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Review

Review on diabetes, synthetic drugs and glycemic effects of medicinal plants

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There has been increased scientific interest in medicinal plants that have been reported to be used traditionally to treat diabetes in humans. This is due to increased efficacy of new plant-derived drugs, growing interests in natural products and the presence of serious side effects of conventional medicines. The development of drugs from plants by drug companies also encourages large pharmaceutical screening of herbs. Accordingly, large numbers of plant and plant products have been scientifically tested and reported to possess the ability to decrease blood glucose levels of normal and/or diabetic animals. Among these are *Coccinia indica, Tragia involucrate*, *Gymnema sylvestre*, *Pterocarpus marsupium*, *Trignonella foenum-graecum*, *Moringa oleifera, Eugenia jambolana, Tinospora cordifolia, Swertia chirayita, Momordica charantia, Ficus benghalensis, Vinca rosea, Premna integrifolia, Macuna prurita, Terminalia bellirica, Sesbinia aegytiaca, Azadirachta indica, Dendrocamalus hamittonni, Zingiber officinale, Aegle marmelos, Cinnamomum tamala, Trichosanthes cucumerina*, *Hyphaene thebaica, Leptadania hastata*, *Anisopus mannii* and *Opium sanctum*. Therefore, the aim of this review is to discuss diabetes, past and recent trend with respect to application of medicinal plants in the management of diabetes and provide readers and researchers with the basic concepts of understanding the condition/disorder of diabetes and the glycemic effects of medicinal plants.

Key words: Diabetes mellitus, hypoglycemia, hyperglycemia, medicinal plants.

INTRODUCTION

The endocrine pancreas consists of approximately 1 million islets of Langerhans interspersed throughout the pancreatic gland. Within the islets, at least four hormone-producing cells are present. Their hormone products include insulin, islet amyloid polypeptide (IAPP, or amylin), whose metabolic function remains undefined glucagon, the hyperglycemic factor that mobilizes glycogen stores; somatostatin, a universal inhibitor of secretory cells, and pancreatic peptide enzyme, a small protein that facilitates digestive processes by a mechanism not yet clarified. The pathology of the pancreas and other related factors such as intake of some drugs such as corticosteroids could lead to diabetes (WHO, 1999).

The basis of diabetes mellitus treatment and management includes patient education regarding the disease, physical exercise, dietary modulation, application of synthetic hypoglycemic agents such as sulfonylureas, biguanides, glucosidase inhibitors, and glinides, which are used as monotherapy or in combination to achieve better glycemic regulation and products from medicinal plants. Many of these oral antidiabetic agents have a number of serious adverse effects; the main disadvantage

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of current drugs such as (biguanide, sulfonylureas) is that they have to be given throughout the life and these produce serious side effects (Halim, 2003). Thus managing diabetes without any side effects is still a challenge, therefore the search for an alternative remedies such as medication from natural product is paramount (Saxena and Kishore, 2004; Maghrani et al., 2005).

Diabetes is a common and very prevalent metabolic disease condition in which there's an abnormal high level of blood sugar that culminates in diabetic complications affecting human and animals in both developed and developing countries (Bastaki, 2005). An estimate of 25% of the world population is affected by this disease that manifests in various forms (Ivorra et al., 1989; Maiti et al., 2004). A patient is considered to be diabetic when his/her blood sugar level is above 180 mg/dl (Albertini, 1997; Kalman et al., 2001; Ian and Soon, 2006). The effect of diabetes includes long term damage, dysfunction and failure of various organs. Diabetes may present with characteristic symptoms such as thirst, polyuria, blurring of vision and weight loss (Bastaki, 2005).

In most severe form of diabetes, ketoacidosis or non ketotic hyper-osmolar state may develop leading to stupor, coma and death. Long term effect leads to progressive complications of retinopathy, renal failure and autonomic nervous system dysfunction (De Vegt et al., 1998). Diabetes is a common widespread disorder occurring in many parts of the world which could be generated as a result of other predisposing factors such as obesity, ageing and antigen/antibody reaction (Bloom and Ireland, 1980). Diabetes as a condition affecting human and animal population is generally classified into two major forms, Diabetes mellitus principally in humans, and Diabetes insipidus in animals especially in the dogs (Acampora et al., 2002).

