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Mini Review

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Phytotherapy in the management of Diabetes mellitus

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Abstract

Diabetes is becoming a scourge of both developed and resource-poor countries. The disease seriously threatens the mere existence and economic survival of many resource-poor countries. The major question in the care of diabetes, especially Type 1 diabetes has to do with the availability and affordability of insulin. Insulin is a very expensive drug for poor countries and many diabetic patients (especially in remote areas) have great difficulty in obtaining supplies. As an alternative, they make recourse to traditional medicine. A good number of plants/herbal preparations have been reported effective in the management of diabetes. Some of these plants include *Anacardium occidentale, Bridelia feruginea, Dioscorea dumetorum, Musa sapientum, Vernonia amygdalina,* etc. The use of phytotherapy to treat human diseases has its roots in pre-historical times. Indigenous communities have long used plant extracts to treat illnesses including diabetes. This work highlights some of these plants and their potential benefit in the management of diabetes.

Keywords: Diabetes mellitus, glycemic control, phytotherapy.

1. Introduction

Diabetes mellitus describes a group of disorders of varying etiology and pathogenesis usually characterized by elevated blood glucose concentration, reduced insulin action or insulin deficiency [1]. It is associated with abnormalities of glucose, lipid and protein metabolism and the development of both acute and long term complications [1]. The incidence of diabetes mellitus is fast attaining epidemic proportions with a WHO [1] projected 122% rise by the year 2005. This translates to an alarming population of about 300 million worldwide [2]. An estimated global prevalence of Type 1 diabetes will increase from 3.5 million in 1995 to 5.5 million in 2010 [3]. The global prevalence of Type 2 diabetes, which is presently estimated to affect more than 100 million people, is set to double by 2010 [3].

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Mortality and morbidity in diabetes are due mainly to the associated chronic complication [4]. Diabetes ketoacidosis is an acute metabolic complication of diabetes relatively common in developed countries with a mortality rate of 2-5% [5]. Foot problems in diabetes could present as cellulites, abscesses, ulcers or gangrene [6].

Successful management of diabetes mellitus hinges on a multidisciplinary healthcare approach which includes a combination of diet, drug and or insulin therapy, exercise and behaviour modification to ensure long term compliance [7]. At present, the targets for good diabetes control are a fasting blood glucose (finger prick test) less than 6 mmol/L and HbA_{1C} less than 7% [8].

Increased physical exercise and reduced calorie intake improve insulin sensitivity and glycemic control [9]. Appropriate diet is also a preventive treatment itself for maintaining normoglycemia [10,11].

Insulin continues to be the mainstay in the management of Type 1 diabetes. It however plays an important but secondary role in the treatment of Type 2 diabetes.

Currently, insulin regimens aim to mimic the physiological secretion of insulin [12]. Orally effective hypoglycemic agents are of primary choice in the management of Type 2 diabetes and include sulphonylureas, biguanides, -glucosidase inhibitors, thiazolidenediones and repaglinide. A number of antidiabetic agents in development include fatty acid inhibitors, glucagon antagonists, somatostatin analogues and β3- adrenoceptor agonists [13].

Unfortunately, glycemic control with oral agents usually becomes increasingly difficult with the progress of the disease [13]. Most patients progress from a single tablet regimen through combination regimens to insulin therapy in an average of 7 years [13]. This makes the oral agents still inadequate in long term control of diabetes.

The availability of insulin is a major issue of care of Type 1 diabetes [14]. Insulin remains a very expensive drug for poor countries and many Type 1 patients particularly in rural areas have great difficulty in obtaining supplies [14].

2. Hypoglycemic Plants

Diabetes is believed to have been first described in an Egyptian papyrus about 3000 years old; this papyrus was discovered in 1882 in the tomb of Thebes [15]. Plants and many plant derived preparations have long been used as traditional remedies and in folklore medicine for the treatment of diabetes in many parts of the world [16,17].

