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A Critical Review on Traditional Herbal Drugs: An Emerging Alternative Drug for Diabetes

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ABSTRACT

Diabetes is a chronic metabolic disease reaching an epidemic proportion in many parts of the world. By the year 2025 it is expected that 333 million people of the world will have diabetes as their main ailment. As today, India assumes the position of the diabetic capital of the world with the highest percentage of its population suffering from diabetes. It is pathetic to mention that in proportion to its people suffering from diabetes, this country has very weak spending power for treatment because of wide spread poverty. Therefore, this review is aimed at opening up new vistas in realizing the therapeutic potential of Ayurveda in treatment of diabetes and other chronic diseases. All drugs which we have discussed in this review have a significant role in therapy of diabetes mellitus.

Keywords: Diabetes Mellitus; Metabolic Disease; Ayurveda; Hyperglycemia; Synthetic Drugs; Herbal Drugs; Metallo Therapy; Oral Hypoglycemic Drugs

1. Introduction

The word diabetes was coined by the Greek physician Aretaeus in the first century AD Diabetes mellitus has been known since ages and sweetness of urine has been mentioned in Ayurveda by Sushruta. Its pharmacotherapy is 80 year old. The presence of sugar in the urine of diabetics was demonstrated by Dobson in 1755 [1]. Yet, as we have spent one decade of new millennium, our knowledge of the nature and treatment of diabetes is still incomplete. Diabetes mellitus is most serious; chronic metabolic and characterized by high blood glucose level [2]. Hyperglycemia is caused by relative or absolute deficiency of insulin or by a resistance to the action of insulin at the cellular level. It is most common endocrine disorder, affecting 41 million individuals in India and as many as 200 million world-wide. The worldwide prevalence of diabetes for all age groups was estimated to be 2.8% in 2000 and it is projected to be 5.4% in 2025. Currently available therapies for diabetes include insulin and oral antidiabetic agents such as sulfonylurea, biguanides, α-glucosidase inhibitors and glinides, in developping countries as products are expensive and not easily accessible [3]. DM (diabetes mellitus) has been become a clinical model for general model for general medicine. The primary defect in fuel metabolism results in widespread, multi-organ complications that ultimately encompass virtually every system of the body. Although from a clinical standpoint, this may be true, our increasing knowledge of patho-physiology of the syndrome, together with the mechanisms of long term complication, has placed diabetes researched at the frontier of immunology and molecular biology [1].

2. Etiology of Diabetes, Cure and Strategy

Diabetic patients are diagnosed by blood or urinary glucose measurement through different techniques. On the basis of etiology DM (Diabetes mellitus) are categories mainly two types *viz*:

1) Primary Diabetes (Type I or Insulin Dependent Diabetes Mellitus).

2) Secondary Diabetes (Type II or Non Iinsulin Dependent Diabetes Mellitus).

Primary DM (Diabetes mellitus) clinically dependent on insulin due to there is decrease in the number of β-cells in the islets of langerhans and thus there is absolute deficiency of insulin hence this is known as Insulin Dependent Diabetes Mellitus (IDDM) or Type I. The main treatment for this Type I of DM (Diabetes mellitus)

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is insulin.

Secondary DM (Diabetes mellitus) is referred as Type II or Non Insulin Dependent Diabetes Mellitus (NIDDM) because these types of patients are insulin resistances as well as loss of insulin secretion contributes to the onset of disease. The patients are usually obese and the treatment is usually dietary, through supplementary oral Hypoglycemic drugs.

As the complications induced by diabetes mellitus are very serious and goes to worst day by day hence, there is potent need of medicine to cure the diabetes mellitus. In this review we will go through the all the possible cure available to preventing the complications and its limitation also, to finding out the alternatives of these synthetic drugs, having no or few side effects with low price and ease to reach the common people.

3. Strategy for Treatment of Diabetes

Basic therapeutic approach to treat diabetes may be to inhibit the absorption of glucose by retarding the action of gastro-intestinal enzymes such as α-glucosidase and α-amylase. Because the complication of disease is mainly due to the higher glucose level in blood which dysfunction the other organs of body. Thus we can say that the effective α-glucosidase inhibitors may serves as chemotherapeutic agents for clinic use in the treatment of diabetes and obesity [4,5].

3.1. Medicine for Treatment of Diabetes Mellitus

3.1.1. Insulin

Insulin increases glucose uptake in cells by stimulating the translocation of the glucose transporter GLUT4 from intracellular sites to the cell surface [6,7]. Insulin circulates in blood as the free monomer and its half life in plasma is about 5 - 6 min in normal subjects. Although glucose is the principal stimulus to insulin secretion in human beings, this process is tightly regulated by the coordinated of nutrients, gastrointestinal and pancreatic hormones and autonomic neurotransmitters [8]. The main draw back of insulin is taken through injection.

3.1.2. Oral Hypoglycemic Drugs

Oral Hypoglycemic drugs are those drugs that lower blood glucose level and taken orally. These drugs are synthetic and complex organic substances. Hence the search for oral active drugs is in demand.

1) Sulfonylureas Drugs

First Generation Drugs

a) Tolbutamine;
b) Chloropropamide;
c) Acetohexamide;
d) Tolazmde.

Second Generation Drugs

a) Gilbenclamide;
b) Glipizide;
c) Gliclazide.

2) Biguanides

a) Phenformin;
b) Metformin.

3) Others

a) Acarbose;
b) Guar Gum.

These drugs are effective in diabetes but having some limitations such as hypoglycemia occurs with regular use of sulfonylurea compounds but occurrences are much fewer than with insulin therapy. It is prescribed by doctors that biguanids should not use in patients with renal diseases. On the other hand the main side effect of Acarbose is flatulence [1].

3.1.3. Metallotherapy

The current literature also shows that metallopharmaceuticals is an area of growing interest as is evident through the clinical trials that are being conducted worldwide for the usages of metals in therapeutics. Metallotherapy is a new therapeutic strategy to treat diabetes with metal complexes. It is first studied by Coulson and Dandona in 1980 that $ZnCl_2$ stimulate lipogenesis in rat adipocytes similarly to the action of Insulin. In three decades there are many researchers reported insulin-mimetic activity, α-glucosidase and α-amylase inhibition with different coordination of different ligand with transition metals. However the strategies to treat the diabetes mellitus through metal complexes are in early stage hence there are no side effects reported at all. Some metal complexes are in trial stage for treating diabetes.