CLASSIFICATION OF DIABETES MELLITUS

Insulin is the principal hormone that regulates uptake of glucose into most cells from the blood (primarily muscle and fat cells, but not central nervous system cells), deficiency of insulin or the in sensitivity of its receptors play a central role in all forms of diabetes mellitus. Therefore, diabetes mellitus as a disease condition is classified into four types depending on their primary causes (Kenneth, 2006).

Type 1 diabetes mellitus (Insulin dependent diabetes mellitus, Childhood diabetes)

This condition may appear at any age, although commonly under 40 years and results due to inadequate production of insulin by the β-cells in the pancreas or abnormality of carbohydrate metabolism, which is linked to low blood insulin level. The hallmark of type 1 diabetes is selective β-cells destruction and severe or absolute insulin deficiency. The impaired insulin action affects fat metabolism, resulting in increased free fatty acid influx and triglyceride levels, and reciprocally low high-density lipoprotein (HDL) levels. Administration of insulin is essential in patients with type 1 diabetes. Insulin dependent diabetes mellitus is further subdivided into those caused by autoimmune and idiopathic factors. The autoimmune form is the most common form of type 1 diabetes. The autoimmune form is mainly triggered by environmental factors such as viruses, diet or chemical exposure in people genetically predisposed. It should be noted that there is no known preventive measure against type 1 diabetes. Diet and exercise cannot reverse type 1 diabetes. This type of diabetes can also affect children. The percentage incidence of this type of diabetes in human population ranges between 5 and 15% (Annette and Jeffrey, 2003; Chauhan et al., 2010).

Type 2 diabetes (Adult-onset diabetes, Maturity-onset diabetes)

Type 2 diabetes, non-insulin-dependent diabetes mellitus, in which the body does not produce enough insulin or improper utilization of this hormone, is the most common form of this condition, accounting for 90 to 95% of the cases. Type 2 diabetes is nearing epidemic proportions as a result of an increased number of elderly people and a greater prevalence of obesity and sedentary lifestyle in people in developed and developing countries (Li et al., 2004; Sy et al., 2005). According to World Health Organization projections, the diabetic population is likely to increase to 300 million or more by the year 2025 (Sy et al., 2005). It results due to a combination of defective insulin secretion and insulin resistance or reduced insulin insensitivity (defective responsiveness of tissue to insulin), which almost certainly involves the insulin receptors in cell membranes. Early hyperglycemia can be reversed by a variety of measures and medications that improves insulin sensitivity or reduce glucose production by the liver, but as the disease progresses the impairment of insulin secretion worsens and therapeutic replacement of insulin often becomes necessary. This type of diabetes is usually precipitated by obesity, excessive carbohydrate consumption when the pancreas is pathologic, lack of exercise and 20% of the case is linked to hereditary conditions (WHO, 1999; Rother, 2007). Individuals with type 2 diabetes may not require insulin to survive, but 30% or more will benefit from insulin therapy to control glucose levels in the blood. It is likely that 10 to 20% of individuals in whom type 2 diabetes was initially diagnosed actually have both type 1 and 2, or have a slowly progressing type 1, and ultimately will require full insulin replacement. Although persons with type 2 diabetes ordinarily may develop ketosis, ketoacidosis may occur as a result of stress, infection, or use of medication that enhances insulin resistance, e.g. corticosteroids. Dehydration in untreated and poorly

controlled individuals with type 2 diabetes can lead to a life-threatening condition called "non-ketotic hyperosmolar coma". In this condition, the blood glucose level may rise from 6 to 20 times the normal range, and an altered mental state develops or the person loses consciousness (WHO, 1999).

Type 3 diabetes mellitus

There are several other causes of diabetes mellitus that do not fit into type 1 or 2 and they include classification as a result of genetic defect in β-cells (autosomal or mitochondrial), genetically-related insulin resistance with or without lipodystrophy (abnormal body fat deposition), disease of the pancreas (chronic pancreatitis, cystic fibrosis), hormonal defects, and chemical or drug induced diabetes, which may occur in compounds such as sulphonylureas, metformins, thiazolidinediones (WHO, 1999; Kenneth, 2006).

