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Medical Plant and Human Health

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1. Introduction

1.1 Primary healthcare and traditional medicine

Primary Health Care (PHC) is the key to the development of a national health policy based on practical, scientifically sound and socially acceptable methods and technology made universally acceptable to individuals and families in the community and through their full participation and at a cost that the community and the country can afford, in order to maintain, at every stage of their development, in the spirit of self-reliance and self determination. It is the first level of contact for the individual, family and the community within the national health care system, bringing health care as close as possible to where people live and work and thus constitutes the first element of a continuing health care process (WHO, 1978a). A health system, based on primary health care was adopted as the means of achieving the goal of health for all. Most developing countries of the world, for which the scheme was designed, have failed to seriously implement it up till this moment.

Traditional Medicine is defined by the World Health Organization (WHO, 1978a) as the sum total of knowledge or practices whether explicable or inexplicable, used in diagnosing, preventing or eliminating a physical, mental or social disease which may rely exclusively on past experience or observations handed down from generation to generation, verbally or in writing. It also comprises therapeutic practices that have been in existence often for hundreds of years before the development of modern scientific medicine and are still in use today without any documented evidence of adverse effects. The explicable form of Traditional Medicine can be described as the simplified, scientific and the direct application of plant, animal or mineral materials for healing purposes and which can be investigated, rationalized and explained scientifically.

1.2 Herbal medicine

The use of *Salix alba*, the willow plant (containing the salicylates) for fever and pains which led to the discovery of aspirin, would belong to this form of Traditional Medicine. Herbal medicines, which squarely belong to this form, are regarded by the World Health Organization, as finished and labeled medicinal products that contain, as active ingredients, aerial or underground parts of identified and proven plant materials, or combination thereof, whether in crude form or as plant preparations. They also include plant juices, gums, fatty oils, essential oils etc (WHO, 1978a). There are several other official modern drugs today, which were originally developed like aspirin through traditional medicine e.g.

morphine, digoxin, quinine, ergometrine, reserpine, atropine, etc and all of which are currently being used by orthodox medicine in modern hospitals all over the world.
The inexplicable form of Traditional Medicine on the other hand, is the spiritual, supernatural, magical, occultic, mystical, or metaphysical form that cannot be easily investigated, rationalized or explained scientifically e.g. the use of incantations for healing purposes or oracular consultation in diagnosis and treatment of diseases. The explanation is beyond the ordinary scientific human intelligence or intellectual comprehension. Plants are reputed in the indigenous systems of medicine for the treatment of various diseases (Arise *et al*., 2009). Phyto-chemicals isolated from plant sources are used for the prevention and treatment of several medical problems including diabetes mellitus (Waltner- Law *et al*., 2002). There are more than 800 plant species showing a hypoglycemic activity. The World Health Organization (1980) has also recommended the evaluation of the effectiveness of plants in conditions where safe modern drugs are lacked.

2. Major groups of antimicrobial compounds from plants

Plants have an almost limitless ability to synthesize aromatic substances, most of which are phenols or their oxygen-substituted derivatives (Geissman 1963). Most are secondary metaboltes, of which at least 12,000 have been isolated, a number estimated to be less than 10% of the total (Schultes 178). In many cases, these substances serve as plant defense mechanisms against predation by microorganisms, insects, and herbivores. Some, such as terpenoids, give plants their odors; others (quinones and tannins) are responsible for plant pigment. Many compounds are responsible for plant flavor (e.g., the terpenoid capsaicin from chili peppers), and some of the same herbs and spices used by humans to season food yield useful medicinal compounds.
Simple phenols and phenolic acids, The mechanisms thought to be responsible for phenolic toxicity to microorganisms include enzyme inhibition by the oxidized compounds, possibly through reaction with sulfhydryl groups or through more nonspecific interactions with the proteins (Mason and Wasserman 1987).Phenolic compounds possessing a C_3 side chain at a lower level of oxidation and containing no oxygen are classified as essential oils and often cited as antimicrobial as well. Eugenol is a well-characterized representative found in clove oil. Eugenol is considered bacteriostatic against both fungi (Duke 1985) and bacteria (Thomson 1978). Quinones are aromatic rings with two ketone substitutions. They are ubiquitous in nature and are characteristically highly reactive. Probable targets in the microbial cell are surface-exposed adhesins, cell wall polypeptides, and membrane-bound enzymes. Quinones may also render substrates unavailable to the microorganism. As with all plant-derived antimicrobials, the possible toxic effects of quinones must be thoroughly examined.Kazmi et al.
Flavones, flavonoids, and flavonols activity is probably due to their ability to complex with extracellular and soluble proteins and to complex with bacterial cell walls, as described above for quinones. More lipophilic flavonoids may also disrupt microbial membranes (Tsuchiya 1996). Tannins are found in almost every plant part: bark, wood, leaves, fruits, and roots (Scalbert 1991). This group of compounds has received a great deal of attention in recent years, since it was suggested that the consumption of tannin-containing beverages, especially green teas and red wines, can cure or prevent a variety of ills (Serafini et al 1994) their mode of antimicrobial action, may be related to their ability to inactivate microbial adhesins, enzymes, cell envelope transport proteins, etc. They also complex with

polysaccharide (Ya et al 1988). The antimicrobial significance of this particular activity has not been explored. There is also evidence for direct inactivation of microorganisms: low tannin concentrations modify the morphology of germ tubes of *Crinipellis perniciosa* (Brownlee et al 1990). Tannins in plants inhibit insect growth (Schultz 1988) and disrupt digestive events in ruminal animals (Butler 1988).

Terpenoids and Essential Oils are secondary metabolites that are highly enriched in compounds based on an isoprene structure. They are called terpenes, their general chemical structure is $C_{10}H_{16}$, and they occur as diterpenes, triterpenes, and tetraterpenes (C_{20}, C_{30}, and C_{40}), as well as hemiterpenes (C_5) and sesquiterpenes (C_{15}). When the compounds contain additional elements, usually oxygen, they are termed terpenoids. The mechanism of action of terpenes is not fully understood but is speculated to involve membrane disruption by the lipophilic compounds. Accordingly, Mendoza et al. (Mendoza et al 1997) found that increasing the hydrophilicity of kaurene diterpenoids by addition of a methyl group drastically reduced their antimicrobial activity.

Alkaloids are Heterocyclic nitrogen compounds. Alkaloids have been found to have microbiocidal effects (including against *Giardia* and *Entamoeba* species Ghosha et al 1996, the major antidiarrheal effect is probably due to their effects on transit time in the small intestine. Berberine is an important representative of the alkaloid group. It is potentially effective against trypanosomes (Freiburghaus et al 1996) and plasmodia Omulokoli et al 1997). The mechanism of action of highly aromatic planar quaternary alkaloids such as berberine and harmane (Hopp 1976) is attributed to their ability to intercalate with DNA (Phillipson and O'Neill 1987). The mechanism of lectins and polypeptides may be back to the formation of ion channels in the microbial membrane (Terras et al. 1993) or competitive inhibition of adhesion of microbial proteins to host polysaccharide receptors (Sharon and Ofek 1986). Recent interest has been focused mostly on studying anti-HIV peptides and lectins, but the inhibition of bacteria and fungi by these macromolecules, such as that from the herbaceous *Amaranthus*, has long been known (De Bolle et al 1996).

2.1 Ethnobotanical study

Out of around 1076 species recorded so far from Semifinal Biosphere Reserve, more than 200 species are attributed with medicinal uses (Rout, 2004). This system of using herbs and different biological active ingredients in treating various diseases had become a part of their culture till recent years. Entrance of market economy gave rise to exploitation of natural resources and thereby depleting our resources base. The most affected part in this process was medicinal plants, which is most sensitive and delicate in the environment of forest. These medicinal plants gain further importance in the region where modern medical health facilities are either not available or not easily accessible. Although our ancient sages through hit and trial method developed herbal medicines, the reported uses of plant species do not certify efficacy.