3.1.4. Herbal Drugs

There are many herbal products/herbal extracts are reported to treat the diabetes mellitus, we can classify these drugs according to their mode of action as:

3.1.4.1. Extracts/Drugs Act as α-Glucisidase or α-Amylase Inhibitor

These types of drugs/extracts are able to reduce the blood glucose level by inhibiting the gastric enzymes which is obligatory for the break the polysaccharides in to the simple sugar.

The aqueous and methanolic extract of *Syzgium cumini* (seed) and *Pisidium guajava* (leaves) shows α-amylase inhibition [9]; while *Rhus verniciflua* stem screened for α-glucosidase inhibition effect mixture of methanol and ethanol extract shows the potent inhibition of α-glucosedase enzyme [10]. There are large number of plants which have the capability to inhibit the α-glucosidase and α-amylase activity and may be used as treatment of diabetes Type I and Type II.

3.1.4.2. Extracts/Drugs Increases Insulin Secretion or *β*-Cell Regeneration

These types of drugs are directly concern with the Type I or IDDM diabetes which are disable to secreting the less or few amount of insulin.

Radix of *Acorus calamus* is used as in the therapy of diabetes in traditional folk medicine of America and Indonesia, this sensitize the insulin activity of its ethyl acetate extract [11]. On the other hand Ginsenoside Rh2 an active compound found in *Panax ginseng* root increased plasma insulin level parallel with lowering the plasma glucose level [12]. Moreover aqueous extract of *Syzgium cumini* bark stimulate *β*-cell regeneration by proliferation of its precursor or cells in the pancreatic duct [13].

3.1.4.3. Extracts/Drugs Act as Hypoglycemic, Antihyperglycemic or Antidiabetic Effect

These classes of herbal drugs reduce the blood glucose level directly, this may be also used to treat the both type of diabetes mellitus (IDDM and NIDDM).

Mangifera indica Linn. (Locally known as mango tree) has antidiabetic property, ethanolic and water extract of leaves and stem bark of *Mangifera indica* shows significant antihyperglycemic effect [14]. Extract of *Hedychium spicatum* rhizomes also show the antihyperglycemic effect [15]. *Ficus bengalensis* bark extract show antidiabetic and ameliorative activity [16]. While alcoholic aqueous extract of *Coccinia indica* (*C. cordifolia*) aerial part exhibit the hypoglycemic effect and fruit of *Ficus glomerata* shows hypoglycemic activity [17,18].

3.1.4.4. Extracts/Drugs Dealing with the Complications of Diabetes Mellitus

Diabetes mellitus is metabolic syndrome characterized by deregulation in carbohydrate metabolism associated with defect in insulin secretion or action by which glucose level of blood increases, the different type of complication occurred. To treat these type of problem many herbal drugs/extract may play a key role.

The aqueous extract of bark of *Ficus religiosa* Linn reduces oxidative stress in Type II diabetes mice model [19]. Extract of fruit of *Benincasa gispida* decrease gastric ulcer index in diabetic rat model [20]. Hexane extract of *Derris scanders* show potent *α*-glucosidase inhibition effect and moderate free radical scavenging activity [21]. *Pongamia pinnata* flower shows antihyperglycemic and antilipid-peroxidative effect with reference drugs glibenclamide [22]. Oral administrations of Coccinia indica leaf extract (200 mg/kg body weight) for 45 days significantly reduce the thiobarbituric acid reactive substances and hydroperoxides. The extract also causes a significant increase in reduced glutathione, superoxide dismutase, catalase, glutathione peroxidase and glutathione-S-transferase in liver and kidney of streptozotocin diabetic rats, which clearly shows the antioxidant property [23]. Some plants are listed in **Table 1** which has the antidiabetic properties.

4. Plants Used for Curing Diabetes Mellitus in Ayurveda

India has a great ancient heritage of traditional medicine. The material medica of Indian provides much information on ethnic folklore practices and traditional aspects of therapeutically important natural products [26,27]. Indian traditional medicine is based on various systems, including Ayurveda, Siddha and Unani (ASU). With the emerging interest of the world in adopting and studied traditional systems and in exploiting their potential from different healthcare perspectives, it is necessary to listing some of plants which are used to curing the diabetes from ancient time are listed in [28-31] **Table 2**.

5. Trials of Traditional Medicines

There are several herbal drugs are formulated according to traditional and modern knowledge of ethanobotany. Bio-active molecules have been cross checked on diabetic models and several are in trail courses. Some of trails are as:

Wendell D. Winters (2003) *et al.* [32] studied inhibition of the progression of Type II diabetes in the C57BL/6J mouse model by an anti-diabetes herbal formula prepare from Chinese herbs which was activated and mixed according to proprietary formula ingredients through standard method. The herbal formula had eight major herbals, Ginseng Radix (17%), Rehmannia Radix (17%), Astragali Radix (10%), Trichosanthis Radix (10%), Ophiopogous Radix (10%), Puerariae Radix (10%), Lycii fructus (10%), Discoreae Rizoma (10%) and found that 4% - 8% of regular feeding with ADHF shows significant reduction in blood glucose level and increase in insulin level further they suggested ADHF should be used as diet supplement.

Ikuko Kimura (1999) *et al.* [33] studied the antihyperglycemic blend effect of traditional Chinese medicine byakko-ka-ninjin-to on alloxan and diabetic KK-CA^{y} Mice and concluded that the water extract of Byakko-Ka-ninjin-to (BN) which have Ginseng root, licorice root, *Anemarrhena asphodeloides* (rhizome), *Fibrosum gypsum* and rice with blend of Ca^{++} shows the antihyperglycemic effect.

In the management of diabetes Type II a trail of Vijayasar (*Pterocarpus marsupium*) had done in different location in India by ICMR group to check the efficacy of Vijayasar in contrast of synthetic drug Tolbutamide. Study shows that Vijayasar is an effective blood glucose lowering traditional Indian plant agent, its glycemic effect being comparable to that of Tolbutamide in treatment

Table 1. Representing list of antidiabetic plants.

