetics in developing countries and given the cheapness of these herbal products which are readily available to rural dwellers, this present review was undertaken to search for some of the herbs used around the world with antidiabetic effects which may be pursued for their clinical usefulness in the management of diabetes mellitus and other associated complications. The search used keywords such as herbal medicine, hypoglycaemic and hypolipidaemic herbs each crossed with the term diabetes mellitus with particular emphasis on experimental animal models, effective dosage and hypoglycaemic/or hypolipidaemic effects of these herbs. The search result revealed fifteen of some of the antidiabetic herbs which are *Vernonia amygdalina, Tapinanthus butungii, Nauclea latifolia, Sarcocephalus latifolus, Benincasa hispida, Azadirachta indica, Momordica charantia, Aloe vera, Ocimum gratissimum, Gongronema latifolium, Gymnema sylvestre, Trigonella foenum graecum, Allium cepa, Zingiber officinale, Allium sativum.* Further research may be necessary to elucidate the pharmacological principle of these herbs which will stimulate future pharmaceutical development of therapeutically beneficial antidiabetic herbal drugs.

(**Keywords**: Herbal medicine, hypoglycaemic, hypolipidaemic, Diabetes mellitus Management)

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Introduction

Diabetes mellitus is a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia (high blood sugar) with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both (1). In 2006, according to the World Health Organization, at least 171 million people world wide suffer from diabetes (2). Its incidence is increasing rapidly and it is estimated that by the year 2030, this number will double (2).

There are two major types of diabetes mellitus (Table 1): (1).Type 1 Diabetes, also called insulin dependent diabetes mellitus (IDDM), is caused by lack of insulin secretion by beta cells of the pancreas and (2). Type 2 Diabetes, also called Non-insulin Dependent Diabetes Mellitus (NIDDM), is caused by decreased sensitivity of target tissues to insulin. The reduced sensitivity to insulin is often called insulin resistance (3).

Table 1: Comparison of Type 1 and Type 2 Diabetes mellitus

Characteristics	**Type 1 Diabetes**	**Type 2 Diabetes**
Level of insulin secretion	None or almost none	May be normal or exceed normal
Typical age of onset	Childhood	Adulthood
Percentage of diabetics	10 -20%	80 -90%
Basic defect	Destruction of β -cells	Reduced sensitivity of insulin's target cells
Associated with obesity	NO	Usually
Genetic and environmental factors important in precipitating overt disease	Yes	Yes
Speed of development of symptoms	Rapid	Slow
Development of ketosis	Common if untreated	Rare
Treatment	Insulin injection, dietary management	Dietary control and weight reduction, occasionally oral hypoglycaemic drugs.

Source: (4).

Diabetes mellitus is currently a chronic disease, without a cure and medical emphasis must necessarily be on managing and avoiding possible short terms as well as long term diabetes –related problems. The primary goal in the management of diabetes mellitus is to control blood glucose levels (5). The theory of treatment of Type 1 diabetes mellitus is to administer enough insulin so that the patient will have carbohydrate, fat and protein metabolism that is as normal as possible (6). When blood homeostasis, is not maintained, pathological complications begins to manifest. In the Type I diabetic, this requires regular insulin injections. When blood homoeostasis is not maintained, pathological complications begin to manifest because diabetics are also at a greater risk of developing cardiovascular disease compared to non diabetics, preventive measures that include dietary and lifestyle modifications are very important. Fundamental to the successful management of type II diabetes is dietary modification including the strict control of simple carbohydrate intake and increasing the percentage of complex carbohydrate, as well as fiber (5). Regular exercise is also important and weight reduction (in overweight individuals). While some cases of type II diabetes can be controlled by weight loss and diet alone, in some instances the use of insulin or oral hypoglycaemic drugs, such as sulphonylureas and biguannidines are necessary to help keep blood glucose at a normal level. Additionally dietary supplements such as chromium may provide benefit to diabetic individuals. The benefits of vitamin E, magnesium and other nutrients are still being elucidated. In the recent years, several plant extracts have been examined for