The present preliminary report on the uses of some plant species need to pharmacologically screened, chemically analyzed and tested for bioactive activities. Pharmacological screening of plant extracts provides insight to both their therapeutic and toxic properties and helps in eliminating the medicinal plants or practices that may be harmful. The plant parts used for medical preparation were bark, flowers, rhizomes, roots, leaves, seeds, gum and whole plants. In some cases the whole plant including roots was utilized. The use of plant derived products containing high of dietary fiber and complex polysaccharide for the management of diabetes have been proposed (Jenkins et al., 1976). Natural products especially of plant

origin have been found to be potential sources of novel molecules for the treatment of diabetes (Farnsworth, 1994; Marles and Farnsworth, 1995).
Considering the rate at which the vegetation is getting depleted in this part of the world, therefore it is needed to document the precious knowledge of these plants and to search for more plants with antidiabetic potential. The search for anti-diabetic agents has been focused on plants because of their ready availability, effectiveness, affordability and probably due to low side effects (Marles and Farnsworth, 1995). Ethnobotanical study has been the method often used to search for locally important plant species with low side effects especially for the discovery of crude drugs (Farnsworth, 1994). The present study therefore is a documentation of plants and plant parts used for the management of diabetes mellitus by traditional healers of the area (Table 1).

Diagnosis methods	**Respondent (%)**
Signs and symptoms	
Loss of body weight	100
Body weakness	100
Excessive urination	100
Presence of sugar in urine	100
Excessive thirsty	53
Duration of treatment	
Short duration	40
Long duration	60
Efficacy of plant treatment on patients	
Disappearance of sugar in urine 100	100
Reduction in body weakness 100	100
Normal body weight 100	100
Reduction in frequency of urination	100
Traditional healers claim of no adverse effect after treatment	
Yes	100
No	0
Traditional healers claim of total cure after treatment	
Yes	80
No	20

Table 1. Diagnosis methods of diabetes mellitus by the herbalists using herbal preparation

2.2 Diabetes mellitus

2.2.1 What is Diabetes?

The word "diabetes" (a Greek word that means "to pass through") was first used by Aretaeous of Capadocia in the 2nd century AD to describe a condition that is characterized by excess of sugar in blood and urine, hunger and thirst (MacFrlance et al.,1997) and the adjective "mellitus" (a latin-greek word that means "honey") was introduced by the English physician John Rollo so as to distinguish the conditions from other polyuric diseases, in which glycosuria does not occur (Rollo 1797). People suffering from diabetes are not able to produce or properly use insulin in the body and therefore chronic hyperglycemia occurs. In addition, the diabetic individual is prone to late onset complications (Fujisawa et al., 2004), such as retinopathy, neuropathy and vascular diseases, that are largely responsible for the morbidity and mortality observed in diabetic patients.

Diabetes mellitus is a chronic metabolic disorder characterized by widespread complications. It is the world's largest endocrine disease associated with increased morbidity and mortality rates (Ghosh and Surawanshi, 2001). The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs (Lyra *et al*., 2006). Liver involvement is one of the leading causes of death in diabetes mellitus. The mortality rate from the hepatic affection is greater than that from the cardiovascular complications. The spectrum of liver implication in diabetes ranges from non-alcoholic fatty liver disease to cirrhosis and eventually hepato-cellular carcinoma (Keith *et al*., 2004). Liver, an insulin-dependent organ, plays a pivotal role in glucose and lipid homeostasis. It participates in the uptake, oxidation and metabolic conversion of free fatty acids and in the synthesis of cholesterol, phospholipids and triglycerides.

Several mechanisms are implicated in the pathogenesis of the functional and morphological alterations of the liver of diabetic patients (Brixova, 1981; Moller, 2001). There are two main types of diabetes, namely type I and type II (World Health Organization. Definition, Diagnosis and Classification of Diabetes mellitus and its omplications. Part 1: Diagnosis and Classification of Diabetes Mellitus (Department of Non communicable Disease Surveillance, Geneva, 1999)). Type I Diabetes, that is called insulin-dependent diabetes mellitus (IDDM) or juvenile onset diabetes develops when the body's immune system destroys pancreatic β-ells, the only cells in the body that produce the hormone insulin that regulates blood glucose. This type of diabetes usually strikes children and adults and the need for insulin administration is determinant for survival. Type I diabetes accounts for 5% to 10% of all diagnosed cases of diabetes and the risk factors may be autoimmune, genetic, or environmental.

On the other hand, type II diabetes, also called non–insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, accounts for about 90% to 95% of all diagnosed cases of diabetes. It usually begins as insulin resistance, a disorder in which the cells do not use insulin properly and as the need for insulin rises; the pancreas gradually loses its ability to produce it. This type of diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity. It must be noted thought that in the last decay type II diabetes in children and adolescents is being diagnosed more frequently (Fagot-Gampagna & Narayan 2001). In the case of the IDDM, insulin is of crucial importance for the survival of the patients. On the other hand, in the case of NIDDM the treatment includes medicines, diets and physical training.

2.2.2 Ant diabetic medicines: Important medicinal plants used in diabetes treatment; important active

2.2.2.1 Compounds involved in diabetes mellitus treatment

Many kinds of antidiabetic medicines have been developed for the patients and most of them are chemical or biochemical agents aiming at controlling or/and lowering blood glucose to a normal level. Despite the impressive advances in health sciences and medical care, there are many patients who are using alternative therapies alone or complementary to the prescribed medication. Traditional plant remedies or herbal formulations exist from ancient times and are still widely used, despite all the controversy concerning their efficacy and safety (Huxtable 1990; Fugh-Berman 2000), to treat hypoglycemic and hyperglycemic conditions all over the world.

It must be noted that many ethno-botanical surveys on medicinal plants used by the local population have been performed in different parts of the world and there is a considerable number of plants described as antidiabetic. In addition a variety of compounds have been isolated (alkaloids, glycosides, terpenes, flavonoids, etc) but further studies need to be done so as these 'leads' to develop into clinically useful medicines. To date, met form in (a biguanide) is the only drug approved for treatment of type II diabetes mellitus. It is a derivative of an active natural product, galegine, isolated from the plant Galega officinalis L. (Witters 2001). The followinf table illustrate some of these plant involved in diabetes mellitus treatment

Scientific name	Family	Active constituent	Part Used	Folk Medical Uses
Abelmoschus moschatus	**Malvaceae**	myricetin	aerial part	hypoglycemic action decrease the plasma glucose concentrations myricetin has an ability to enhance glucose utilization to lower plasma glucose in diabetic rats with deficient insulin levels.
Azadirachta indica	**Meliaceae**		dried powder of root and leaves	caused significant lowering of blood sugar and reduction in serum lipids
Cornus macrophylla	**Cornaceae**			prevent and treat diabetic complications
Achyranthes aspera L.	**Amaranthaceae**		powdered whole plant	hypoglycemic effect
Achyrocline satureioides	**Asteraceae**	achyrofuran	powdered whole plant	lowered blood glucose levels
Acosmium panamense	**Fabaceae**		water and butanolic extracts	lowered the plasma glucose levels
Aegle marmelose	**Rutaceae**		leaf extract	similar hypoglycemic activity to that of insulin treatment Treatment with the leaf extract showed improved functional state of pancreatic β cells. The results indicate the potential hypoglycemic effect of the leaf extract, possibly involved in processes for the regeneration of damaged pancreas.

Table 2. Important medicinal Plants used in Diabetes treatment.

Scientific name	Family	Active constituent	Part Used	Folk Medical Uses
Allium sativum L	**(Liliaceae**	allicine		decreased the concentration of serum lipids, blood glucose and activities of serum enzymes like alkaline phosphatase, acid phosphatase and lactate dehydrogenase and liver G6Pase
Allium cepa L.	**(Liliaceae**	S-methyl cysteine sulfoxide		lowered the levels of malondialdehyde, hydroperoxide and conjugated dienes in tissues exhibiting antioxidant effect
		(SMCS)		on lipid peroxidation in experimental diabetes The hypoglycemic and hypolipidaemic actions of Allium cepa were associated with antioxidant activity, since onion decreased SOD activities while no increased lipid hydroperoxide and lipoperoxide concentrations were observed in diabetic rats treated with Allium cepa
Aloe vera	**(Liliaceae**		leaf pulp and gel extracts	contain a hypoglycemic agent which lowers the blood glucose levels showed hypoglycemic activity on type I and II diabetic maintained the glucose homeostasis by controlling the carbohydrate metabolizing enzymes (Rajasekaran et al., 2004).
Aloe barbadensis	**Liliaceae**		leaves	the bitter principle may be mediated through stimulating synthesis and/or release of insulin from the β cells of Langerhans
Andrographis paniculata	**Acanthaceae**	andrographolide	crude ethanolic extract	antidiabetic effect may be attributed, at least in part, to increased glucose metabolism andrographolide can increase the glucose utilization to lower plasma glucose in diabetic rats lacking insulin.