S. N.	Plant name (botanical)	Family	Part(s) used	Effects observed	Reference(s)
1	*Abroma augusta*	Sterculiaceae	Root	Hypoglycemic and antilipidemic	[40]
2	*Acacia arabica*	Fabeceae	Bark	Ameliorate the dearrangmrnt in lipid metabolism in diabetes	[41]
3	*Acalypha wilkesiana*	Euphorpiaceae	Leaves	Hypoglycemic and antioxidant	[42]
4	*Acer saccharum* (*maple*)	Sapindaceae	Juice	α-Amylase and α-glucosidase inhibition	[43]
5	*Acorus calamus*	Acoraceae	Leaves/bark	α-Glucosidase inhibition and hypolipidemic	[11]
6	*Aegle marmelos*	Rutaceae	Leaves/bark/root	Antioxidant and anti cataract activity	[44]
7	*Afzelia africana*	Fabaceae	Stem bark	Antidiabetic and hematological effect	[45]
8	*Alhagi camelorum*	Fabaceae	Aerial part	α-Glucosidase inhibition	[46]
9	*Allium sattivum*	Alliaceae	Bulb	Antidiabetic	[3]
10	*Aloe vera*	Xanthorrhocaceae	Leaves	Hypoglycemic	[47]
11	*Alpinia officinarum*	Zingiberaceae	Rhizomes	α-Glucosidase inhibition	[46]
12	*Amaranthus spinosus*, *Amaranthus caudatus*, *Amaranthus viridis*	Amaranthaceae	Leaves	α-Amylase inhibition, antioxidant and anticholesrolemic	[48,49]
13	*Annona squamosa*	Annonaceae	Fruits	Antidiabetic	[3]
14	*Anogeissus acuminate*	Combretaceae	Whole plant	Antioxidant	[50]
15	*Areca catechu*	Arecaceae	Seed	Antidiabetic	[3]
16	*Artemis sphaerocephala krasch*	Compositae	Gum/seed powder	Antidiabetic	[51]
17	*Artemisia dracunculus* (L.)	Asteraceae	Aerial part	Antidiabetic	[52]
18	*Artemisia herba-alba asso*	Asteraceae	Whole plant	Antihyperglycemic and antihyperlipidemic	[53]
19	*Artemisia pallens*	Asteaceae	Leaves and Flower	Antidiabetic	[3]
20	*Ascophyllum nodosum*	Algae	-	α-Glucosidase inhibition and α-amylase	[54]
21	*Aspidosperma macrocarpon*	Apocynaceae	Steam/Bark Root wood	α-Amylase inhibition	[55]
22	*Atractylodes macrocephala*	Asteraceae	Whole plant	α-Glucosidase inhibition	[56]
23	*Azadirachta indica*	Meliaceae	Leaves, flower and seed	Antidiabetic and antihypertension	[3,57,58]
24	*Barringtonia racemosa*	Lecythidaceae	Seed	α-Glucosidase and α-amylase inhibition	[59,60]
25	*Bauhinia forficate*	Leguminosae	Leaves	Antidiabetic	[3]
26	*Belamcanda chinensis*	Irdaceae	Leaves	Hypoglycemic	[61,62]
27	*Benincasa hispida*	Cucurbitaceae	Fruit	Ameliorat the derangement in lipid metabolism in diabetics.	[41]
28	*Benincasa hispida*	Cucurbitaceae	Fruit	Antidiabetic	[20,63]
29	*Berberis vulgaris*	Berberidaceae	Leaves	Hypoglycemic	[64]
30	*Beta vulgaris*	Amaranthaceae	Root	Antidiabetic	[3]

Continued

31	*Borerhavia diffusa*	Nyctaginaceae	Whole plant	Antidiabetic	[3]
32	*Brassica juncea*	Brassicaceae	Seed	Hypoglycemic	[65]
33	*Buchholzia coriaceae*	Capparaceae	Seed	Hypoglycemic	[66]
34	*Caesalpinia ferrea Martius*	Leguminosae	Bark	Hypoglycemic activity	[67]
35	*Camellia sinensis*	Theaceae	Fruit peel/leaves	α-glucosidase and α-amylase inhibition, antihyperglycemic	[3,68,69]
36	*Capparis deciduas*	Capparaceae	Fruit	Hypoglycemic/antidiabetic	[3,70]
37	*Cassia auriculata*	Caesalpiniaceae	Aerial part	Antioxidant	[71]
38	*Catharanthus roseus*	Apocynaceae	Leaves/bark/root	Antioxidant and anticataract activity	[44,72]
39	*Catunaregam tormentosa*	Rubiaceae	Whole plants	Antioxidant and antihyperglycemic	[50]
40	*Centauriun erythrea*	Gentianaceae	Whole plant/leaves	Antihyperglycemic, antihyperlipidemic, antioxidant and prevent β-cell damage	[53,73]
41	*Chaenomeles sinensis*	Rosaceae	Fruit	α-Glucosidase and β-glucosidase inhibition	[74]
42	*Chiliadenus iphionoides*	Asteraceae	Shrub	Increased β-cells numbers and Insulin secretion	[75]
43	*Cinnamomum cassia*, *Cinnamomum zeylanicum*	Lauraceae	Leaves/bark	α-Glucosidase inhibition, antioxidant and antidiabetic	[3,56,76]
44	*Coccinia cordifolia*	Cucurbitaceae	Herb	Hypoglycemic	[17]
45	*Coccinia indica*	Cucurbitaceae	Leaves	Antioxidant, antihyperglycemic and antilipidemic	[23,24,40]
46	*Cocos nucifera*	Arecaceae	Coconut kernel protein	Antidiabetic	[77]
47	*Codonopsis pilosula*	Campanulaceae	Whole plant	α-Glucosidase inhibition	[56]
48	*Coffea arabica*, *Coffea canephora*	Rubiaceae	Beans/seed	α-Amylase isoenzyme inhibition	[78,79]
49	*Combretum micranthum*	Combretaceae	Leaves	Antidiabetic	[3]
50	*Commbretum micranthum*	Combretaceae	Leaves	Hypoglycemic and antidiabetic	[3,80]
51	*Commiphora mukul*	Burseraceae	Gum resin	Antihyperglycemic and antioxidant	[81]
52	*Coriandrum sativum*	Apiaceae	Seed	Hypolipidemic and hypoglycemic	[82]
53	*Corus kousa*	Cornaceae	Leaves	Antihyperglycemic	[83]
54	*Costus pictus*	Zingiberaceae	Leaves	α-Glucosidase and α-amylase inhibition	[84]
55	*Cucumis melo var. utlissimus Duthie*	Cucurbitaceae	Fruit	Antioxidant and hyperglycemic	[63]
56	*Cucurbita maxima*	Cucurbitaceae	Fruit	Antioxidant and hyperglycemic	[63]
57	*Cuminum cyminum*	Apiaceae	Seed	Aldose reductase and α-glucosidase inhibition	[85]
58	*Cynodon dactylon*	Poaceae	Leaves	Antidiabetic, antioxidant, hypolipidemic and improve diabetes associated neurological disorder	[86,87]
59	*Derris scandens*	Fabaceae	Whole plant	α-Glucosidase inhibition	[21]