antidiabetic activity in an effort to identify alternative treatment strategies that pose less of a risk for diabetics (5). Although herbs can be very effective in helping to manage elevated blood glucose, they should not be used in place of insulin in persons with type I or Type II diabetes requiring insulin. Oral antidiabetic agents exert their effects by various mechanisms: (1). stimulating beta cells in the pancreas to produce more insulin (sulfonylureas and meglitinides) (2). increasing the sensitivity of muscles and other tissues to insulin (thiazolidinediones) (3). decreasing gluconeogenesis by the liver (biguanides) and (4).delaying the absorption of carbohydrates from the gastrointestinal tract (alpha-glucosidase). (7). These treatments are associated with adverse effects and some may produce toxic effects (eg. Thiazolidinediones may cause liver toxicity) (8). Blood glucose monitoring is an essential task for patients suffering from diabetes; thus any change caused by herbal products to blood glucose levels may alter the amount of medication needed to control blood glucose. Herbal Medicine is the use of plant based formulations to alleviate diseases. It is estimated that roughly 80% of Africa's 750 million population use herbal medicine due to the prohibitive cost of many modern medicine (9). The annual sale of medicinal herbs and related commodities in the United States now exceeds two billion dollars (10). The current shift to the use of herbal preparations could be due to presumed effectiveness and less side effects, relatively low cost and low toxicity. This present search designed to review the literature on some herbal remedies used around the world in the management of diabetes, will help pharmaceutical industry in antidiabetic drug formulations and researchers in the field of pharmacology on recommendations for future research. There is therefore no doubt that this review on herbal medicine and diabetes mellitus management is timely and antidiabetic medicinal herbs could provide an important source of new oral hypoglycaemic compounds for development as pharmaceutical entities or as simple dietary adjuncts to existing therapies.

Research Design and Methods

A comprehensive literature search was made from internet and serial materials of Nnamdi Azikiwe library, University of Nigeria, Nsukka. Different scientific Journal articles, proceedings of learned societies on ethnopharmacology, diabetes and alternative therapy, World Health Organization documents and textbooks were consulted vis-à-vis of herbal medicine and diabetes mellitus management. The search used keywords such as herbal medicine, hypoglycaemic and hypolipidaemic herbs, each crossed with the term diabetes mellitus. Studies were limited to those articles published in the English language. The findings are presented in Table 2.

Results

The search revealed fifteen species of herbs around the world with antidiabetic effects (hypoglycaemic/ or hypolipidaemic) as gleaned from the scientific literature that is available (Table 2).

Table 2: Some of the herbs around the world with antidiabetic effects

Scientific name of herbs	Experimental animal model	Effective Dosage	Antidiabetic effects	Reference(s)
1. Vernonia amygdalina	Diabetic rats	80mg/kg	Hypoglycaemic	**11**
2. Tapinanthus butungii	Diabetic rat	300mg/kg	Hypoglycaemic	**12**
3. Nauclea latifolia	Diabetic rat	200mg/kg	Hypoglycaemic	**13**
4. Sarcocephalus latifolus	Diabetic rats	unstandardized	Hypoglycaemic	**14**
5. Benincasa hispida	Diabetic rats	200mg/kg	Hypoglycaemic	**15**
6. Azadirachta indica	Diabetic rats	500mg/kg	Hypoglycaemic	**16, 17**
7. Mormordica charantia	Diabetic animal model	500mg/kg	Hypoglycaemic	**18**
8. Aloe vera	Diabetic rats	50mg/day	Hypoglycaemic	**19, 20, 21**
9. Ocimum gratissimum	Diabetic rats	200mg/kg	Hypoglycaemic, Hypolipidaemic	**22**
10. Gongronema latifolium	Diabetic rats	unstandardized	Hypolipidaemic	**23**
11. Gymnema sylvestre	Diabetic rabbits	400mg/day	Hypoglycaemic,	**24**
12. Trigonella foenum graecum	Diabetic animal	10 – 15g/day	Hypoglycaemic, Hypolipidaemic	**5**
13. Allium cepa	Diabetic rats	200, 250 and 300mg/kg	Hypoglycaemic, Hypolipidaemic	**25**
14. Zingiber officinale	Diabetic rats	200, 250 and 300mg/kg	Hypoglycaemic, Hypolipidaemic	**26**
15. Allium sativum	Diabetic rats	200, 250 and 300mg/kg	Hypoglycaemic, Hypolipidaemic	**27, 28**