Table 2. Important medicinal Plants used in Diabetes treatment. (continuation)

Scientific name	Family	Active constituent	Part Used	Folk Medical Uses
Angylocalyx pynaertii	**Leguminosae**	sugar-mimic alkaloids	pod extract	specific inhibitors of alpha-L fucosidase with no significant inhibitory activity towards other glycosidases
Areca catechu		arecolin		Arecoline have hypoglycemic activity in animal model of diabetes upon s.c. administration
Averrhoa bilimbi L.	**Oxalidaceae**		ethanolic extract	ethanolic extract has hypoglycemic, hypotriglyceridemic, anti-lipid peroxidative and anti-atherogenic properties in STZ-diabetic rats.
Bauhinia forficata L.	**Leguminosae**	kaempfer itr in	n-butanol extract	blood glucose-lowering effect in normal and diabetic rats
Beta vulgaris L. var. cicla	**Chenopodiaceae**	Betavulgaroside I, II, III and IV	roots	hypoglycemic effects that was demonstrated by a per os glucose tolerance test in rats after their per os administration
Bidens pilosa	**Asteraceae**	3-beta-D-glucopyranosyloxy-1-hydroxy-6(E)-tetradecene-8,10,12-triyne	Butanol extract of whole plant	inhibited the differentiation of naive helper T cells (Th0) into Th1 cells but enhanced their transition into type II helper T (Th2) cells using an in vitro T cell differentiation assay
Bryonia alba L.	**Curcubiaceae**	derivatives of trihydroxyoctadecadienoic acid	roots	Restore the disordered lipid metabolism of alloxan-diabetic rats
Bumelia sartorum	**Sapotaceae**	bassic acid	ethanol extract of root bark	altered glucose tolerance in alloxan-induced diabetic rats, enhanced glucose uptake in skeletal muscle and significantly inhibited glycogenolysis in the liver.
Caesalpinia ferrea Mart	**Leguminosae**	ellagic acid and 2′-(2,3,6-trihydroxy-4-carboxyphenyl) ellagic aci		might contribute to the relief of the long-term diabetic complications
Camellia sinensis	**Theaceae**	epigallocatechin-3-O-gallate		may be beneficial in the prevention of diabetes mellitus
Cassia tora	**Fabaceae**	a-tocopherol, ascorbic acid and maltodextrin	soluble fiber extracted	improve serum lipid levels in type II diabetic subjects without serious adverse effects

Table 2. Important medicinal Plants used in Diabetes treatment.(continuation)

Scientific name	Family	Active constituent	Part Used	Folk Medical Uses
Cecropia obtusifolia Bertol	**Cecropiaceae**	isoorientin and 3-caffeoylquinic acid	water and butanolic extracts prepared from leaves	beneficial effects on carbohydrate and lipid metabolisms when it was administered as an adjunct on patients with type II diabetes with poor response to conventional medical treatment.
Cleome droserifolia (Capparidaceae)				possessed a postprandial hypoglycemic effect but also suppressed the hepatic glucose release in the fasting state in a comparable way to this of insulin. The plant also possessed hypo-cholesterolemic effect, most pronounced on the LDL cholesterol.
Cnidium officinale Makino	**Apiaceae**			inhibited the high glucoseinduced proliferation of GMCs partially through TGF-beta1 production
Coccinia indica	**Cucurbitaceae**		ethanolic extract of Coccinia indica leaves	normalized blood glucose and caused marked improvement of altered carbohydrate metabolizing enzymes during diabetes.
Commelina communis	**Commeliaceae**	pyrrolidine alkaloid, 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine and four piperidine alkaloids, 1-deoxymannojirimycin, 1-deoxynojirimycin, alpha-homonojirimycin and 7-O-beta-D-glucopyranosyl alpha-homonojirimycin	methanolic extract	inhibitoryactivity against alpha-glucosidase

Table 2. Important medicinal Plants used in Diabetes treatment. (continuation)

Scientific name	Family	Active constituent	Part Used	Folk Medical Uses
Croton cajucara	**Euphorbiaceae**	trans-hydrocortin		The mentioned compound also effectively lowered the blood sugar levels in glucose fed normal rats.
Cryptolepis sanguinolenta	**Asclepiadaceae**	cryptolepine		antihyperglycemic effect of cryptolepine leaded to a significant decline in plasma insulin concentration, associated with evidence of an enhancement in insulin mediated glucose disposal. Finally, cryptolepine increased glucose uptake by 3T3-L1 cells.
Dioscorea dumetorum	**Dioscoreaceae**	dioscoretine	methanol extrac	normal and alloxan diabetic rabbits produced significant hypoglycemic effects and the hypoglycemic effects were compared to those of to butamide (Iwu et al., 1998)
Galega officinalis L.	**Leguminosae**	Metformin		Treat symptoms now ascribed to type II diabetes
Gentiana olivieri Griseb	**Gentianaceae**	isoorientin		Isoorientin exhibited significant hypoglycemic and antihyperlipidemic effects
Gymnema sylvestre	**Asclepiadaceae**	gymnemic acid I	Water soluble extracts the leaves	Gymnemic acids II and III showed potent inhibitory activity on glucose uptake.
Hintonia latiflora	**Rubiaceae**	coutaraegenin		coutareagenin, one of the active substances contained in the Hintonia latiflora bark, produces a reduction of the diabetic elevated blood sugar levels
Hydnocarpus wightiana	**Arcariaceae**	Hydnocarpin, Luteolin, And isohydnocarpin	acetone extract of the seed hulls	the presence of antioxidant molecules along with their enzyme inhibitory activities in the acetone extract of Hydnocarpus wightiana seed hulls may be responsible for the antidiabetic Properties

Table 2. Important medicinal Plants used in Diabetes treatment. (continuation)

Scientific name	Family	Active constituent	Part Used	Folk Medical Uses
Lagerstroemia speciosa L.	**Lythraceae**	Lagerstroemin and flosin B	hot-water extract from banaba leaves	effects on controlling of the level of plasma glucose in type II diabetes mellitus.
Larrea tridentata	**Zygophyllaceae**	masopropol		lower plasma glucose concentration in two mice models of type II diabetes after per os administration (Luo et al., 1998)
Myrcia multiflora	**Myrtaceae**	myrciacitrin I	ethyl acetate-soluble portion,	show inhibitory activities on ALR2 and alpha-glucosidase as well as on the increase of serum glucose level in sucrose-loaded rats and in alloxan-induced diabetic mice (Yoshikawa et al., 1998).
Paeonia lactiflora Pall.	**Panunculaceae**	paeoniflorin		the mentioned glucoside reduced the elevation of blood sugar in glucose challenged rats. Increase of glucose utilization by paeoniflorin can thus be considered (Hsu et al., 1997).
Pandanus odorus Ridl.	**Pantadaceae**	4-hydroxybenzoic acid		4-hydroxybenzoic acid caused a decrease in plasma glucose levels dose-dependently. The compound did not affect serum insulin level and liver glycogen content in the diabetic model, but increased glucose consumption in normal and diabetic rat diaphragms.
Phyllanthus sellowianus	**Euphorbiaceae**	isoqu ercitrin and rutin		hypoglycemic and diuretic agent reduction in blood glucose levels
Pueraria thunbergiana	**Leguminosae**	kaikasaponin III		kaikasaponin III (as a mixture of isomers), may exhibit its hypoglycemic and hypolipidemic effects by up-regulating or down-regulating antioxidant mechanisms via the changes in Phase I and II enzyme activities .
Stevia rebaudiana Bertoni	**Compositae**	stevioside		Stevioside was able to regulate blood glucose levels by enhancing not only insulin secretion, but also insulin utilization in insulin-deficient rats; the latter was due to decreased PEPCK gene expression in rat liver by stevioside's action of slowing down Gluconeogenesis (Chen et al., 2005).