Continued

60	*Dichrostachys glomerata*	Fabaceae	Whole plant	Antioxidant and hypoglycemic	[88]
61	*Dillenia indica*	Dilleniaceae	Leaves	Antidiabetic and hypolipidemic	[89]
62	*Dioecrescis erythroclada*	Rubiaceae	Whole plant	Antioxidant and antihyperglycemic	[50]
63	*Dioscorea opposite*	Dioscoreaceae	Leaves	α-Glucosidase inhibition	[56]
64	*Elephantopus scaber*, *Elephantopus mollis*	Asteraceae	Whole plant	Antidiabetic, α-glucosidase inhibition and apoptotic	[3,90]
65	*Eleutherine americana*	Iridaceae	Bud	α-Glucosidase inhibition	[91]
66	*Embelia ribes*, *Embelia officinalis*	Myrsinaceae	Leaves/aerial part	Antihyperglycemic	[92,93]
67	*Eriobotrya japonica*	Rosaceae	Leaves	Antihyperglycemic	[94]
68	*Euclea undulata*	Ebenaceae	Root/bark	α-Glucosidase inhibition and hypoglycemic	[95]
69	*Eucommia ulmoides*	Eucommiaceae	Whole plant	α-Glucosidase inhibition, antidiabetic and antioxidant	[56]
70	*Ficus bengalensis Linn*	Moraceae	Bark	Antidiabetic, antihyperglycemic and ameliorative	[3,16,96]
71	*Ficus golmerata*	Moraceae	Bark/fruit	Antioxidant, anti cataract activity	[18,44]
72	*Ficus religiosa*	Moraceae	Bark	Antihyperglycemic, antioxidant and antidiabetic	[19]
73	*Flos ionicerae*	Caprifoliaceae	Whole plant	α-Glucosidase inhibition	[56]
74	*Foenum graecum*	Fabaceae	Whole plant	Antihyperglycemic	[97]
75	*Glycine max*	Fabaceae	Seed	α-Amylase inhibition	[98]
76	*Grateloupia elliptica*	Algae	-	α-Glucosidase inhibition	[99]
77	*Gyanandropsis gynandra*	Capparidceae	Root	Antidiabetic	[3]
78	*Gymnema sylvestre*, *Gymnema montanum*	Asclepiadaceae	Leaves/callus/stem	Regeneration of β cell, reduce blood glucose level, increase plasma insulin level and hypolipidemic	[3,100-102]
79	*Gynura divaricata*	Asteraceae	Aerial part	Hypoglycemic, α-glucosidase, α-amylase inhibition	[103]
80	*Hedychium spicatum*	Zingiberaceae	Rhizome	α-Glucosidase inhibition and antihyperglycemic	[15]
81	*Helicteres igora*	Sterculiaceae	Bark	Antihyperglycemiv and antiperoxidative	[104]
82	*Helleborus purpurascens*	Ranunculaceae	Leaves, bark	Antidiabetic	[105]
83	*Hypericum perforatum*	Hypericaceae	Leaves	Antidiabetic and antinociceptive	[106]
84	*Jatropha curcus*	Euphorbiaceae	Leaves	Ameliorate the dearrangment in lipid metabolism in diabetes	[41]
85	*Juniiperus oxycedrus*	Cupressaceae	Fruit/leaves	Hypoglycemic and antidiabetic	[107]
86	*Kielmeyera coriacea*	Calophyllaceae	Stem/bark	α-Amylase inhibition	[55]
87	*Lagenaria siceraria*	Cucurbitaceae	Fruit	Antioxidant and antihyperglycemic	[63]
89	*Lantana camara*	Verbenaceae	Leaves	Antidiabetic	[3]
90	*Levisticum officinale*	Apiaceae	Root	α-Glucosidase inhibition	[46]

Continued

91	*Ligusticum chuanxiong*	Apiaceae	Aerial part	Reduce kidney damage caused by diabetes	[108]
92	*Liriope spicata*	Liliaceae	Root	Antidiabetic	[3]
93	*Lithocarpus polystachyus*	Fagaceae	Leaves	α-Amylase, α-Glucosidase inhibition and Hypoglycemic	[109,110]
94	*Lpomoea batatas*	Convolvulaceae	Whole plant	Antihyperglycemic	[97]
95	*Luffa acutangula*	Cucurbitaceae	Fruit	Antioxidant and antihyperglycemic	[63]
96	*Malmea depressa*	Annonaceae	Root	Block hepatic glucose production (gluconeogenesis)	[111, 112]
97	*Mangifera indica*	Anacardiaceae	Stem bark/leaves	Antihyperglycemic	[14]
98	*Marrubium vulgare*	Lamiaceae	Leaves	Antihyperglycemic and dyslipidemia effect	[113]
99	*Mimosa pudica*	Fabaceae	Whole pant	Antihyperglycemic	[50]
100	*Momordica charantia*	Cucurbitaceae	Fruit	Hypoglycemic effect, Antidiabetic effect	[3,114-117]
101	*Morinda cetrifolia*	Rubiaceae	Leaves	Antioxidant and anticancerous activity	[44]
102	*Morus alba Morus nigra*	Moraceae	Whole plant	α-Amylase inhibition, α-Glucosidase inhibition antihyperglycemic and antioxidant	[118-120]
103	*Mucuna pruriens*	Fabaceae	Seed	Hypoglycemic	[121]
104	*Murraya koenigii*	Rutaceae	Leaves	Antioxidant and renal pain disorder among diabetes	[122]
106	*Nephelium lappaceumrin*	Magnoliopsida	Peel	α-Amylase, α-Glucosidase inhibition and antihyperglycemic	[123,124]
107	*Nervilia plicata*	Orchiaceae	Stem	Antidiabetic	[125]
108	*Nymphaea stellata*	Nymphaeaceae	Flower	α-Glucosidase inhibition	[126]
109	*Ocimum sanctum*	Labiatae	Whole plant	Antioxidant, anti cataract activity, ameliorate the derangement in lipid metabolism in diabetics and antidiabetic	[41,44,127]
110	*Olea europaea*	Oleaceae	Whole plant	Antidiabetic	[76]
111	*Ophiopogon japonicas*	Asparagaceae	Whole plant	Hypoglycemic, antiischemic and reduce insulin resistance	[128]
112	*Opuntia humifusa Opuntia dillenii*	Cactaceae	Stem, aerial part	Hypoglycemic and hypolipidemic	[129,130]
113	*Opuntia streptacantha*	Cactaceae	Leaves	Antihyperglycemic	[131]
114	*Palo fierro*	Fabaceae	Seed	α-Amylase inhibition	[132]
115	*Panax ginseng*	Araliaceae	Root	Increase plasma insulin level	[12,33,133-135]
116	*Panax quinquefolius*	Araliaceae	Bark	Hypoglycemic	[136]
117	*Parinari excelsa*	Chrysobalanaceae	Bark	Antidiabetic	[3]
118	*Peltophorum pterocarpum*	Fabaceae	Leaves/bark	α-Amylase, α-Glucosidase inhibition, aldose reductase inhibition, antioxidant and antiglycemic.	[137]
119	*Phyllanthus amarus*	Phyllanthaceae	Whole plant	Antidiabetic	[3,138]