Type 4 diabetes mellitus or gestational diabetes

This type of diabetes involves the combination of inadequate insulin secretion and tissue responsiveness, resembling type 2 diabetes in several respects. It develops during pregnancy and may improve or disappear after delivery. During pregnancy, the placenta and placental hormones create an insulin resistance that is most pronounced in the last trimester. Even though it may be transient, gestational diabetes may damage the health of the fetus or mother and about 20 to 50% of women with gestational diabetes develop type 2 diabetes later in life. Gestational diabetes mellitus (GDM) occurs in about 5.5 to 8.8% of all pregnancies (Kenneth, 2006). It is temporary and fully treatable, but if untreated, may cause problems with the pregnancy such as macrosomia (high birth weight), fetal malformation and congenital heart disease. Fetal and neonatal risks associated with GDM include congenital anomalies such as cardiac, central nervous system and skeletal malformations. Increased fetal insulin may inhibit fetal surfactant production and cause respiratory distress syndrome. Hyperbilirubinaemia may result from red blood cell destruction in this type of diabetes. In severe cases perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment (Kenneth, 2006).

DRUGS USED IN THE MANAGEMENT OF DIABETES MELLITUS

Insulin

This is a hormone produced by beta cells of the islets of Langerharns in the pancreas of animals, humans and synthetically. Insulin has an AB heterodimeric structure with one intrachain (A6 to A11) and two interchain disulfide bridges (A7 to B7 and A20 to B19). The A and B chains could be synthesized in the laboratory, but attempts at a biochemical synthesis of the mature insulin molecule yield very good result. The reason for this became apparent when it was discovered that insulin is synthesized as a preprohormone (molecular weight approximately 11,500), which is the prototype for peptides that are processed from larger precursor molecules. The hydrophobic 23-amino-acid pre, or leader, sequence directs the molecule into the cisternae of the endoplasmic reticulum and then is removed; this results in the 9000-MW proinsulin molecule formation, which provides the comformation necessary for the proper and efficient formation of disulfide bridges. The proinsulin molecule undergoes a series of site-specific peptides cleavages that results in the formation of equimolar amounts of mature insulin and C peptide.

CLASSIFICATION OF INSULINS

Insulins are divided into very rapid acting, rapid acting, intermediate acting, long acting and pre mixed insulins based on the number of hours their peak action is observed. Peak action occurs when the concentration of insulin is greatest in the blood, and has its greatest glucose lowering effect.

Very rapid acting insulins

These are insulin analog, the first of such is known as humalog (Insulin Lispro), in which a chemical change has been made to the insulin molecule. This gives the insulin a very desirable property of extreme rapid absorption. Peak action of Lispro insulin is about 30 min after injection, and insulin levels decrease rapidly after 1 to 2 h. This allows the insulin given before meal control the post-meal rise of glucose much better, and to reduce the chance of hypoglycemia, because insulin levels drop faster (Laakso et al., 1990).

Rapid-acting (Short-acting) insulins

These include Humulin and Novolin-Toronto (also known as regular) insulins. The rapid acting insulins start being absorbed in 30 to 60 min, and their peak action is within 2 to 3 h of injection in most individuals. Their duration of action is approximately 6 to 8 h, but there is a great degree of variation. Short acting insulins are often used before eating to control the large rise of blood glucose that often occurs after meal. Ideally short acting insulin is taken 30 to 45 min before the meal, as it takes up to 2 h to see its main effect (Brand-Miller and Colagari, 1994).

Intermediate-acting insulins

These insulin which include neutral protamine Hagedorn (NPH) and Lente, start being absorbed 3 to 4 h post administration and have their peak effect after 7 to 9 h. There is considerable variation as the duration of action may be as much as 12 to 16 h after injection (Neel, 1962).

Long-acting insulins

This mainly includes the Ultra Lente insulins. The peak action of this is seen within 10 to 12 h and very occasionally longer and its duration of action is between 16 and 18 h. It is not a popular insulin. It may be used in individuals in whom intermediate-acting insulin taken at bed time act too quickly, resulting in hypoglycemic reactions (Raven, 1988; Zimmet, 1995; Ziv et al., 1996).