Table 2. Important medicinal Plants used in Diabetes treatment. (continuation)

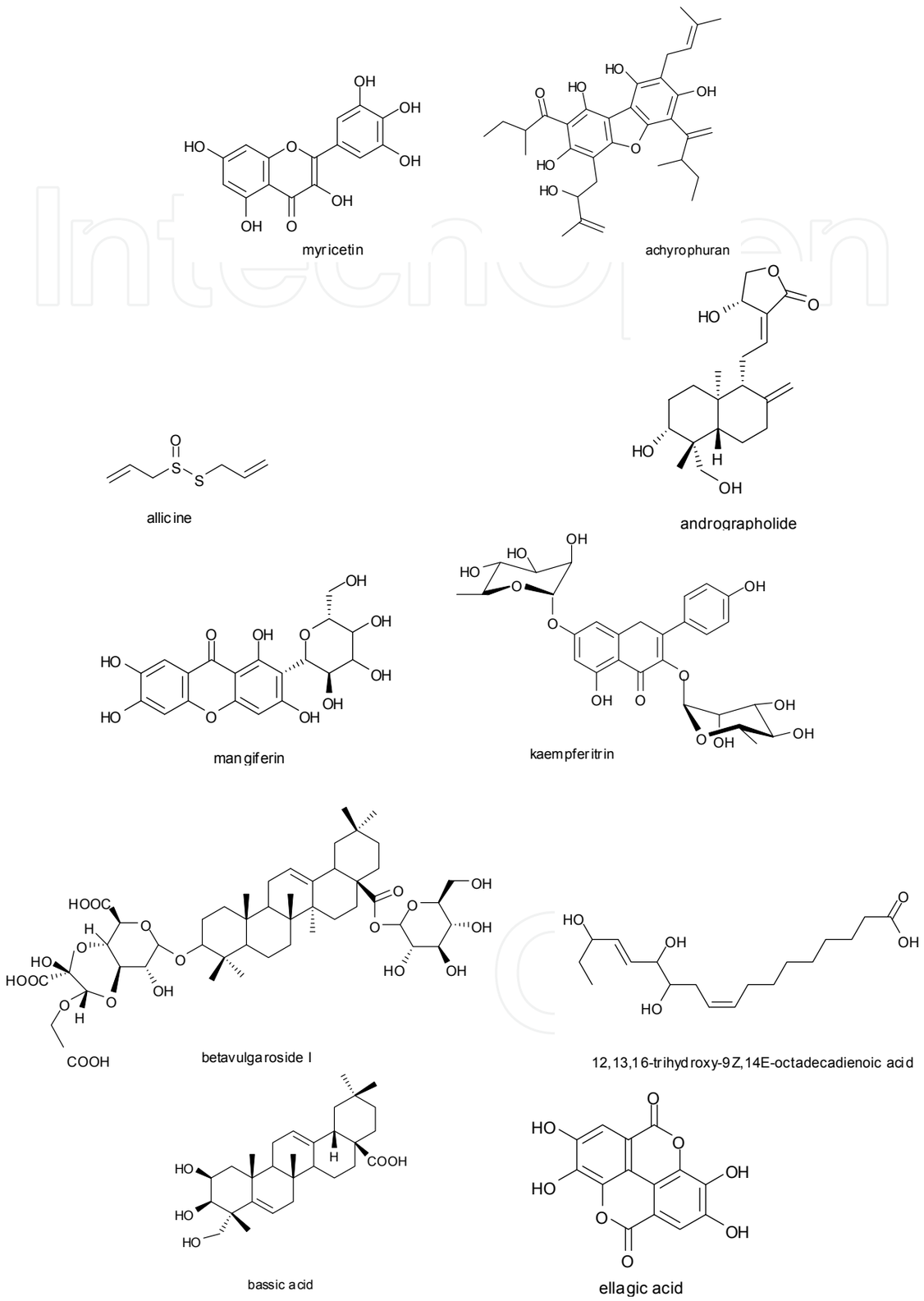


Fig. 1. Some important active compound involved in diabetes mellitus treatment.

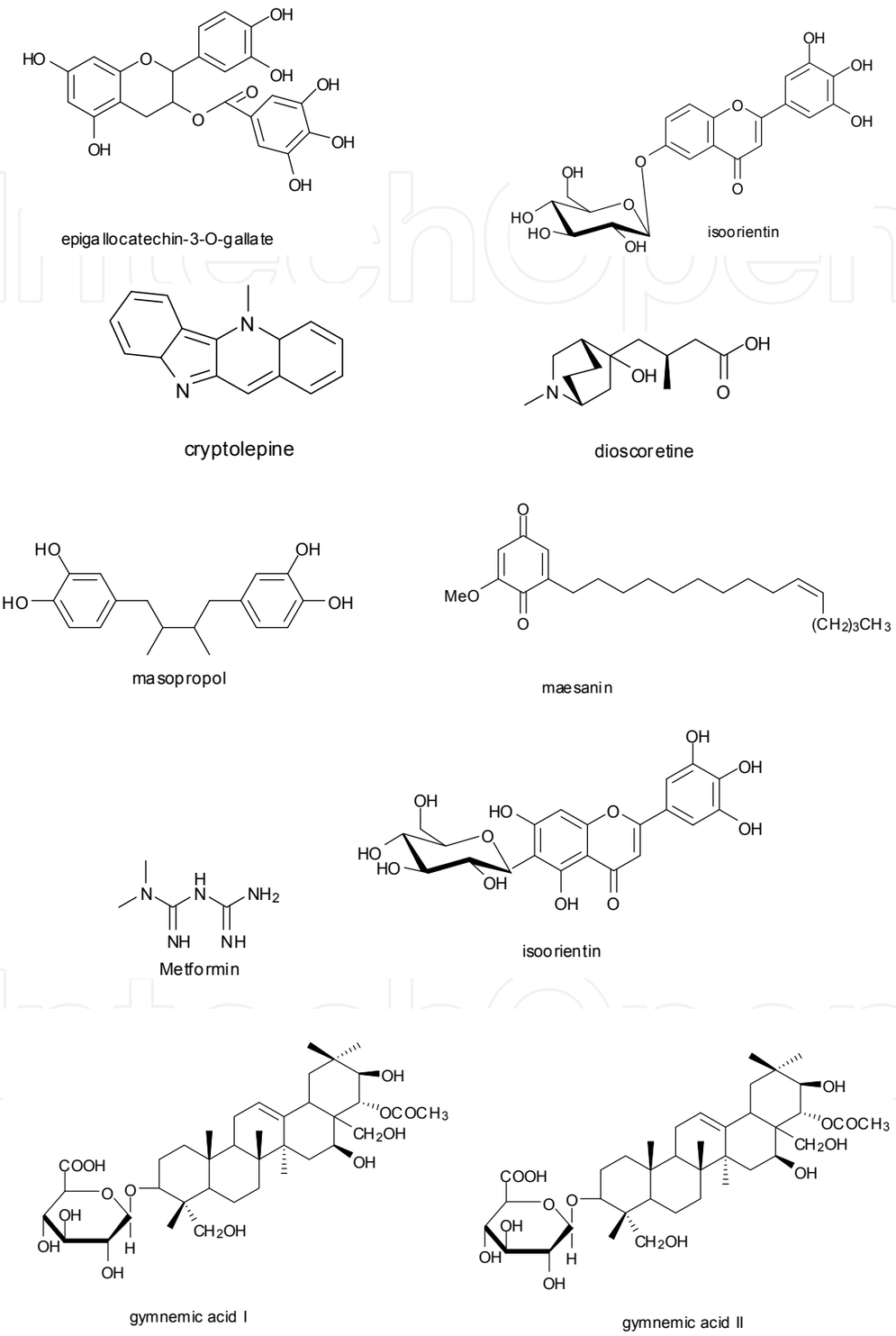


Fig. 1. Some important active compound involved in diabetes mellitus treatment. (continuation)