Discussion

1. Vernonia amygdalina

Fresh extracts of *V. amygdalina* has been reported to contain alkaloids, saponins, tannins, flavonoids and proteins (29), as well as vitamins and minerals (30). *V. amygdalina* has numerous uses as in malaria and stomach disorders (31), The leaf decoction of the plant is popular in traditional medicine as an antidiabetic remedy; the potency and safety of which has been documented (29). The hypoglycaemic potential of *V. amygdalina* has been documented (11). Although several biologically active constituents were reported present in the extracts (30, 29). It was not demonstrated which of the groups of phytochemicals were responsible for its antidiabetic effects and the mechanism of action. The prompt and remarkable reduction in blood glucose in both the fasting normal and alloxan diabetic rats points to a mechanism of action different from that of sulphonylureas, and unrelated to insulin secretion from pancreatic β- cells (11).

2. Tapinanthus butungii

Aqueous extracts of the leaf of *T. butungii* induced significant dose dependent reduction in blood glucose concentration of normoglycemic, hyperglycaemic and alloxan induced diabetic rats (12). The fact that *T. butungii* extracts caused significant reductions in blood glucose levels in alloxan induced diabetic rats suggests that *T. butungii* may act in yet undertermined ways apart from stimulating insulin production from the pancreatic islets since these would have been severely damaged by alloxan (12). Significant reduction in blood glucose levels in hyperglycaemic rats by the extracts may suggest that *T. butungii* could, at least in part stimulate insulin production and glucose utilization, like glibenclamide and chloropropamide, to bring its hypoglycaemic effect in the mammalian experimental model used (12).

3. Nauclea latifolia

The aqueous extract of the leaves of *N. latifolia* caused a 19.5% decrease in blood glucose levels of the diabetic rats within 1hr of administration compared to 0.67% for glibenclamide within the same period (13). The maximal reduction of 44.5% was observed at 4hrs while for glibenclamide the maximal reduction of 40% was also observed at 4hrs (13). The hypoglycaemic activity was not similar with that of glibenclamide, an oral hypoglycaemic drug that lower blood glucose in both normal and diabetic subjects (21).

4. Sarcocephalus latifolus

Phytochemical analysis of *S. latifolus* aqueous extracts showed that it contains carbohydrates, glycosides, reducing sugar, alkaloids, saponins, tannins, terpenoids and sterols (14). The aqueous extracts of the roots of *S. latifolus* caused a 29.26% decrease in blood glucose levels of the diabetic rats within 1hr of administration (14). A maximal reduction of 76.2% was attained at 6h, this compared with the maximal reduction for glibenclamide at the 5hrs. Treatment of non- diabetic rats with the same dosage, for the same duration, did not however, show the same hypoglycaemic activity (14). The hypoglycaemic activity was not similar with that of glibenclamide, (32, 21).

5. Benincasa hispida

Alcoholic extracts of *B. hispida* produced a dose dependent percentage blood glucose reduction in normal and diabetic rats (15). In normal treated rats a significant percentage blood glucose reduction was observed up to 24hrs and maximum percentage blood glucose reduction was observed at 6hrs, where as in diabetic rats also significant reduction in blood glucose was maintained up to 24hrs and maximum at 6hrs (15). The percentage blood glucose reduction produced by the extract at 200mg/kg in diabetic rats was highly significant and greater than the percentage reduction observed in tolbutamide treated rats. Phytochemical analysis of *Benincasa hispida* alcoholic extracts showed the presence of alkaloids, flavonoids, saponins and steroids. Different mechanisms of action to reduce blood glucose levels with the help of plant extracts already exist. Some plants exhibits properties similar to the well known sulfonylurea drugs like tolbutanide, they reduce blood glucose in normoglycemic animals (33).