Continued

120	*Pilea microphylla*	Urticaceae	Leaves	Antihyperlipidemic and antioxidant	[139]
121	*Pimpinella tirupatiensis*	Apiaceae	Tuberous root	Repress oxidative stress induced by diabetes	[140]
122	*Pine*	Pinaceae	Pine bark	A-Amylase and α-Glucosidase inhibition	[141]
123	*Pistacia vera*	anacardiaceae	Fruits hull	A-Glucosidase inhibition	[46]
124	*Pongamia pinnata*	Fabaceae	Seed/flower	Antioxidant, β-carotene degradation, α-Amylase and α-Glucosidase inhibition	[22,142]
125	*Portulaca oleracea*	Portulacaceae	Seed	Hypoglycemic, hypolipidaemic and reduce insulin resistance	[143]
126	*Prosopis glandulosa*	Fabaceae	Leaves	Increase insulin secretion	[144]
127	*Prunus amygdalus*	Rosaceae	Seed	Antidiabetic	[3]
128	*Psidium guajava*	Myrtaceae	Leaves	Relief in cardiovascular complication associated with diabetes and α-Amylase inhibition	[9,145]
129	*Psoralea corlifolia*	Fabaceae	Leaves	Antioxidant	[44]
130	*Pterocarpus santalinus*, *Pterocarpus marsupism*	Fabaceae	Bark/wood bark/leaves	Hypoglycemic, improve hyperlipidema, antihyperglycemic and prevent mucosal ulceration	[34,146-148]
131	*Pueraria lobata*	Fabaceae	Root	Antidiabetic, α-Amylase and α-Glucosidase inhibition	[56,149]
132	*Pumpkin*	Cucurbitaceae	Fruit/seed	Hypoglycemic	[150,151]
133	*Punica granatum*	Lythraceae	Fruit	Antidiabetic	[3]
134	*Rauwolfia serpentine*	Apocyanaceae	Leaves	Hypoglycemic	[50]
135	*Rheum emodi wall ex.*	Polygonaceae	Rhizome	α-Glucosidase inhibition	[152]
136	*Rhus verniciflua*	Anacardiaceae	Stem	α-Glucosidase inhibition	[10]
137	*Ricinus communis*	Euphorbiaceae	Root	Antidiabetic	[3]
138	*Ramulus cinnamomi*	lauraceae	Aerial part	α-Glucosidase inhibition	[56]
139	*Rosa damascene*	Rosaceae	floret	α-Glucosidase inhibition	[46]
140	*Rosmarinus officinalis*	Lamiaceae	Aerial part	Antidiabetic and α-Glucosidase inhibition	[46,76]
141	*Rumex patientia*	Polygonaceae	Seed	Antihyperglycemic and antihyperlipidemia	[153]
142	*Salacia reticulate*, *Salacia oblonga wall*	Celastraceae	Leaves/root bark	α-Glucosidase inhibition, Antidiabetic	[3,154]
143	*Salvadora persica*	Salvadoraceae	wood	α-Glucosidase inhibition	[46]
144	*Sanguisorba minor*	Rosaceae	Aerial part	α-Glucosidase inhibition	[46]
145	*Sarcopoterium spinosum*	Rosaceae	Root	Antidiabetic	[3]
146	*Selaginella tamariscina*	Selaginellaceae	Aerial part	Antihyperglycemic and antihyperlipidemia	[155]
147	*Sechium edule*	Cucurbitaceae	Fruit	Antioxidant and hyperglycemic	[63]
148	*Silybum marianum*	Asteraceae	Whole plant	Antihyperglycemic	[97]

Continued

149	*Smallanthus sonchifolius*	Asteraceae	Root/leaves	Hypolipidemic, antidiabetic	[3,156]
150	*Solanum melongena*	Solanaceae	Fruit	Antioxidant and hyperglycemic	[63]
151	*Solanum torvum*	Solanaceae	Fruit	Antihyperglycemic and regeneration of β-cell	[157]
152	*Sorghum*	Cereal crop	Grain	α-Amylase and α-Glucosidase inhibition	[158]
153	*Stevia rebaudiana*	Asteraceae	Leaves	Hypoglycemic	[159-161]
154	*Swertia punicea Swertia chirata*	Gentianaceae	Whole plant	Antidiabetic	[3,162]
155	*Symplocos cochinchinensis*	Symplocaceae	Leaves	Antidiabetic	[163]
156	*Syzygium cumini*	Myrtaceae	Leaves/fruit/seed/bark	α-Amylase inhibition, anti inflammatory, reduce oxidative stress and β-cell regeneration	[9,13,39,164-167]
157	*Tectona grandis*	Lamiaceae	Flower	Antidiabetic, antihyerlipidemic and antioxidant	[168]
158	*Terminalia bellerica*	Cobretaceae	Fruit	Antioxidant, α-Amylase, α-Glucosidase inhibition, promote insulin secretion, regenerate β-cells and antiglycation	[93,169]
159	*Teucrium capitatum*	Lamiaceae	Whole plant	Antidiabetes	[76]
160	*Thymus serpyllum*	Lamiaceae	Aerial part	α-Glucosidase inhibition	[46]
161	*Tinospora cordifolia*	Menispermaceae	Stem	Antioxidant, anti cataract activity, meliorate the derangement in lipid metabolism in diabetes	[41,44]
162	*Tribulus terrestris*	Zygophyllaceae	Whole plant	Antioxidant and anti cataract activity	[44]
163	*Tetracera scandens*	Dilleniaceae	Leaves	Antihyperglycemic	[170]
164	*Trichosanthes cucumerina*	Cucurbitaceae	Fruit	Antioxidant and Hypoglycemic	[63]
165	*Trigonella berythea*	Fabaceae	Whole plant	Antidiabetic	[76]
166	*Uncaria tomentosa*	Rubiaceae	Leaves/bark	Anti immune mediated diabetes	[171]
167	*Vaccinium arcto-staphylus*	Ericaceae	fruits	α-Glucosidase inhibition	[46]
168	*Vaccinium bracteatum tumb*	Ericaceae	Leaves	Hypoglycemic	[172]
169	*Verbascum kermanensis*	Scrophulariaceae	Leaves	α-Glucosidase inhibition	[46]
171	*Vernonia amygdalina*, *Vernonia anthelmintica*	Asteraceae	Aerial part/seed	Hypoglycemic and inhibition of hepatic G6pase, antidiabetic	[3,173]
172	*Vitis vinifera L.*	Vitaceae	Seed/skin	α-Amylase, α-Glucosidase inhibition and antihyperglycemic	[174,175]
173	*Zataria multiflora*	Lamiaceae	Aerial part	α-Glucosidase inhibition	[46]
174	*Zhumeria majdae*	Lamiaceae	leaves	α-Glucosidase inhibition	[46]
175	*Zingiber officinale*	Zingiberaceae	Root	Hypoglycemic and antioxidant	[176]
176	*Zizyphus spinachristi*	Rhamnaceae	Leaves	Increase insulin secretion and Hypoglycemic	[177]
177	*Zygophyllum album*	Zygophyllaceae	Leaves/root	Recovery β-cell damage and antioxidant	[178]