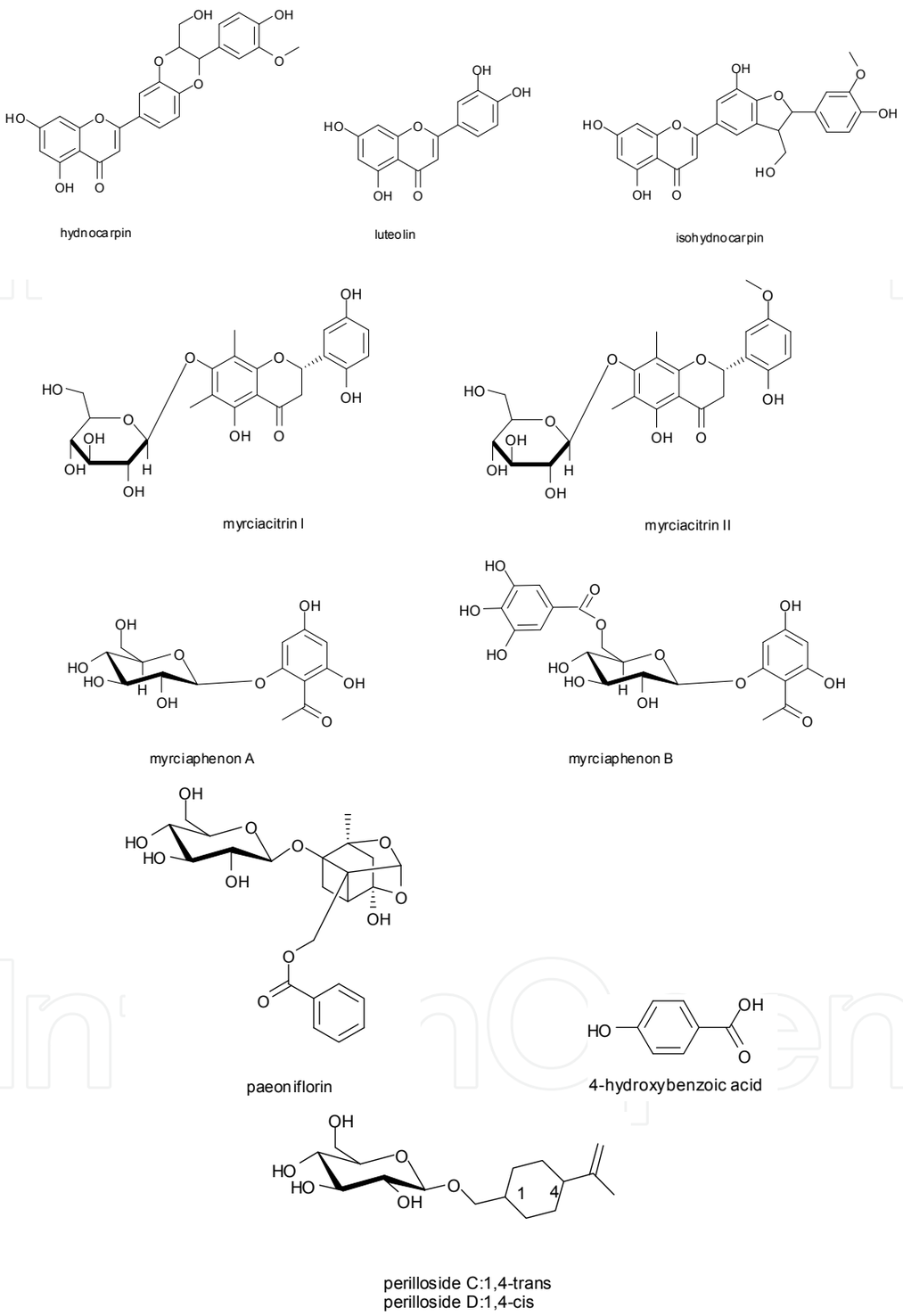


Fig. 1. Some important active compound involved in diabetes mellitus treatment. (continuation)

3. Some biomedical application for some plant used in treating hypoglycemic and hyperglycemic conditions

A- Amelioration of hyperglycemia in STZ-diabetic rats.

Several approaches were conducted in order to investigate the hypoglycemic and hypolipidemic activities of plant extract on experimental animals (STZ-diabetic rats). The derived data showed that some extracts are potent in the amelioration of hyperglycemia in STZ-diabetic rats and is a potential source for the isolation of new per os active agent(s) for anti-diabetic therapy like what observed in Averrhoa bilimbi ethanolic extract which has hypoglycemic, hypotriglyceridemic, anti-lipid peroxidative and anti-atherogenic properties in STZ-diabetic rats (Purshparaj et al., 2001). Another way was by the inhibition of myeloperoxidase activity and decreased lipid peroxidation, induced by ascorbyl radical either in microsomes or in asolectin and phosphatidylcholine liposomes as what observed in Bauhinia forficate due to the kaempferitrin effect .that showed high reactivity with the free radical 1,1-diphenyl-2-picryl hydrazyl (DPPH),

In the plant *Beta vulgaris L. var. cicla (Chenopodiaceae*) the anti-diabetic effect in experimental animals may be to the reduction in blood glucose levels by the regeneration of the β cells (Bolkent et al., 2000). Betavulgarosides I, II, III, IV and oleanolic acid oligoglycosides produced hypoglycemic effects that was demonstrated by a per os glucose tolerance test in rats after their per os administration (Yoshikawa et al., 1996). Or through stimulating the synthesis/release of insulin from the β cells of Langerhans like the effect of *Biophytum sensitivum* and/or also mediated through enhance secretion of insulin from the β cells of Langerhans or through an Extra pancreatic mechanism (*Catharanthus roseus L. (Apocynaceae*)). Or by increasing the number of islet β cells and that of islet α cells was decreased in STZ-diabetic rats like what happen in Dendrobium candidum (Orchidaceae), Its mechanism of action probably involves the stimulation of the secretion of insulin from β cells and the inhibition of the secretion of glucagons from α cells and it can probably decrease the decomposition of liver glycogen and increase the synthesis of liver glycogen.

The Administration of *Coccinia indica (Cucurbitaceae*) leaf extract, an indigenous plant used in Ayurvedic medicine in India, to normal and STZ-diabetic animals exhibited significant hypoglycemic and antihyperglycemic effect and reversed the associated with diabetes biochemical alterations (Venkateswaran & Pari 2002). The results indicated that the per os administration of Coccinia indica leaf extract to diabetic animals normalized blood glucose and caused marked improvement of altered carbohydrate metabolizing enzymes during diabetes. The antioxidant effects of an ethanolic extract of Coccinia indica leaves was studied in STZ-diabetic rats (Venkateswaran & Pari 2003). Per os administration of Coccinia indica leaf extract resulted in a significant reduction in thiobarbituric acid reactive substances and hydroperoxides and a significant increase in reduced GSH, SOD, CAT, glutathione peroxidase and glutathione-S-transferase in liver and kidney of STZ-diabetic rats, which clearly showed the extract's antioxidant property. The ethnopharmacological use of *Gongronema latifolium* in ameliorating the oxidative stress found in diabetics and indicating promise of possible use in lessening morbidity in affected individuals.

The obtained result by Kim et al 2006 suggest that the administration of *Chrysanthemum coronarium* and *Morus alba,* have a hypoglycemic effect in diabetic rats and their effect was

equivalent to that of glibenclamide. The administration of *C.unshiu* shows more antihyperlipidemic effect than antidiabetic effect. The effect of aqueous extracts from four medicinal plants on the blood glucose levels of experimental animals was determined at various time intervals for 9 h after oral administration at 100 mg dose kg-1 b.wt. (Fig. 2). There was a significant elevation in the blood glucose level by 3.3-5 times during experimental time period in alloxan-induced diabetic rats, when compared to normal rats. The administration of *C. coronarium* extract caused the blood glucose levels of diabetic rats to 83.4, 67.6, 75.1, 81.1 and 74.3% at the time interval of 1, 3, 5, 7 and 9 h, respectively ($p<0.05$). Maximum reduction of 32.4% was observed 3 h after treatment. The administration of *M. alba* extract produced the most significant reduction ($p<0.05$) among four medicinal plants in the blood glucose levels of 34, 41, 33 and 35% at 3, 5, 7 and 9 h respectively.