In present times, available evidence suggests a high prevalence of utilization of alternative medicines for the treatment of diabetes in some regions of the world. The use of teas prepared from several plants is widespread in Brazil [18] and in other countries [19-21] and some of these teas are used as remedies in diabetes mellitus [22].

In Africa, some of the plants used by traditional healers for the treatment of diabetes include *Bridelia feruginea* [23] and *Dioscorea dumetorum* [24]. Bitter principles from plants such as root of *Coccinia indica* and fruit of *Momordica charantia* have also been associated with improvement in the symptoms of diabetes millitus [25,26]. There are mounting evidence about the hypoglycemic effects of some medicinal plants, at least in experimental animals [27] and some of these data are discussed below.

2.1 Agarista mexicana (Ericaceae)

A. mexicana is a small tree usually 1-2.5 m tall [28]. The water extract of its leaves has long

been in use in Mexican folklore for the treatment of diabetes mellitus [28]. Chloroform extracts of the bark of *A. mexicana* showed significant hypoglycemic activity on alloxan-induced hyperglycemic mice [28].

However, in consideration of the potency of the effect obtained, it was suggested that the extract of *A. mexicana* might be useful in controlling the blood glucose level in mild diabetes [28,29].

2.2 Anacardium occidentale (Anacardiaceae)

A. occidentale is a shrub or ornamental tree which grows up to 10 m high. It is widely distributed in tropical countries and occurs in Senegal [30]. It is cultivated in the rain forest region [31]. *A. occidentale* is one of the plants used in South Cameroon by traditional healers as well as in other countries like Nigeria as folk remedy for diabetes mellitus [32-34]. Aqueous leaf extract of *A. occidentale* has been shown to significantly inhibit streptozotocin-induced hyperglycemia in rats [30].

The extract also reduced fasting blood sugar levels of both normal and alloxanized rabbits [34]. Pretreated animals reportedly presented no gylcosuria, normal weight gain, and a non-significant increase in food and fluid intake at the end of the treatment compared to the normal control [30].

The extract was found to be ineffective beyond 3 h [34] which may imply a short duration of action. The extract was suggested to act by directly inhibiting streptozotocin by competing with it for glucose-associated receptors on β - cell membranes [30]. The extract may also act by increasing the resistance of β-cells by a direct activation of superoxide dismutase (SOD) [30], a widely distributed enzyme that scavenges superoxide radicals [35] which may determine the toxic effects of streptozotocin [36,37].

The protective effects of *A. occidentale* against streptozotocin-induced hyperglycemia has been attributed to glucose and (-) epicatechin present in the plant extract [30]. Loss of diabetogenic action of alloxan and streptozotocin has been reported upon pretreatment with glucose [38, 39] and (-) epicatechin [40].

2.3 Azadirachta indica (Meliaceae)

A. indica also known as Neem is an indigenous plant widely available in India and Burma [41]. It is also common in Nigeria especially in the Northern parts where it is used to check desert encroachment. The seed oil of Neem (Margosa oil) has been widely used in Asian medicine [42]. Different parts of this plant have been reported to exhibit pharmacological activity like hypoglycemia, antimalarial, antiseptic, wound healing, antiulcer and anti-inflammatory activities [42-44].

Aqueous portion of alcoholic leaf extract of *A. indica* was found to possess significant blood sugar lowering effect in glucose fed and adrenaline-induced hyperglycemia in rats [45]. Further work has demonstrated that *A. indica* extract substantially lowered hepatic glycogen content [46]. The effect of insulin in this regard was also potentiated by the extract [46].

Due to the selective effectiveness of *A. indica* extract on glucose fed and adrenaline induced hyperglycemia in rats and its anti-serotonin activity, it was suggested that the extract could act by blocking the inhibitory action of the intracellular compartmentalized serotonin pool and thereby potentiates the insulin release triggered off by adrenaline or glucose meal [41].

Based on its effect on hepatic glycogen content, it has been proposed that *A. indica* leaf extract may act by potentiation of extra insulin secretion in response to other stimuli like glucose load [46].