Table 2. List of medicinal herbs used in ayurveda having antidiabetic activity.

S. No.	Vernacular name	Botanical name	Family	Parts used
1	Adulsa	*Adhatoda vasica*	Acanthaceae	Leaves Jaswand
2	Arjunsal	*Terminella arjuna*	Comberetaceae	Dried stem
3	Aswagandha	*Withania somnifera*	Solanaceae	Root, leaves
4	Babhul	*Acacia Arabica*	Leguminaceae	Gummy exudation of stem and bark
5	Behda	*Terminalia belleric*	Combretaceae	Fruits
6	Betel nut	*Areca catechu*	Palmitaceae	Dried ripe seeds
7	Bitter gourd	*Mimordica chirantia*	Cucurbitaceae	Fresh green leaves
8	Brahmi	*Bacopa monniera*	Scrophulariaceae	Aerial parts
9	Chirait	*Swertia chirata*	Gentinaceae	Entire herbs
10	Gudmar	*Gymnema sylvestre*	Asclepidaceae	Dried leaves
11	Guggul	*Commiphora mukul*	Burseraceae	Oleo gum resin incision of stem bark
12	Gulvel	*Tinospora cardifoilia*	Menispermaceae	Stem, roots
13	Hirda	*Terminlia chebula*	Combretaceae	Fruits
14	Jambuphal	*Syzygium cumini*	Myrtaceae	Mature fruits, dried seeds
15	Jaswand	*Hibiscusrosa sinensis*	Malvaceae	Flower
16	Kutas	*Petrocarpus marsupium*	Leguminaceae	Dried Juice of plant
17	Nagarmotha	*Cyprus rotandus*	Cyperaceae	Rhizome
18	Pimli	*Piper longum*	Piperaceae	Leaves
19	Sunth	*Zingiber officinalis*	Zingiberaceae	Rhizome
20	Tagar	*Valarina wallichi*	Valerianaceae	Rhizome, stolen, root
21	Tulsi	*Ocimum sanctum*	Labiateae	Entire herbs
22	Yasti	*Glycyrrhiza glabra*	Leguminaceae	Roots, stolen

patient with Type II diabetes and free from any significant side effect [34].

6. Herbal Drugs and Its Organic Compounds for Treatment of Diabetes Mellitus

Mordern treatments (synthetic drugs) of diabetes mellitus are focused on lowering the glucose level to normal level into blood while traditional medicines/drugs/extracts are complex in nature as well as their mechanism of action. Ayurvedic formulations, often complex with several herbal-mineral ingredients, are governed by well-described pharmacological principles of preparation, compatibility and administration.

Classic texts contain descriptions of classic formulations, traditional Ayurvedic practitioners often modify them to suit the individual constitution (*prakriti*), which confers genetic predisposition toward disease and therapy response, and is vital to ensure medication safety [183]. It is very hard or laborious work to isolate and identify each and every compound found in plant extracts. However researchers find out some compounds from extract of plants and their actions are also studied. List of some plants, their isolated compounds and mechanism of action are tabled in **Table 3**.

7. Need and Importance of Herbal Medicine

As we mention above the cure of diabetes mellitus is mentioned in Ayurveda. Ayurvedic researches undertaken during the last 50 years have not been very rewarding, except for the extremely useful exercise of literary research. Further the age of synthetic drugs comes but unfortunately, after the introduction of sulfonylurea and metformin about 50 years no major lead has been obtained in the direction of proper treatment of diabetes. This is the big question mark on synthetic drugs for answering the diabetes mellitus.

Table 3. List of compounds found in herbal plants.

S. No.	Plant name (botanical)	Isolated compounds	Structure of compounds	Effects observed	Reference(s)
1	*Myrcia multiflora* DC	Myrciacitrin I to V	**Figure 1**	Aldose reductase Inhibitory activity	[179]
2	*Stephania tetrandra* S. Moore	Tetrandrine 2'-N-β-oxide	**Figure 2**	Antihyperglycemic	[180]
		Tetrandrine 2'-N-α-oxide	**Figure 2**	Antihyperglycemic	[180]
		Tetrandrine 2-N-β-oxide	**Figure 3**	Antihyperglycemic	[180]
		Fangchinoline 2'-N-α-oxide	**Figure 3**	Antihyperglycemic	[180]
		2'-N-norfangchinoline	**Figure 3**	Antihyperglycemic	[180]
		2'-N-methyltetrandrinium chloride	**Figure 3**	Antihyperglycemic	[180]
3	*Syzygium malaccense* (L.)	Casuarine 6-O-α-glucoside	**Figure 4**	α-Glucosidase inhibition	[181]
4	*Tecoma stans* (L.)	Tecomine	**Figure 5**	Insulin-mimic	[182]
		5β-hydroxyskitanthine	**Figure 5**	Insulin-mimic	[182]
		Boschniakine	**Figure 5**	Insulin-mimic	[182]