6. ***Azadirachta indica***

Water soluble portion of alcoholic extract of leaves of *A. indica* possesses significant anti-inflammatory, antiserotonin, antifertility and hepatoprotective activity (34). Significant blood sugar lowering effect of *A. indica* in alloxan and streptozotocin induced diabetic rats have been reported by several investigators. (16, 17). Chemical analysis of *A. indica* leaf extract reveals the following six compounds; quercetin-3-O-B—D-glucoside, myricetin-3-0-rutinoside,quercetin-3-0-rutinoside, kaempferol-3-0-rutinoside, kaempferol-3-0-B-D-glucoside, quercetin-3-0-L-rhamnoside (35). It is presumed that these compounds either wholly or partly may be responsible for antihyperlipidemic activity (36). Thus it is evident from experimental findings that the levels of total serum cholesterol, triglycerides, total lipids, VLDL and LDL – cholesterol which are actually raised in diabetes can be lowered with *A. indica* leaf extracts. Its antihyperlipidaemic effect could represent a protective mechanism against the development of atherosclerosis characteristic of diabetes mellitus.

7. Momordica charantia

(18) reported that *M. charantia* showed a significant reduction in blood glucose levels, glycosylated haemoglobin levels, serum cholesterol and triglyceride levels in both *M. charantia* extract and glibenclamide treated rats. *M. charantia* and glibenclamide elevated the reduced serum insulin, total protein and liver glycogen levels (18). The increase in serum insulin levels suggested that *M. charantia* like glibenclamide enhances the secretion of insulin from the beta cells of the islets of langerhans (18). Histopathological studies revealed that *M. charantia* and glibenclamide significantly improved the histological architecture of the islets of langerhans (18). The rats treated with *M. charantia* (150 and 300mg/kg) and glibenclamide (4mg/kg) showed greater persistence of the islets of langerhans and lesser degree of necrotic changes as compared to the untreated alloxan diabetic rats (18). (18) concluded tentatively that the possible mechanism(s) by which *M. charantia* brings about its antihyperglycemic action may be through potentiation of pancreatic secretion of insulin from the intact β- cells of islets coupled with extra-pancreatic mechanisms like decreased glycogenolysis and enhanced glycogenesis by the liver and/or enhanced transport of blood glucose to peripheral tissue. *M. charantia* direct effect on the regulation of the islets of pancreas was also evidenced by the restoration of the architecture of the islets of langerhans in histopathological studies.

8. Aloe vera

A. vera has been shown to have antidiabetic and hypoglycaemic properties (19, 20). It was postulated that the hypoglycaemic effect of *A. vera* could be mediated through stimulation of synthesis and/ or release of insulin from the β- cells of langerhans (20). The mechanism of the reduction in mean glucose levels produced by *A. vera* has not been yet elucidated. In recent study, prevention of the destruction of pancreatic islets by *Aloe arborescens* boiled leaf skin components was attributed to its free radical scavenging effect (19). Acute treatment with Aloe leaf pulp resulted in 30 and 34% decreases in blood sugar levels of no- STZ- diabetic rats, after 2 and 3 hrs of administration of the extract respectively (21), and 11 and 14% reductions in blood glucose levels 3 and 4hrs after administration of Aloe leaf gel extract. Neither glibenclamide nor aloe extract showed any stimulation of the pancreatic β cells in type 2 diabetic rats which suggests that any decreases in blood glucose levels caused by Aloe extracts is not mediated by insulin release from β- cells, but by extra pancreatic usage of glucose. Administration of extracts of *Aloe barbadensis* leaves significantly reduced serum tricylyglycerol and LDL – cholesterol in diabetics (37).

9. Ocimum gratissimum

The leaves of *O. gratissimum* contain a great quantity of thymol oil which has been regarded as highly antiseptic agent hence, its use by most people as mosquito repellent (38). The juice of the fresh leaves is used as eye drops and is said to be a quick cure for conjunctivitis (39). It has also been revealed that it may be anti-haemorrhage (40), antihypertensive, antimicrobial (39), psychostimulant effects (41). (22) indicated that the administration of aqueous leaf extracts of *O. gratissimum* produced both hypoglycaemic, hypolipidaemic and antioxidant effects. There are many bioactive constituents present in the extract and hence, at present it is not certain which of them is/ are responsible for the observed effects. However some reports have shown that flavonoids, tannins and saponins may play some roles in antioxidative and hypolipidaemic effects (42). Extracts of *O. gratissimum* produced a marked decrease in blood glucose of diabetic rats (22). Its hypolipidaemic and lowering of oxidative stress may be due to decreased oxidative load. It may also act directly by scavenging the reactive oxygen metabolites, due to the presence of various antioxidants compounds (43) or by increasing the synthesis of antioxidant molecules.