2.4 Bignonia tuira (Bignoniaceae)

B. tuira is abundantly distributed in the Amazons where extract or infusion of the leaves is popularly used in the treatment of diabetes and related disorders [47]. Aqueous extract of the leaves of *B. tuira* administered orally has been reported to lower blood sugar levels in alloxan-induced diabetic animals [47]. The extract was found ineffective in normal animals [47]. Due to these observed activities, it was proposed that the extract could exert its hypoglycemic effect by promoting the regeneration of β-cells [47].

2.5 Brassica oleraceae (Cruciferae)

B. oleraceae is used as vegetable in India and commonly known as "knoll khol" [48]. Aqueous extract of fresh stem (bulbs) of the plant has been shown to cause hypoglycemic effect in non-diabetic as well as in alloxan induced diabetic rats [48]. The mechanism of the observed effect is not known but a possible interference with glucose in the gut has been suggested [48]. *B. capitata* is another specie of the genus also consumed as vegetable [48] and reported to possess hypoglycemic activity [48, 49].

2.6 Bridelia ferruginea (Euphorbiaceae)

B. ferruginea is a medium sized tree common along the West Coast of Africa. In Eastern part of Nigeria the leaves are used to prepare a special type of soup locally known as "ora soup". The leaf extract of the plant have been reported to lower the fasting blood sugar levels in Type 2 diabetic patients even in the presence of ketosis [23]. Both the pure rutin and the flavonoid mixture from the extract of the leaves have been shown to reduce blood sugar of fasted rabbits [50]. We have also shown that at 25 mg/kg, the tablets prepared from the leaves lowered blood sugar levels in normal healthy rabbits by about 40% [51].

2.7 Clutytia richardiana (Euphorbiaceae)

C. richardiana grows in Saudi Arabia [52]. Pharmacological investigation revealed that the petroleum ether extract of the plant produced significant reductions in the blood glucose level in alloxanized rats [53]. Saudin is a novel diterpene isolated from the petroleum ether extract of *C. richardiana* and was found to produce hypoglycemic effect in fed but not fasted non-alloxanized and alloxanized rats [53].

It has been suggested that Saudin may exert its actions through other mechanism than insulin secretion since the hypoglycemic effect was associated with significant decrease in plasma insulin activity [53]. It has been speculated that Saudin may act through inhibition of insulin release [54].

2.8 Dioscorea dumetorum (Dioscoreaceae)

The extracts of the tubers of *D. dumetorum* have been employed to treat diabetes mellitus in African traditional medicine [55]. Investigations have shown that the crude extract of the plant produced remarkable hypoglycemic effect in fasted normal rats and rabbits as well as in alloxan-induced diabetic rabbits [24]. The hypoglycemic principle, dioscoretine, isolated from the tubers [56] has been shown to be as effective as tolbutamide in lowering blood sugar levels in both normal and alloxan-induced diabetic rabbits [57].

2.9 Eugenia uniflora (Myrtaceae)

E. uniflora is a plant widely distributed in South America, Southern Asia and Africa [58]. In Paraguay, *E. uniflora* is called "Nangapiry"and has been used for the treatment of obesity and diabetes [59,60]. Six fractions NP-1 to NP-6 obtained from solvent fractionation of ethanolic leaf extract of *E. uniflora* have demonstrated varied degrees of hypoglycemic activity [58]. The separated fractions were shown to be effective

in reducing post prandial hyperglycemia and hypertriglyceridemia [58]. These extracts were assumed to act through the inhibition of sugar and fat decomposition, and glucose absorption [58]. The leaf extracts may be useful for diabetes and obesity especially since the latter is a predisposing factor for diabetes.

2.10 Globuria alypum (Globulariaceae)

G. alypum is a herbaceous plant widely distributed in the Mediterranean areas [61]. It is sold in Morocco and traditionally used in diabetes management [62]. Leaf infusion of *G. alypum* exhibited hypoglycemic effect in normoglycemic and alloxanized rats after oral and intraperitoneal administration [62]. The effect produced was comparable to that of metformin and glibenclamide [62]. The mechanism of action was attributed to an enhancement of peripheral glucose metabolism though not excluding a possible increase in insulin release [62].