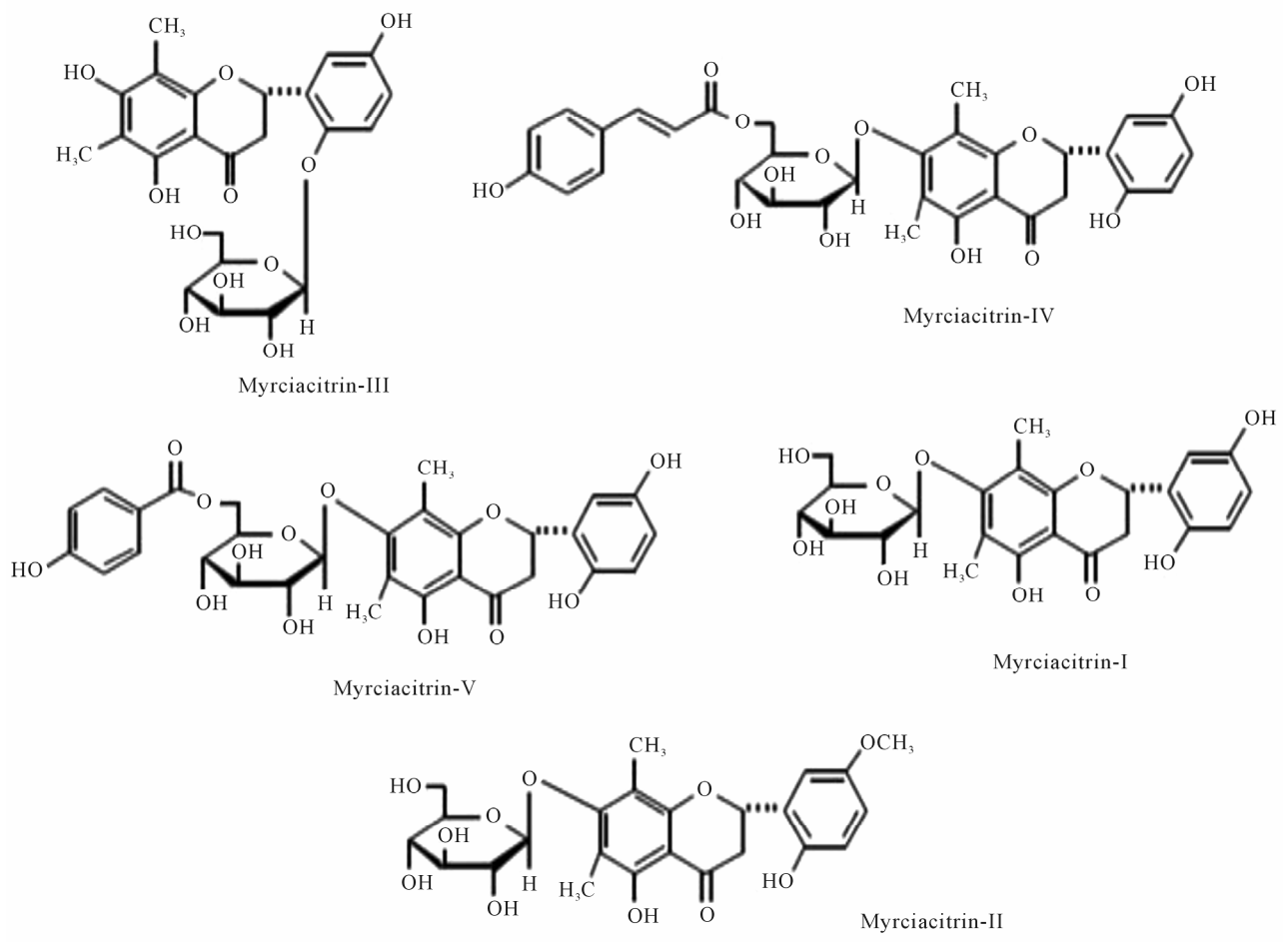


Figure 1. Representing Structure of Myrciacitrin I to V. These molecules were isolateted from *Myrcia multiflora* DC. (Myrtaceae).

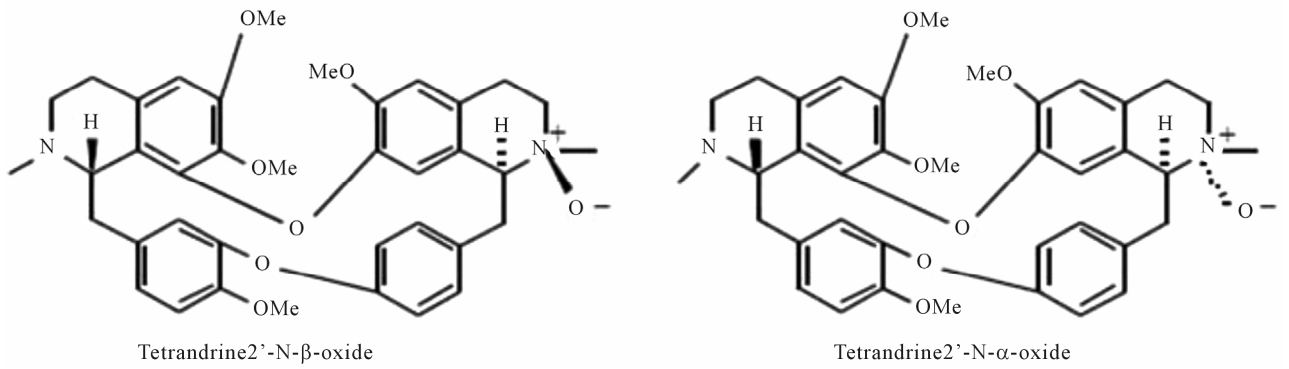


Figure 2. Representing structure of six bis-benzylisoquinoline-type alkaloids. These molecules were separated from *Stephania tetrandra* S. Moore (Menispermaceae).