Premixed insulins

When people have type 2 diabetes, their body either does not make enough insulin or does not use insulin as well as it should. Many people with type 2 diabetes need to take insulin shots. Premixed insulin combines two kinds of insulin. The first kind helps the body control blood sugar (blood glucose) all through the day. The second kind helps the body control blood sugar at meal times. There are different types of premixed insulin. The different types of premixed insulin work equally well to lower your A1c. The A1c is a blood test that shows your average blood sugar over the past 2 to 3 months. The chance of your blood sugar dropping too low is the same with the different types of premixed insulin (Garber et al., 2007).

ORAL ANTIDIABETIC AGENTS

Sulfonylureas

These were the first widely used oral hypoglycemic medications and are most widely used drugs for the treatment of type 2 diabetes. They are insulin secretagogues, triggering insulin release by direct action on the K_{ATP} channel of the pancreatic beta cells. These drugs are classified into first-generation and second generation agents. Sulfonylureas may also have extra-pancreatic effects, one of which is to increase tissue sensitivity to insulin, but the clinical importance of these effects is minimal. Hypoglycemia and weight gain are some the side effects of these agents. These agents are effective and inexpensive. The first-generation agents are Tolbutamide, Acetohexamide, Tolazamide, Chlorpropamide and the second-generation agents are Glibenclamide, Glipizide (Glucotrol), Glyburide (Diabeta), Glimepiride (Amaryl) and Gliclazide (Diamicron) (Eurich et al., 2007).

Biguanides

These reduce hepatic glucose output and increase uptake of glucose by the periphery, including skeletal muscle. Although, it must not be used in patients with impaired liver and kidney function. The main use for metformin is in the treatment of diabetes mellitus type 2, especially in overweight people. In addition to suppressing hepatic glucose production, metformin 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. Increased peripheral utilization of glucose may be due to improved insulin binding to insulin receptors (Rendell, 2000; Collier et al., 2006; Dell'Aglio et al., 2009).

Meglinitides (repaglinide, nateglinide)

Meglinitides help the pancreas to produce insulin and are called “short acting secretagogues. Their mechanism of action is through affecting potassium channel, by closing potassium channel of the pancreatic beta cells; they open the calcium channel, hence enhancing insulin exocystosis (Rendell, 2000).

Thiazolidinediones (glitazones)

This is a nuclear regulatory protein involved in transcription of genes regulating glucose and fat metabolism. Thiazolidinediones reduces insulin resistance by activating PPAR-γ in the gastrointestinal tract. The side effects of these agents include increased liver enzymes, weight gain, edema, mild anemia (Rendell, 2000).

Alpha-glucosidase inhibitors (Miglitol, Acarbose)

These are not technically hypoglycemic agents, because they do not have direct effect on insulin secretion or sensitivity. These agents slow down the digestion of starch in the small intestines, so that glucose from starchy meal enters the blood stream more slowly, and can be matched more effectively by an impaired insulin response or insensitivity. The site of action is in the fats and muscles. It is very effective in the treatment of type 2. α-Glucosidase inhibitors decreases postprandial plasma triglyceride levels diabetes, with major side effects such as diarrhea, abdominal pain, flatulence, and serum levels of transaminases increases at higher doses (Haffner, 2007).

Peptide analogues (**incretin**)

This is insulin secretagogues (Haffner, 2007).

DRUGS USED IN THE EXPERIMENTAL INDUCTION OF DIABETES

Streptozotocin

1-methyl-1-nitroso-3-[2, 4, 5-trihydroxy-6-(hydroxymethyl) oxan-3-yl-urea] is a naturally occurring chemical that is particularly toxic to insulin producing beta cells of the pancreas of mammals. It is used in medicine for treating certain cancers of islets of Langerharns and used in medical research to produce an animal model for type 1 diabetes (Brentjens, 2001). However, it carries a substantial risk of toxicity and rarely cures cancer, thus its use is generally limited to patients whose cancer cannot be removed by surgery. In these patients, streptozotocin can reduce the tumor size and reduce symptoms. The molecular formula of streptozotocin is $C_8H_{15}N_3O_7$ and molecular mass is 265.221 g/mol. The mechanism of action of streptozotocin is by causing damage to DNA molecule in the cells (Wang and Gleichmann, 1998).