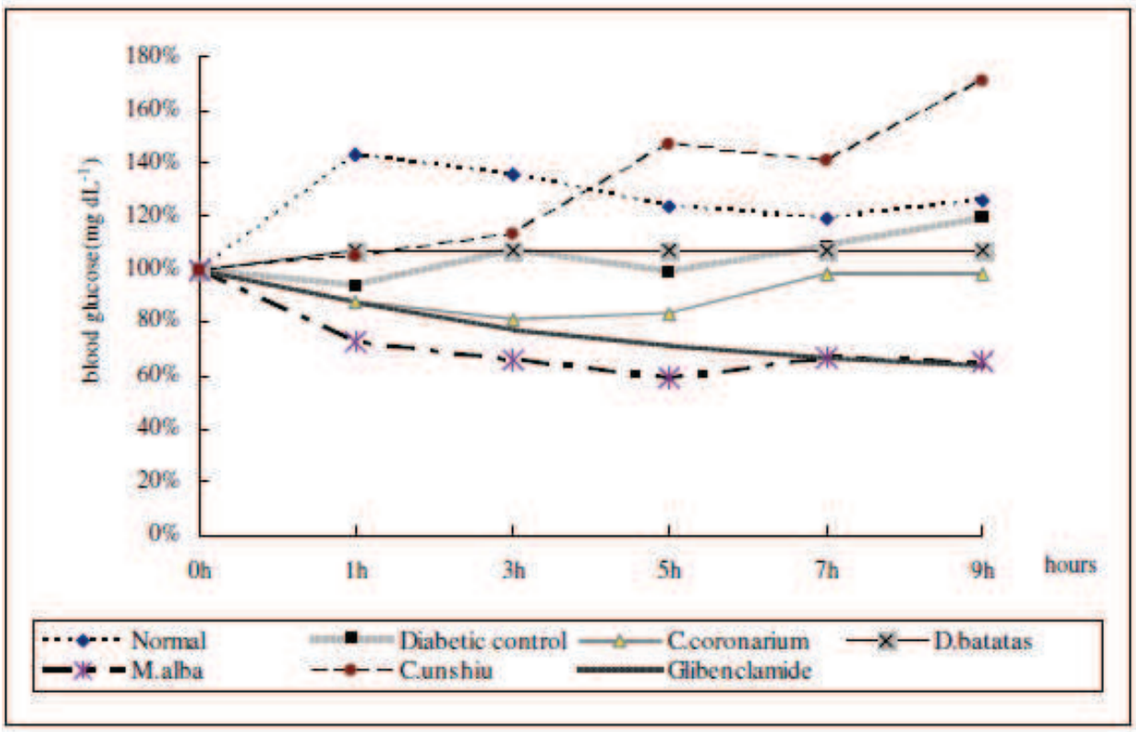


Fig. 2. Percentage of effect of experimental plants on plasma glucose levels compared with 0 h data in alloxaninduced diabetic rats (%). Values are mean percent of blood glucose concentration (n= 6). According to the study obtained by Kim et al., 2006.

B- Hypoglycemic, hypolipidemic hypotriglyceridemic, anti-lipid peroxidative and anti-atherogenic properties of these agents in different medicinal plant:

Insulin resistance (hyperinsulinemia) is now recognized as a major contributor to the development of glucose intolerance, dyslipidemia and hypertension in type II diabetic patients. Aqueous extracts of Pterocarpus marsupium bark (Fbaceae) and Trigonella foenum-graecum. (Leguminosae) seeds have been shown to exert hypoglycemic/antihyperglycemic effect in experimental as well as in clinical settings (Grover et al., 2005). Results of this study, in addition to previous clinical benefits of

Pterocarpus marsupium seen in type II diabetic subjects, are suggestive of usefulness of its bark in insulin resistance, the associated disorder of type II diabetes. Though several antidiabetic principles (epicatechin, pterosupin, marsupin and pterostilbene) have been identified.

The administration of trihydroxyoctadecadienoic acid and its derivatives obtained from the roots of the native Armenian plant *Bryonia alba (Curcubiaceae*) was found to restore the disordered lipid metabolism of alloxan-diabetic rats (Karageuzyan et al., 1998). These derivatives of trihydroxyoctadecadienoic acid can correct major metabolic abnormalities typical of severe diabetes mellitus they can influence the profile of the formation of stable prostaglandins by actions such as downstream of prostaglandin endoperoxides. In *Camellia sinensis (Theaceae*) species, the blood glucose lowering activity of Camellia sinensis was studied by many workers. It has recently been reported that the major green tea polyphenolic constituent, epigallocatechin 3- gallate, mimics the cellular effects of insulin including the reductive effect on the gene expression of rate-limiting gluconeogenic enzymes in a cell culture system (Koyama et al., 2004). Per os administration of green tea that contains this polyphenolic constituent caused a reduction in the levels of mRNAs for gluconeogenic enzymes, PEPCK and G6Pase in the mouse liver. Epigallocatechin 3-gallate alone was also found to down-regulate the gene expression of these enzymes in vitro.

Bumelia sartorum (Sapotaceae), the hypoglycemic effect may be similar to chlorpropamide and possibly due to an enhanced secretion of insulin from the islets of Langerhans or an increased utilization of glucose by peripheral tissues. Besides hypoglycemic activity, the ethanol extract also elicited significant anti-inflammatory activity, but did not show any significant effects on blood pressure, respiration or on the various isolated tissue preparations studied. Bassic acid, an unsaturated triterpene acid isolated from an ethanol extract of Bumelia sartorum root bark, elicited significant hypoglycemic activity in alloxan-diabetic rats and altered the pattern of glucose tolerance in these animals when administered per os (Naik et al., 1991). In addition, bassic acid treatment increased significantly the glucose uptake process and glycogen synthesis in isolated rat diaphragm. Bassic acid treatment increased plasma insulin levels significantly in alloxandiabetic rats. It was therefore suggested that the hypoglycemia activity of bassic acid may be mediated through enhanced secretion of insulin from the pancreatic β cells.

Compelling evidence of *Bidens pilosa (Asteraceae)* suggests that infiltrating CD4 type I helper T (Th1) cells in the pancreatic islets play a pivotal role in the progression of diabetes in non-obese diabetic mice. Treatment with a butanol fraction of Bidens blood glucose and insulin in non-obese diabetic mice in a dose-dependent manner and elevated the serum IgE levels regulated by Th2 cytokines (Chang et al., 2004). Moreover, the butanol fraction inhibited the differentiation of naive helper T cells (Th0) into Th1 cells but enhanced their transition into type II helper T (Th2) cells using an in vitro T cell differentiation assay. The butanol fraction of *Biderns pilosa* and its polyacetylenes can prevent diabetes possibly via suppressing the differentiation of Th0 cells into Th1 cells and promoting that of Th0 cells into Th2 cells.

The results of a reported study of *Gongronema latifolium (Asclepiadaceae)* suggest that the extracts from leaves could exert their antidiabetic activities through their antioxidant properties (Ugochukwu & Bababy 2002). The aqueous and ethanolic extracts were tested in order to evaluate their effect on renal oxidative stress and lipid peroxidation in non-diabetic

and STZ-diabetic rats after per os administration (Ugochukwu & Makini 2003). The ethanolic extract appeared to be more effective in reducing oxidative stress, lipid peroxidation, and increasing the GSH/GSSG ratio, The antihyperglycemic effects of aqueous and ethanolic extracts from Gongronema latifolium leaves was also investigated on glucose and glycogen metabolism in liver of non-diabetic and STZ-diabetic rats (Ugochukwu & Bababy 2003). The data showed that the ethanolic extract from the plant's leaves had antihyperglycemic potency, which was suggested to be mediated through the activation of HK, PFK, G6PD and inhibition of GK in the liver.

According to the study occurred by Mohammad Khalil, et al. (2010), it is found found that, the treatment of the diabetic rats with *Citrullus colocynthis* pulp extract, in the livers showed, more or less, an improvement in the histological architecture with persistence of the cytoplasmic vacuoles in some hepatocytes that could be attributed to the residual adverse effect of the diabetic affliction. But the noticed apparent general improvement signifies that *Citrullus colocynthis* could possess cyto-protective abilities on the hepatocytes. The present findings are supported by those announced by Aburjai *et al*. (2007) who confirmed the anti-diabetic properties of *Citrullus colocynthis* extract. Also, Sebbagh *et al*. (2009) stated that this plant could improve the streptozotosin-induced diabetes in rats. Bujanda *et al*. (2008) owed the similar steatotic inhibitory effect of resveratol to inhibition of the tumor necrosis factor alpha production, lipid per-oxidation and oxidative stress.

The damaged sinusoids, the aemorrhage and the inflammatory cell infiltration encountered in the liver of the diabetic animals, might be due to the hyperglycemic state. Seifalian *et al*. (1999), in an analogous study in rabbits, stressed on that the sinusoidal affection is correlated with the severity of fat accumulation in the parenchymal cells. According to the findings of Khan and Chakarabarti (2003); Hayden *et al*. (2005) and Ban and Twigg (2008), hyperglycemia is the main offending factor in the onset of the micro-vascular diabetic complications. Fortunately, following *Citrullus colocynthis* intake, in their study, the damaged sinusoids, the haemorrhage and the inflammatory cell infiltration subsided indicating a beneficial role of such a remedy. These findings are supported by those claimed by Alarcon-Aguilar *et al*. (2000). Despite the obvious antidiabetic effect of *Citrullus colocynthis* pulp extract, its use in normal rats, in the current work, caused hepatocytic poration and few hapatocytes had condensed or fragmented nuclei indicating minimal hepatotoxicity.