10. Gongronema latifolium

Ethanolic extracts of *G. latifolium* significantly reduced blood glucose levels, which in turn could have reduced the potential glycation of the enzymes and the ensuing decrease in their activities (23). Both ethanolic and aqueous extracts of *G. latifolium* significantly reduced the triglyceride levels in treated diabetic rats when compared to untreated diabetic rats (23). The ethanolic extracts was also able to significantly decrease the total cholesterol concentration in treated diabetic rats when compared to both untreated diabetic rats and diabetic rats treated with the aqueous extracts (23). These reductions could be beneficial in preventing diabetic complications as well as improving lipid metabolism in diabetics (44).

11. Gymnema sylvestre

In the diabetic rabbit model, administration of *G. sylvestre* was shown to not only bring about blood glucose homeostasis, but also increase the activities of enzymes involved in glucose utilization (24). The investigators reported an increase in the activity of certain insulin- dependent enzymes that are normally lowered in diabetic tissues, suggesting that the herb may act to increase insulin availability. Also in a manner similar to insulin, *G. sylvestre* caused a reduction in the activities of enzymes that are normally increased in the diabetics, such as glycogen phosphorylase, gluconeogenase. Additionally, the investigators reported that glycogen depletion in the liver and lipid accumulation in the diabetic animals was reversed as a result of *G. sylvestre* therapy. Recently it has been reported that oral administration of *G. sylvestre* to diabetic rats increased the number of pancreatic islet and beta cells as well as insulin levels, suggesting a possible repair or regeneration of the endocrine pancreas. The investigators speculate that some residual pancreatic function is necessary for this effect to occur, as the extract showed no hypoglycaemic effect in pancreatectomised animal (45).

12. Trigonella foenum graecum

More recently, several studies have demonstrated hypoglycaemic properties of *Trigonella foenum graecum* seeds in both animal and human studies, thus giving support to its traditional use (46). Research further suggests that *Trigonella foenum graecum* has a lowering effect on plasma cholesterol and triglyceride levels. The hypoglycaemic effect of *Trigonella foenum graecum* is thought to be largely due to its high content of soluble fiber, which acts to decrease the rate of gastric emptying thereby delaying the absorption of glucose from the small intestine. Also fiber in general (except for cellulose) enhances fecal excretion of bile acids and cholesterol, which would explain in part *Trigonella foenum graecum* hypocholesterolemic properties (5). It is believed that the soluble fiber portion of *Trigonella foenum graecum* is largely responsible for its effects on lowering post prandial blood glucose levels, it is likely that other factors contributes to *Trigonella foenum graecum* antidiabetic properties as well (5).

13. Allium cepa

A. cepa extracts is used as diuretic and expectorant but these properties have not been scientifically investigated. Other properties of *A. cepa* extract are; anthelmintic, antispasmodic, carminative, stomachic, tonic and gargle for sore throats (47). *A. cepa* aqueous extracts produced a dose dependent significant reduction in blood glucose levels, total serum lipids and total serum cholesterol levels when compared with that of the control rats (25). The most effective percentage reduction in blood glucose levels, total serum lipids and cholesterol were observed at 300mg/kg (25). With this verified hypoglycaemic effects and hypocholesterlemic properties, *A. cepa* may have a promising future in the treatment of diabetes and heart diseases. The active ingredient appears to be allyl propyl disulfide (APDS) though other active sulphurous compounds are present (47). Another study of the extracts of the bulb of *A. cepa* showed that when administered orally or injected subcutaneously into rabbits, it acts in a way similar to that of insulin. Oral administration of 0.25g/kg was shown to produce an equivalent lowering of blood glucose as the same dose of tolbutanide (47). The hypoglycaemic effect of *A. cepa* may be due to a rise in the insulin level. It is not clear whether the rise is due to increased insulin secretion or decreased insulin degradation rate (47).