Alloxan monohydrate

This drug is a cytotoxic compound which causes oxidative base damage to nuclear and mitochondrial DNA. It also inhibits pancreatic cancer by selectively destroying pancreatic islet cells. It also inhibits gall bladder cancer. The mechanisms by which Alloxan monohydrate brings about its diabetic state includes selective destruction of pancreatic insulin secreting beta cells, which make cells less active (Junod et al., 1969) and lead to poor glucose utilization by tissues (Marles and Farnsworth, 1995). The IUPAC name is 2,4,5,6 (1H, 3H)-pyrimidinetetrone. H_2O, with a chemical formula of $C_4H_2N_2O_4$, molecular weight of 142.0 g and comes in 5, 10 and 20 g sample. The drug is also used in medical research to produce an animal model for type1 diabetes (Pour, 1997).

Glucose over-dosage

This has been used experimentally in the laboratories to induce diabetes in experimental animals (Roman-Ramos et al., 1992; Neef et al., 1995).

TRENDS IN MEDICINAL PLANTS RESEARCH

There has been increased scientific interest in medicinal plants research that has been reported to be used traditionally to manage/treat diabetes in man. This is due to increase efficacy of new plants derived drugs, growing interests in natural products, and the presence of serious side effects of conventional medicines (Cheng et al., 2003). The development of drugs from plants by drug companies also encourages large pharmaceutical screening of herbs (Sanni, 2007). Medicinal plants and their bioactive constituents are used for the treatment of diabetes mellitus throughout the world. Although several medicinal plants have gained importance of diabetes mellitus, many remain to be scientifically investigated (Punitha et al., 2006). Medicinal plants play an important role in the management of diabetes mellitus especially in developing countries where resources are meager. Several medicinal plants have been used as dietary adjunct and in the treatment of numerous diseases without proper knowledge of their function. Although phytotherapy continue to be used in several countries, few plants have received scientific or medical scrutiny. Moreover, a large number of medicinal plants possess some degree of toxicity. For example, it was reported that about one third of medicinal plants used in the treatment of diabetes are considered to be toxic (Ivora et al., 1989).

Plant based drugs have been in use against various diseases since time immemorial. The primitive man used herbs as therapeutic agents and medicaments, which they were able to procure easily. In nature there are abundant plants used for the welfare of man and animals. The essential values of some of these plants have long been published, but a large number of them remain unexplored. So there is a necessity to explore their uses and to conduct phamacognostic and pharmacological studies to ascertain their therapeutic properties (Baquar, 1989).

The most popular analgesic aspirin was originally derived from species of *Salix* (Tripathi and Tripathi, 2003). *Phytolacca dodecandra*, *Tetrapleura tetraptera* and *Swartzia madagascariensis* has become of interest internationally for the control of schistosomiasis (Adewumi, 1981; Chitme et al., 2003). Gedunin and niombolide, two of the several limonoids in *Azardirachta indica* were pruned down as antimalarial constituents (Khalid and Deddeck, 1989). The root of *Cryptolepis sanguinolenta*, used for treating urinary infections in traditional medicine is strongly antimicrobial with Crytolepine identified as the active principle. The common chewing sticks from that used by Africans in various communities for traditional dental care have been reported to possess actions against oral microbial flora and to contain various minerals which can hinder plaque formation (Sofowora, 1993). The most outstanding of the chewing sticks *Garcinia kola* and *Zanthoxylum zanthoxyloides* (Lam) Waterm. (Rutaceae) which is also an antisickling and anticancer plant was found to contain the following alkaloids: berberine, fagaronine, chelerytrine, canthin-6-one and benzoic acid derivatives as the main active ingredients. *Ancistrocladus abbreviatus*