2.11 Mangifera indica. (Anacardiaceae)

M. indica is also known as "mango" in English and is popular as an antidiabetic in Brazil. An estimated 5% of diabetic patients were found to be using mango as a presumed hypoglycemic treatment [63]. In an earlier study, Rahaman and Zaman reported the hypoglycemic activity of *M. indica* [64]. A recent investigation has, however revealed that an infusion of the leaves of this plant did not exhibit hypoglycemic effect in normal and streptozotocin induced diabetes in rats and also in healthy volunteers in whom it was administered *ad libitum* [63].

2.12 Musa sapientum (Musaceae)

M. sapientum is also called "banana", "ney povan" and commonly grown in South India, and other parts of the world for its flowers, fruits, stem, roots and leaves [65]. Various parts of *M. sapientum* have been used for medicinal purposes including treatment of diabetes mellitus [65]. The juice of the flowers is claimed to have beneficial effects in reducing blood sugar level by local practitioners [65]. The unripe fruit is claimed to exhibit a variety of pharmacodynamic effects such as antidiabetic, astringent, antiscorbutic and antiulcerogenic activities [66,67].

The unripe fruit powder of *M. sapientum* has shown hypoglycemic effect in normal experimental rabbits in a dose dependent fashion. However, in alloxan-induced diabetic rabbits, no hypoglycemic effect was observed [68]. The hypoglycemic constituents of unripe fruits of *M. sapientum* may lack insulin-like activity, but may exert hypoglycemic effect in normal rabbits by triggering the release of insulin [68].

Further experimental evidence suggests that the chloroform flower extract of *M. sapientum* produced significant and consistent hypoglycemic effect in alloxan diabetic rats by a direct effect [65]. The extract reversed weight loss in alloxan diabetic rats and prevented increase in blood glucose levels without inducing hypoglycemic state in glucose fed rats [65].

The hypoglycemic effect in alloxanized rats suggests a potentiation of insulin release from pancreatic cells which is indicative of activity in Type 2 diabetes [65]. The significant and consistent hypoglycemic effect of the extract in diabetic rats after 30 days prolonged administration implies stimulation of peripheral glucose utilization in line with earlier findings [69,70]. Unripe banana diet is popular among diabetic patients in Nigeria.

2.13 Ocimum gratissimum (Lamiaceae)

O. gratissimum is a shrub traditionally used in the treatment of bacterial infections and diarrhea. It is popularly used as spice [71] in food and traditionally claimed to be effective in the native treatment of diabetes. Results of preliminary antidiabetic studies of the methanol leaf extract

of the plant indicated a greater than 50% reduction in blood sugar levels in both normal and alloxanized rats [72].

2.14 Parinari polyandra (Rosaceae)

P. polyandra is a plant commonly found in the Savannah rainforest and open grassland. It yields an excellent charcoal used by blacksmiths in Niger State Nigeria. The cold preparation of a hot water infusion of the stem bark is used in the treatment of diabetes mellitus. In experimental rats, the methanol stem bark extract of *P. polyandra* showed hypoglycemic activity [73].

The extract administered orally caused a slight fall in fasting plasma glucose level of normoglycemic rats and significantly lowered the plasma glucose level in streptozotocin diabetic rats [73]. The hypoglycemic effect was found to be greater than that of chlorpropamide [73].

2.15 Tecoma stans. (Bignoneaceae)

Since the pre-Colombian times in Mexico, decoctions of *T.stans* have been thoroughly used to treat diabetes mellitus [74]. Chronically administered aqueous extract of *T. stans* has been found to reduce glycemia and improve body weight in rats with streptozotocin-induced diabetes [75]. The extract did not exhibit any activity in acute test [75]. The mechanism of the observed effects is yet to be determined.

2.16 Teucruim species (Labiatae)

Species of this genus include *T. polium*, *T. chamaedrys*, *T. scordium* and *T. cubense*, which are widely used in folk medicine in many countries including Turkey [76-78]. The hypoglycemic effect of *T. cubense* has been demonstrated in experimental rabbits [79].