This herbal therapy of *Gymnema sylvestre (Asclepiadaceae*) appears to bring about blood glucose homeostasis through increased serum insulin levels provided by repair/regeneration of the endocrine pancreas. Also, the effectiveness of the water extract from the leaves of *Gymnema sylvestre*, in controlling hyperglycemia was investigated in type II diabetic patients as conventional per os anti-hyperglycemic agents (Baskaran et al., 1990). The obtained data suggested that the β cells may be regenerated / repaired in type II diabetic patients on the extract's supplementation. This was supported by the raised insulin levels in the serum of patients after the supplementation. Furthermore, the antihyperglycemic action of a crude saponin fraction and five triterpene glycosides (gymnemic acids I-IV and gymnemasaponin V) derived from the methanol extract of leaves of *Gymnema sylvestre* was investigated in STZ-diabetic mice (Sugihara et al., 2000).

The results indicated that insulin-releasing action of gymnemic acid IV, administered i.p., may contribute to the antihyperglycemic effect by the leaves of Gymnema sylvestre.

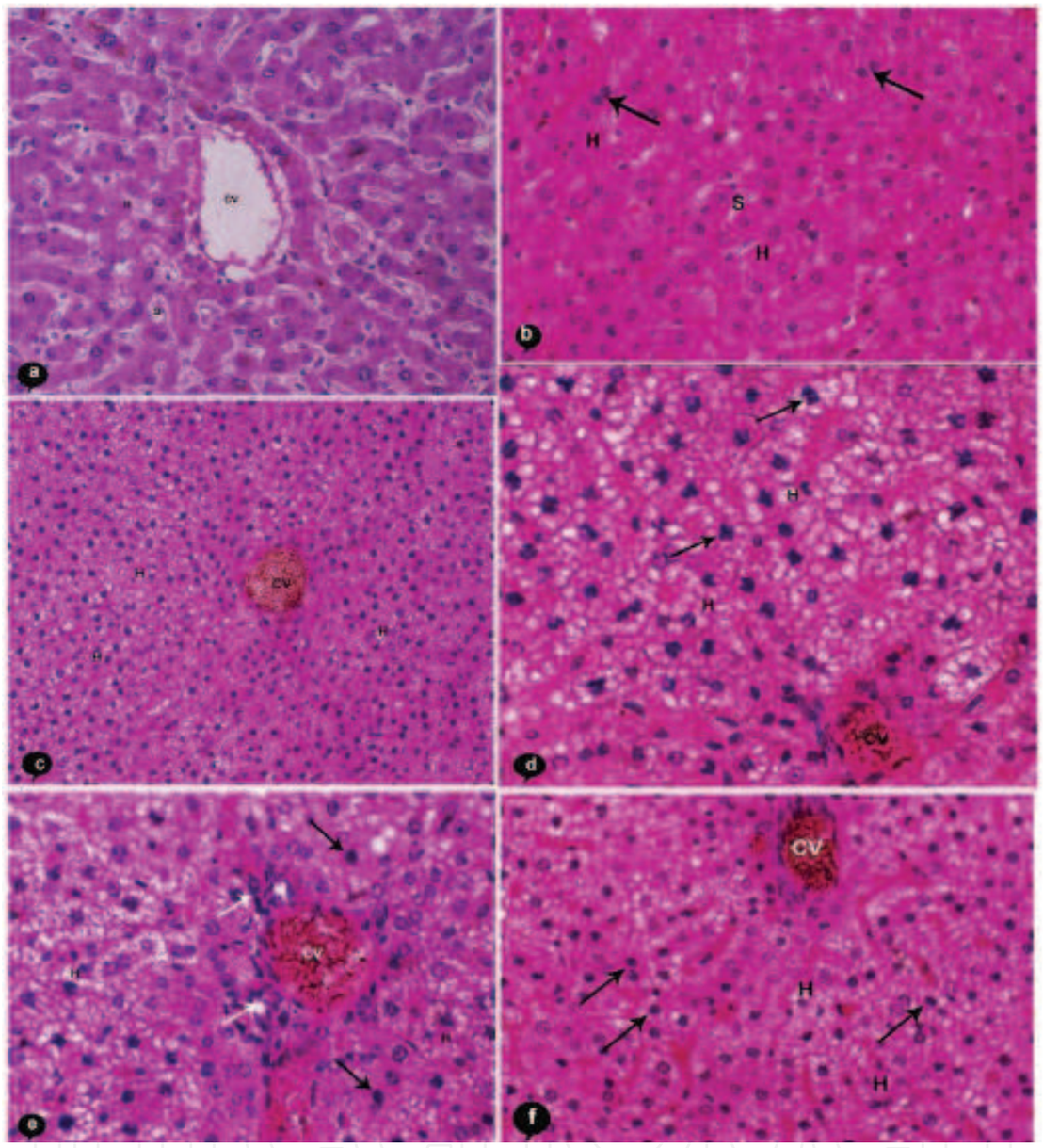


Fig. 3. Photomicrographs of the livers of control, *Citrullus colocynthis*- treated, diabetic and *Citrullus colocynthis*treated diabetic rats, H&E stain; (a) Liver of control rats, ×40; (b) Liver of *Citrullus colocynthis* treated rats, showing few hapatocytes had condensed or fragmented nuclei ×40; (c) Liver of diabetic rats, showing disorganized hepatic cords, reduced sinusoids and many hepatocytes having cytoplasmic vacuolization, ×20; (d) Higher magnification of (c), showing most hepatocytes with cytoplasmic vacuolar degeneration and pyknotic nuclei (arrows), ×40; (e) Liver diabetic rats, showing a central inflammatory cell infiltration (white arrows) and hepatocytes with cytoplasmic vacuolar degeneration and pyknotic nuclei (black arrows), ×40; (f) Liver of diabetic rats treated with *Citrullus colocynthis*, showing recovered hepatocytes with less cytoplasmic vacuolization compared with diabetic animals. Few hepatocytes with cytoplasmic vacuolization and pyknotic nuclei are still seen (arrows), ×40. According to the study occurred by Mohammad Khalil, et al. (2010).

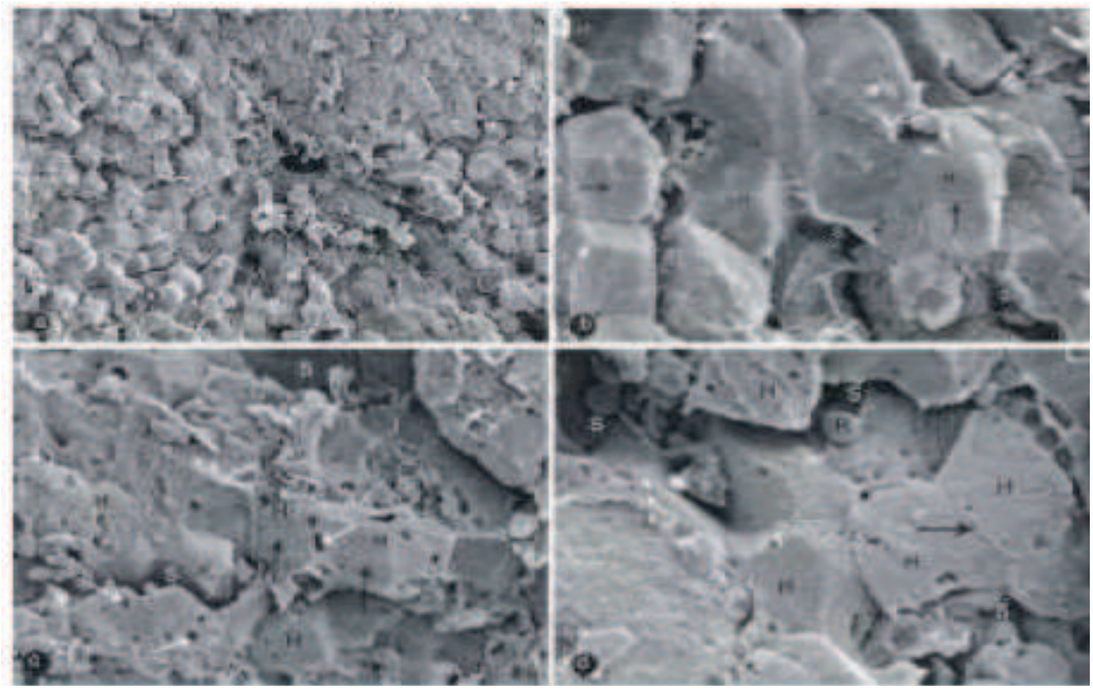


Fig. 4. Scanning electron micrographs of livers of control and *Citrullus colocynthis*-treated rats. (a) SEM of the liverof control rats showing normal hepatic cord around a Central Vein (CV), ×450; (b) Larger magnification of (a) showing normal Sinusoids (S) and normal Hepatocytes (H) with normal intercellular boundaries (arrows), ×1500 (c); SEM of the liver of *Citrullus colocynthis*-treated rats, showing rows of Hepatocytes (H) containing few pores (white arrows). Note the blood Sinusoids (S) and the intercellular boundaries (black arrows), ×1100; (d) Higher magnification of (c), showing blood Sinusoids (S), Hepatocytes (H), intercellular spaces (black arrows) and erythrocytes (R), ×1500. According to the study occurred by Mohammad Khalil, et al. (2010).