(Ancistrocladaceae), a Cameroon plant known for its strong anti-HIV activity in the laboratory of the National Cancer Institute in the U.S.A. The antiviral component has been pinned down to Michelamine B, which was being developed for people living with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS). Many plant drugs, even in the crude form are well-known in the international markets today, and African countries are among the top world producers. Examples are *Rauwolfia vomitoria* (Family: *Apocynaceae*), which is the major source of reserpine, a major tranquilizer and an antihypertensive; *Physostigma venemosum* Balf. (Family: Leguminosaceae) also known as the Calabar bean, produces physostigmine or eserine used in ophthalmology; *Syzigium aromaticum* (Linn.) (Family: Myrtaceae), is a dental remedy and also *Chrysanthemum cinerariifolium* (Family: Asteraceae), called pyrethrum flower, produces a natural pyrethrins, a class of insecticides. Others include *Cantharanthus roseus* (Linn.) G. Don (Family: Apocynaceae), also called the vinca or the Madagascar Rose periwinkle, used in the management of leukemia and Hodgkin's disease; *Sisalana perrine* (Family: Agavaceae), exported by Tanzania, is rich in hecogenin and is employed for the partial synthesis of steroidal drugs such as corticosteroids and oral contraceptives; and *Cinchona succirubra* Pav. (Family: Rubiaceae) which yields quinine, a key antimalarial drug (Wallis, 1967).

MEDICINAL PLANTS WITH POTENTIAL HYPOGLYCEMIC AND ANTIDIABETIC ACTIVITIES

Large number of plant and plant products have been scientifically tested and reported to possess the ability to decrease blood sugar levels of normal and/or diabetic animals.

1. Oral administration of 2, 3, and 4 g/kg of *Achyranthes aspera* produced a significant dose-related hypoglycemic effect in normoglycemic and alloxan-induced diabetic rabbits. In these animals, water and methanol extract also decreased blood sugar levels (Akhtar and Iqbal, 1991).
2. Single doses of unroasted seed of *Cajanus cajan* Millsp. (pigeon pea) caused a significant reduction in serum glucose levels 1 to 3 h after oral administration to healthy and alloxanized mice (Amalraj and Ignacimuthu, 1998).
3. Oral administration of bakuchiol, a compound isolated from the extract of *Otholobium pubescens* reduced glycemia in diabetic mice in a dose-dependent fashion. In a new model of type 2 diabetes (fat-fed, streptozotocin treated rats) an oral dose of 150 mg/kg of *O. pubescens* produced a strong reduction in blood glucose and triglycerides levels (Krenisky et al., 1999).
4. The antidiabetic activity of *Magnifera indica* L (mango) was seen when an extract of the leaves was given to rats 60 min before glucose was administered. The hypoglycemic effect of this plant may be due to the reduction in the intestinal absorption of glucose (Aderibigbe et al., 1998).
5. Ginseng polypeptide isolated from the root of *Panax ginseng* Mey (Asiatic ginseng) decreased the level of blood sugar and liver glycogen when injected to rats at doses of 50 to 200 mg/kg without affecting total blood lipid concentration. When mice were injected subcutaneously with the daily doses of 50 and 100 mg/kg for 7 successive days, Ginseng polypeptide was also found to decrease glucose and liver glycogen and stimulated the release of insulin (Kimura et al., 1999).
6. Saponins isolated from the leaves of *Acanthopanax senticosus* injected to mice (100 and 200 g/kg intraperitoneally) decreased experimental hyperglycemia induced by injection of adrenaline, glucose and alloxan, without affecting the levels of blood sugar in untreated mice (Sui et al., 1994).
7. Daily oral administration of *Eruka sativa* seed 2 weeks before or after the induction of diabetes by single injection of alloxan (100 mg/kg) ameliorated hyperglycemia and improved lipid profile in rats (El-Missiry and El-Gindy, 2000).
8. The aqueous fraction of a methanolic extract of *Discorea dumetorum* Linn. has an hypoglycemic effect in healthy and alloxan diabetic rabbits when administered intraperitoneally (20 g/kg). In contrast, the chloroform fraction raised blood glucose level in healthy rabbits (Iwu et al., 1990).
9. Oral administration of leaf infusion of *Salvia fruticosa* Mill. reduced the glycemic level in alloxan-induced diabetic rabbits but not in normoglycemic animals. The plant is known to act mainly by reducing intestinal absorption of glucose, without modifying plasma insulin levels (Perfumi et al., 1991).
10. S-allyl cysteine sulpoxide, a sulphur containing amino acid of *Allium sativum* (garlic) that is the precursor of allicin and garlic oil, has been found to show significant antidiabetic effect in alloxan diabetic rats. Administration of a dose of 200 mg/kg significantly decreased the concentration of serum lipids and blood glucose (Augusti and Sheela, 1996).
11. Oral administration of *Allium cepa* L. (Onion) S-methyl cysteine sulphoxide daily at the dose of 200 mg/kg body weight for a period of 45 days to alloxan diabetic rats controlled the blood glucose level and lipid in the serum (Babu and Srinivasan, 1997).
12. Oral administration of an aqueous extract of *Tinospora cordifolia* roots produced a significant decrease in glycemia and brain lipid in alloxan induced diabetic rats (Stanley et al., 2000).
13. Maximum hypoglycemic activity of *Olea europea L.* olive leaf administered at the dose rate of 16 g/kg has been observed. The mechanism of action of this plant may be due to 2 mechanisms, potentiation of glucose-