T. polium is used as hypoglycemic agent in folk medicine [76-78]. This, however, has not been substantiated experimentally since an orally administered decoction of *T. polium* did not exhibit hypoglycemic effect in rats [80]. Experimental evidence using other animal species is not yet available.

2.17 Tricosanthes diodica (Cucurbitaceae)

Ethanolic extract of the whole plant and aerial parts of *T. diodica* have been shown to be effective in lowering blood sugar in fasted animals [81]. They suppressed the acute rise in glucose loaded rats which became more pronounced with prolonged extract administration. However, *T. diodica* did not produce any significant blood sugar lowering effect in diabetic model induced by streptozotocin and in glucose tolerance test [81].

2.18 Verbesina persicifolia (Compositae)

V. persicefolia is a herb that grows wildly and abundantly in local fields and commonly known as “Huichim” [28].

In many countries of the Veracruz State of Mexico, the natives use a decoction made from fresh leaves as a popular folk remedy for the treatment of diabetes [28]. Experimental evidence suggests that the chloroform leaf extract of *V. persicifolia* produced significant hypoglycemic activity on alloxan-induced hyperglycemia in mice. The extract also showed a pronounced effect on the fasting blood glucose level and on the ability of the animal to tolerate external glucose load [28].

This is suggestive of the effectiveness of *V. persicifolia* in controlling the blood glucose level after a heavy carbohydrate diet. The mechanism of the observed effects is attributed to an enhanced secretion of insulin from the islets of Langerhans or an increased utilization of glucose by peripheral tissues [28,82].

2.19 Vernonia amygdalina (Compositae)

V. amygdalina (bitter leaf) is a common medium seized shrub abundant in the South eastern part of Nigeria. It contains abundant bitter principles

in every part of the plant and is widely used in Nigeria for both therapeutic and nutritional purposes [83] where it serves as ingredient of a delicacy called "bitter leaf soup".

The leaf decoction of the plant is traditionally employed as an antidiabetic remedy. Aqueous leaf extract of *V. amygdalina* caused prompt and marked reduction of blood glucose in normal, fasted and alloxanized rabbits [23] through a yet to be substantiated mechanism. The activity was attributed to the presence of bitter principle in the plant.

3. Overview

Diabetes mellitus is a life long chronic disease causing medical and economic problems to both the developed and resource poor countries. The cost of treatment, especially with insulin is high and varies greatly between countries.

This is a major problem particularly in developing countries where the cost of treatment must be paid by the patients. Can Phytotherapy be an alternative? Plant extracts have been shown to be a useful source for new compounds to be employed directly or as targets that could be manipulated to achieve improved glycemic control. Some hypoglycemic plants have been subjected to clinical tests for diabetic control.

Among these, *Gongronema latifolia* aqueous leaf extract, mist tea prepared from *Viscum album,* extract of mature fruits of *Carica papaya* and bark extract of *Chlorantia enantia* were shown to improve diabetic indices such as urine sugar, blood sugar level and total urine volume discharged [84].

The active constituents responsible for the hypoglycemic activity of some plants have been isolated and identified. These include: allyl-propyldisulphide, allicin and methylallin from the bulbs of *Allium cepa* (Liliaceae); 2-propenyl disulphide and 3,5-allylcysteine sulphoxide from the dried heads of *Allium sativum L.* (Liliaceae); phalloidin, phallicin and phallicidin from whole plant of *Amanita phalloides* (Agaricaseae); Kolaviron from the seeds of *Garcinia kola* (Gutiferae) and -sitoterol-D-glucoside from the stem bark of *Picus religiosa* (Moraceae) [84].

These plants have demonstrated hypoglycemic activity in several animal species. In this review, we have discussed some findings and results suggesting possible role for plant products in glycemic control. It is expected that the development of new and improved techniques of extraction, assay and identification of new hypoglycemic compounds from plants will improve the life of diabetic patients.

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