14. Zingiber officinale

Zingiber officinale contains a number of pungent constituents and active ingredients. Steam distillation of powered *Zingiber officinale* produced ginger oil, which contains a high proportion of sesquiterpene hydrocarbons, predominantly zingiberene (48). The major pungent component in *Zingiber officinale*, from studies of the lipophilic rhizome extracts have yielded potentially active gingerols, which can be converted to shogaols, zingerone and paradol (48). The compound 6-gingerol appears to be responsible for its characteristic taste. Zingerone and shogaol are found in small amounts in fresh ginger and in larger amounts in dried or extracted products. The compound 6- gingerol and 6-shogaol have been shown to have a number of pharmacological activities, including antipyretic, analgesic, antitussive and hypotensive effects (49). *Zingiber officinale* aqueous extracts produced a dose dependent significant reduction in blood glucose levels, total serum lipids and total serum cholesterol levels when compared with that of the control rats (26). The most effective percentage reduction in blood glucose levels, total serum lipids and cholesterol were observed at 300mg/kg (26). In rabbit fed high cholesterol diet, ginger extracts had antilipemic effects reducing serum cholesterol and high lipid level (50). Studies of experimental mice showed that ginger extract had significantly impaired cholesterol biosynthesis and lowered serum cholesterol concentrations (51). These researches suggest ginger might increase insulin levels and could have an additive effects with medications used to treat diabetes and cause hypoglycaemia. *Zingiber officinale* extracts may act by stimulating insulin production from the pancreatic islets or by increasing peripheral utilization and inhibition of the proximal tubular reabsorption mechanism for glucose in the kidney which have a glucose lowering effect (32). The mechanism of the hypoglycaemic effects still remains speculative, further studies are required to unravel the mechanism of its hypoglycaemic action.

15. Allium sativum

The potentially active chemical constituent in *Allium sativum* are sulphur compound allicin, ajoene, allylpropyl disulfide, diallyltrisulfide, s- allyl cysteine, vinyldithines, s-allylmercaptocystein and others (52). *Allium sativum* aqueous extracts produced a dose dependent significant reduction in blood glucose levels, total serum lipids and total serum cholesterol levels when compared with that of the control rats (27). The most effective percentage reduction in blood glucose levels, total serum lipids and cholesterol were observed at 300mg/kg (27). *Allium sativum* aqueous extracts at 300mg/kg bw ip reduced total serum lipids 44.4% and total serum cholesterol by 39.8% after 6 weeks of administration of extracts (28). Its possible mechanism of hypoglycaemic action may be by increasing either the pancreatic secretion of insulin from beta cell or its release from bound insulin. The hypolipidaemic and hypoglycaemic effect of garlic extracts may act as a protective mechanism against the development of hyperglycaemia and hyperlipidaemia common in diabetes mellitus.

Conclusions

Herbal based therapies for diabetes mellitus has been in use for a long time and has been popularized world over by leading pharmaceuticals. Despite the significant popularity of

several herbal medicine in general and antidiabetic herbs in particular, they are still unacceptable management modalities for diabetes mellitus. The limiting factors that contribute to this unacceptability are (i) lack of standardization of herbal drugs (ii) lack of identification of active ingredient(s)/principle (s) and (iii) lack of toxicological evaluation of the herbal drugs. There is need for more experimental and clinical studies on these antidiabetic herbs to define their active principle, mode of action, toxicity, drug interaction and side effects. Compounds that stimulate insulin biosynthesis and secretion or promote peripheral glucose uptake and utilization are with high potentials in antidiabetic herbs. Physicians and diabetic patients are in need of effective therapeutic agents with low incidence of side effects which several herbal medicine potentially hold solutions to. Therefore treating diabetics with plant-derived compounds which are accessible and do not require laborious pharmaceutical synthesis is urgently needed. In this review article, an attempt has been made to compile some of the reported antidiabetic herbs from around the world and it will be very useful to health care professionals, scientists working the field of pharmacology and therapeutics to develop evidence–based alternative medicine to cure different kinds of diabetes in man and animals. As we further our understanding of antidiabetic herbs, we might begin to develop a framework for a medical system capable of incorporating herbal medicine proven to be beneficial.

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