induced insulin release and increased peripheral uptake of glucose (Gonzalez et al., 1992).
14. The leaf extract of *Aegle marmelose L.* was found to be as effective as insulin in the restoration of blood glucose and body weight to normal level (Ponnachan et al., 1993).
15. An unsaturated triterpenes acid isolated from an ethanolic extract of *Bumelia sartorum* root and bark produced hypoglycemic effect in alloxan induced diabetic rats (Naik et al., 1991).
16. Oral administration of *Zygophyllum gaetulum* (0.7 g/kg) caused a significant reduction in glycemia in healthy and diabetic rats. It produced a significant increase in insulin level in healthy rats (Jaouhari et al., 2002).
17. Oral administration of the flavonoids content (8%) of the seed of *Cuminum nigrum* caused a significant blood glucose lowering at the dose range of 0.5 to 1.5 g/kg, both in normoglycemic and alloxan induced diabetic rabbits (Ahmad et al., 2000).
18. Oral administration of the aqueous fraction of an alcoholic extract of the leaves of *Vinca rosea* L, *C. roseus* led to marked lowering of glycemia in normal and streptozotocin-induced diabetic rats (Benjamin et al., 1994).
19. The hypoglycemic effect of neutral detergent fiber from *Cocos nucifera L.* (Coconut) was tested in rats fed 5, 15 and 30% glucose. Increase in fiber intake caused a significant lowering in glycemia and serum insulin (Sindurani and Rajamohan, 2000).
20. An ethanol extract of the leaves of *Gynura procumbens* Merr. at single doses of 50, 150 and 300 mg/kg given orally significantly reduced glycemia in streptozotocin-induced diabetic rats. The optimum hypoglycaemic dose was 150 mg/kg. In normoglycemic subjects, the extract did not show any hypoglycaemic effect when it was administered (Zhang and Tan, 2000).
21. *Psacalium peltatum* Cass. significantly decreased the area under glucose tolerance curve in healthy rabbits subjected weekly to oral glucose tolerance test as compared to control, there was significant decrease in blood glucose level in diabetic rabbits (Roman-Ramos et al., 1992).
22. The root decoction of *Psacalium decompositum* reduces the glycemia in normal mice after intraperitoneally administration and lowered the hyperglycemic peak by 17.1% in rabbits with temporal glycemia (Gupta, 1994; Alarcon-Aguilar et al., 1997; Kar et al., 2003).
23. The water extract obtained from the root of *P. decompositum* significantly lowered blood glucose in dose dependent manner in healthy mice after intraperitoneally administration (Alarcon-Aguilar et al., 1994).
24. Intraperitoneal administration of 300 mg/kg of chloroform extract from *Parmentiara edulis* DC (Bignoniaceae) to diabetic mice decreased the blood glucose level by 43.75%. This extract administered to normal mice reduced glycaemia by 29.61% (Perez-guitierre et al., 1998).
25. A stem bark decoction from *Spathodea campanulata* caused a decrease in plasma levels of glucose in mice (Niyonzima et al., 1999).
26. In normoglycemic rats, a water extract of *Spergularia purpurea* produced a significant lowering of glycemia 4 h after single oral administration, and 1 week after repeated oral administration (Jouad et al., 2000).
27. Oral administration of *Ipomea batata* L (White-skinned sweet potato) produced a reduction in hyperinsulinaemia in zucker fatty rats by 23, 26, 60, and 50% for 3, 4, 6, and 8 weeks after treatment, respectively (Kusano and Abe, 2000).
28. The boiled extract of *Ipomea aquatica* produced significant decrease in glycemia after glucose loading in healthy Wister rats with both single (33%) and multiple (25%) doses. The optimum dose was 3.4 g/kg, while the optimum activity was observed 2 h after administration of the extract (Malalavidhane et al., 2000).
29. Male Swiss mice were orally loaded with glucose after oral administration of the extract of *Adianthum capillus veneris* and were shown to have improved glucose tolerance (Neef et al., 1995).
30. The oral administration of the aqueous extract of mesocarps of the fruits of *Balanities aegyptiaca* exhibited prominent antidiabetic activity in streptozotocin-induced diabetic mice. Saponins were thought to have caused the antidiabetic activity (Kamel et al., 1991).
31. The hot water extract of *Camellia sinensis* L. (Black tea) significantly reduced the blood glucose level of streptozotocin-induced diabetic rats; this extract was found to posses' preventive and curative effect on experimentally produced diabetes in rats (Gomes et al., 1995).
32. The oral administration of aqueous seed extract of *Moringa oleifera* experimentally produced significant decrease in blood glucose level in wistar albino rats, 6 to 18 h post administration (Auwal et al., 2010).
33. The oral administration of aqueous extract of *Hyphaene thebaica* (doumpalm) mesocarp experimentally produced significant decrease in blood glucose level in wistar albino rats, 12 to 18 h post administration (Auwal et al., 2012).
The oral administration of aqueous and fractionated portions of *Acacia nilotica* pods experimentally produced significant decrease in blood glucose level in wistar albino rats, 6 to 18 h post administration (Auwal et al., 2013).
34. Oral administration of aqueous root extract of *Leptadania hastata* at dosage of 600 to 800 mg/kg body weight have significantly ($p < 0.05$) decreased blood glucose level in normal albino rats (Sanda et al., 2013).