Gymnemic acid IV may be an anti-obese and antihyperglycemic prodrug. The inhibitory activity of each triterpene glycoside on the glucose uptake in rat small intestine fragments was examined, in order to determine its impact on the increase of serum glucose level in glucose-loaded rats (Yoshikawa et al., 1997). It was found that Gymnemic acids II and III showed potent inhibitory activity on glucose uptake. Gymnemoside b and gymnemic acids III, V, VII were found to exhibit a little inhibitory activity against glucose uptake, and the principal constituents, gymnemic acid I and gymnemasaponin V, lacked this activity. It is noteworthy that, although Gymnema saponin constituents such as Gymnemic acids II and III show no effect on serum glucose levels in oral-loaded rats, they exhibit potent inhibitory activity on the glucose uptake and further studies need to be contacted.

The hypoglycemic activity of a decoction from *Juniperus communis* (juniper berries) both in normal glycemic and in STZ-diabetic rats was studied (Sanchez et al., 1994). Juniper decoction decreased glycemic levels in normal glycemic rats through an increase of peripheral glucose utilization or a potentiation of glucose induced insulin secretion.

The per os administration of the decoction to STZ diabetic rats resulted in a significant reduction both in blood glucose levels and in the mortality index, as well as the prevention

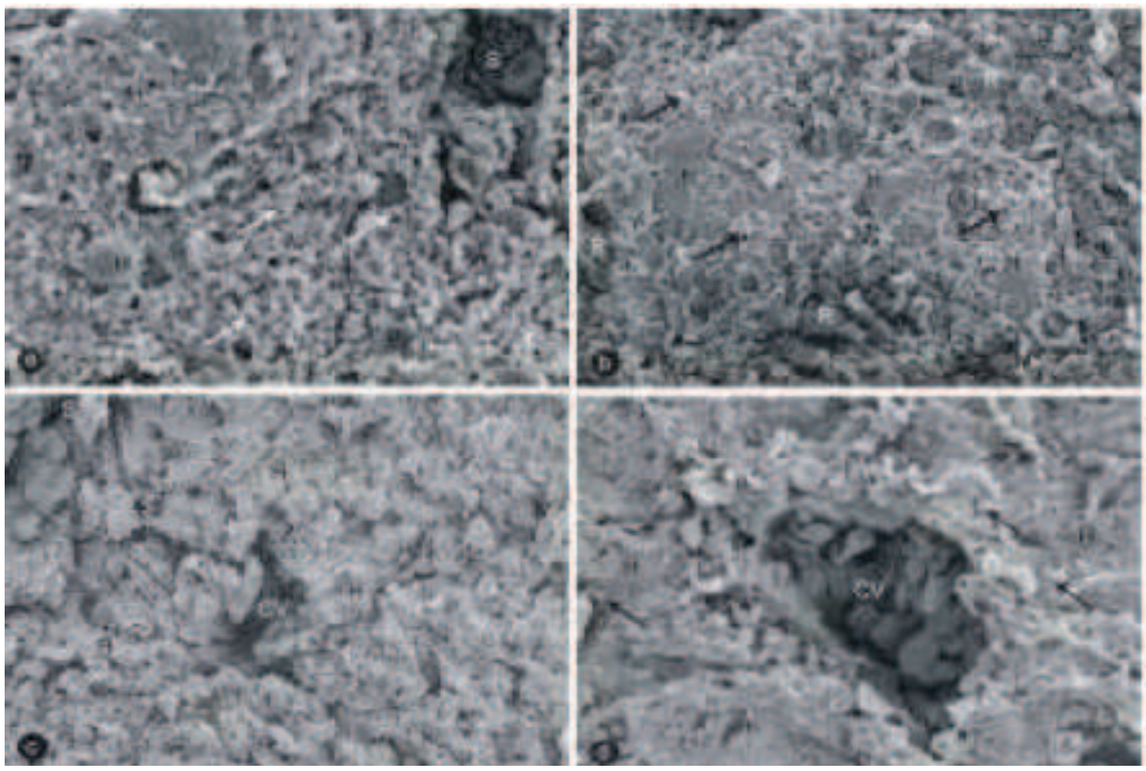


Fig. 5. Scanning electron micrographs of livers of diabetic and *Citrullus colocynthis*-treated diabetic rats. (a) SEM of the liver of diabetic rats showing degenerating Hepatocytes (H) having a plenty of lipid droplets (white arrows). Damaged blood Sinusoids (S) are also seen as well as some erythrocytes (R) are spread inside hepatocytes, ×450; (b) SEM of the liver of diabetic rats showing hemorrhage of erythrocytes (R) between Hepatocytes (H). Lipid degeneration (black arrows) of hepatocytes is also seen, ×450; (c) SEM of the liver of *Citrullus colocynthis*-treated diabetic rats, showing intact Hepatocytes (H) and blood Sinusoids (S). Only fewhepatocytes around the central vein have some vacuoles, ×450; (d) SEM of the liver of *Citrullus colocynthis* treated diabetic rats (300 mg) with higher magnification, showing intact Hepatocytes (H) and a Central Vein (CV) containing a lot of erythrocytes. A few hepatocytes around the central vein have a few lipid droplets (arrows), ×1100. According to the study occurred by Mohammad Khalil, et al. (2010).

of the loss of body weight. This effect seemed to be mediated by the peripheral action of juniper while in Olea europaea (Oleaceae) plant species, the hypoglycemic activity may result from two mechanisms: (a) potentiation of glucose induced insulin release, and (b) increased peripheral uptake of glucose.

The hypoglycemic effect of the rhizomes of *Polygala senega* (Polygalaceae) was proposed that after i.p. administration was without altering the insulin levels and with the need of the presence of insulin in order to act. In addition, one of the active components of this hypoglycemic effect was identified as a triterpenoid glycoside, senegin-II (as a mixture of isomers). *Solanum lycocarpum (Solanaceae***)** has been widely employed for diabetes management, obesity and to decrease cholesterol levels. Some of the polysaccharides slowed gastric emptying and act on the endocrinous system affecting the liberation of

gastrointestinal hormones, lowering blood glucose levels. The hypocholesterolemic activity could be due to the increased fecal bile acid excretion as well as to the action of the short-chain fatty acids, coming from fermentation, on the synthesis of deltaaminolevulinate and by the increase of the cholesterol 7-alpha-hydroxylase and 3-hydroxy-3-methylglutaryl CoA reductase synthesis (DalAgnol & Lino von Poser 2000).

4. Conclusions and future directions

Scientists from divergent fields are investigating plants anew with an eye to their antimicrobial usefulness. A sense of urgency accompanies the search as the pace of species extinction continues. Laboratories of the world have found literally thousands of phytochemicals which have inhibitory effects on all types of microorganisms in vitro. More of these compounds should be subjected to animal and human studies to determine their effectiveness in whole-organism systems, including in particular toxicity studies as well as an examination of their effects on beneficial normal microbiota. It would be advantageous to standardize methods of extraction and in vitro testing so that the search could be more systematic and interpretation of results would be facilitated. Also, alternative mechanisms of infection prevention and treatment should be included in initial activity screenings. Disruption of adhesion is one example of an anti-infection activity not commonly screened for currently. Attention to these issues could usher in a badly needed new era of chemotherapeutic treatment of infection by using plant-derived principles.

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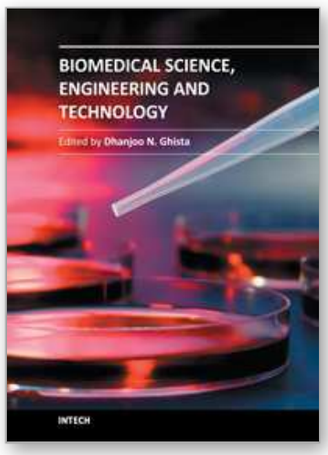
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