PHYTOCHEMICALS IN PLANTS EXHIBITING HYPOGLYCEMIC AND ANTIDIABETIC ACTIVITY

Medicinal plants exhibits hypoglycemic and antidiabetic activity as a result of the presence of certain very

important active principles and minerals in these plants that include terpenoids, alkaloids, phenolics, flavonoids, saponins, carbohydrates, cardiac glycosides, copper, zinc and manganese (Schroeder, 1974; Chakravarti et al., 1980; Kamel et al., 1991; Sui et al., 1994; Ahmad et al., 2000; Anila et al., 2002; Mankil et al., 2006; Sanni, 2007).

MECHANISM OF ACTION OF PLANTS WITH HYPOGLYCEMIC AND ANTIDIABETIC ACTIVITY

Medicinal plants have various mechanisms of action through which their effects are exhibited that include promoting regeneration of β cells of islets of Langerhans in the pancreas as exhibited by *Pterocarpus marsupium*, enhancement of insulin release and activity on the cells as exhibited by *O. europea* L. olive leaf, decrease peripheral glucose uptake at the duodenal cellular level and other aspects of small intestine exhibited by *M. indica* and *O. europea* L. olive leaf extracts and by restricting the rise of blood glucose levels caused by pituitary hormones responsible for inhibiting peripheral utilization of glucose as well as glycogenolysis exhibited by *Gymnema sylvestre*, and the presence of high level of fiber in plants which interferes with carbohydrate absorption (Nelson et al., 1991; Gonzalez et al., 1992; Yusuf et al., 1994; Pour, 1997; Ahmad et al., 2000; Hongxiang et al., 2009).

CONCLUSION

Conclusively, occurrence of phytochemicals such as terpenoids, alkaloids, phenolics, flavonoids, saponins, carbohydrates, and cardiac glycosides exhibiting glycaemic potential in combination in medicinal plant products yield good results in the management of various forms of hyperglycaemia as compared to synthetic drugs that usually contain single active principle, that on continuous administration could predispose various forms of idiosyncrasies in diabetic patients. Important minerals such as copper, zinc and manganese in natural plant products are also seen to potentiate hypoglycaemic activity of medicinal plants.

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