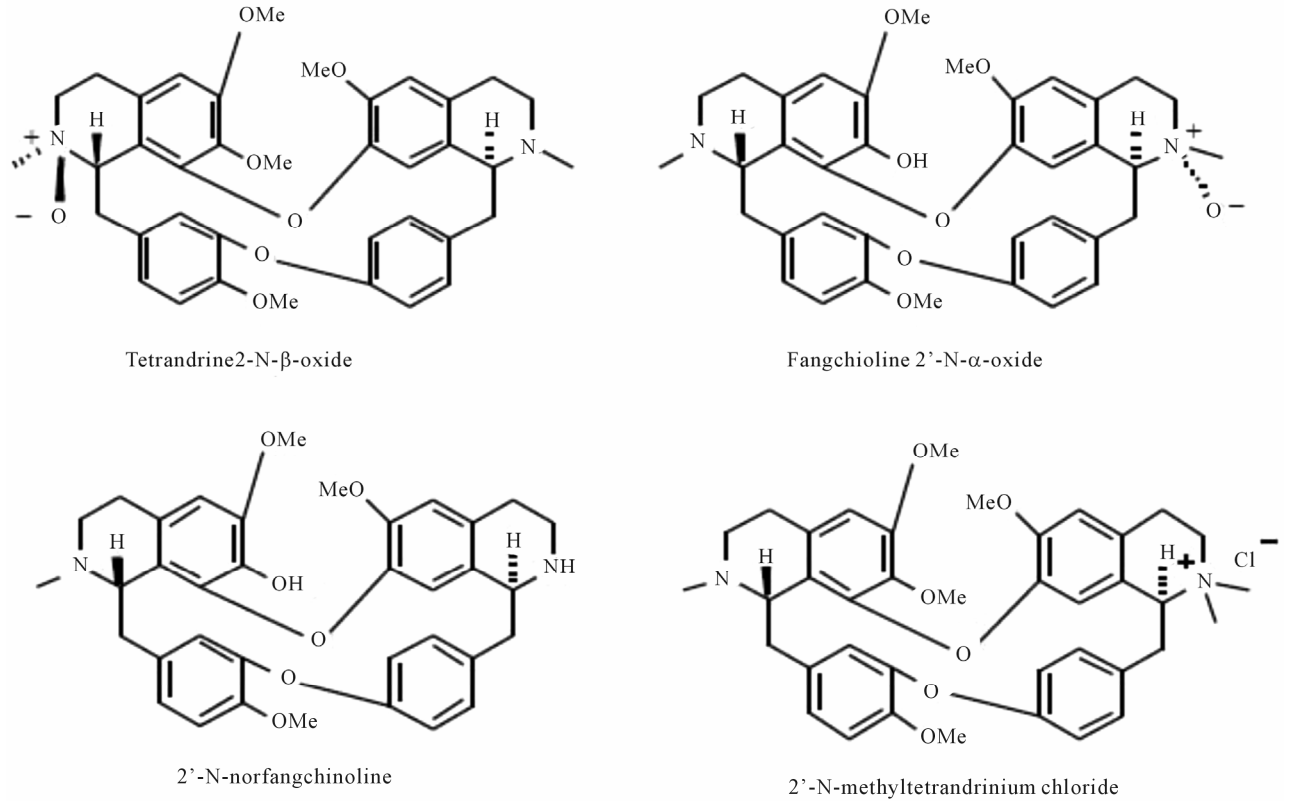


Figure 3. Representing structure of six bis-benzylisoquinoline-type alkaloids. These molecules were separated from *Stephania tetrandra* S. Moore (Menispermaceae).

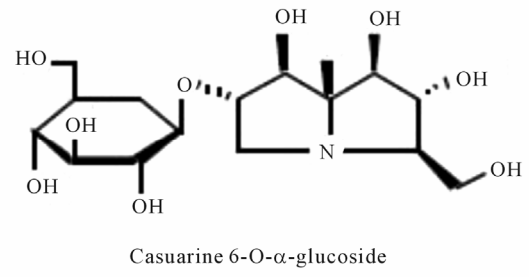
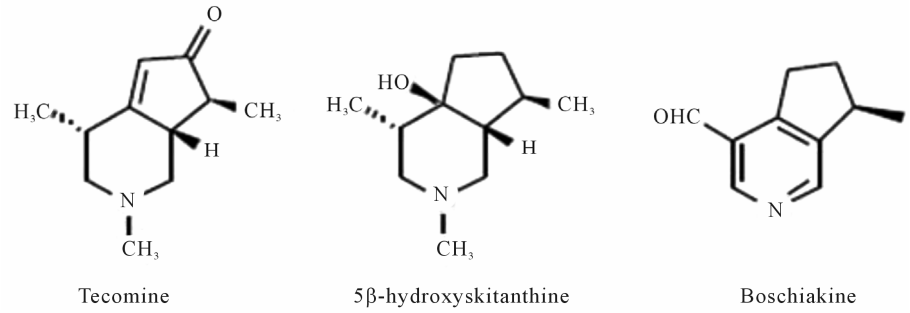


Figure 4. Representing structure of casuarine 6-O-*α*-glucoside alkaloids. This molecule was isolated from *Syzygium malaccense* (L.) Merrill & L. M. Perry (Myrtaceae).



Tecomine 5β-hydroxyskitanthine Boschiakine

Figure 5. Representing structure of molecules isolated from *Tecoma stans* (L.) Juss. Ex kunth (Bignoniaceae).

Plant extract or different folk plants preparations are being prescribed by the traditional practitioners and also accepted by the users for diabetes and other diseases in many countries especially in third world countries. Therefore, a proper scientific evaluation and searching plants by pharmacological test followed by chemical investigation is potentially necessary.

The plants drugs or extract have the marvelous efficacy to curing the diabetes and its complication without having any side effects. At present there are several Chinese traditional formulated drugs available in market but the right answer for diabetes mellitus is awaited.

According to the WHO about 65% - 80% of world population in developing counties depends on all intents and purposes on plant for their primary health care due to scarcity and lack of access to modern medicine [35]. Historically all medicinal preparation were derive from plants, whether in the simple form of plant parts or in the more complex form of crude extract mixture etc. The primary benefits of using plant-derived medicines are that they are relatively safer than synthetic alternative drug [36]. Use of ethanobotanical information in medicinal plant research has gain considerable attention in segment of the scientific community [37].

As we know that India has ancient heritage of traditional medicine. In India where 75% population belong from the remote area and more than 50% of people survives below the poverty line enthusiastically use plants for the treating the diseases. During the last few decease there has been an increasing interest in the study of medicinal plant and their traditional use in different part of India.

In the recent years numbers of reports on the use of plants in traditional healing by either tribal people or indigenous communities of India is increasing [38]. Muniappan Ayyanar *et al.* 2011 [39] conducted a study in Tirunelveli hills of Western Ghats in India and found that *Costus speciosus* smith (Costaceae), *Gymnema sylvestre* Linn (Apocynaceae) are used for treating diabetes mellitus. In this review we have concluded that plants are best sources for developing the alternative drug to curing diabetes mellitus, which has no side effects and low cost by which it is simple to a common man to be treated. There is a need of searching our traditional medicines. Some of ethanobotanical plants are listed here in **Tables 1** and **2** which has antidiabetic properties.

8. Conclusion

All drugs which we have discussed in this review have a significant in their mode of action and therapy of diabetes mellitus, in contrast of plants bioactive phyto-molecules are less known about their mode of action but there is no doubt about the role of plants to treating diabetes.

It is also important to screening the world's plant diversity extensively for more and specific bioactive phyto-molecules which are helpful in treating diabetes mellitus. On the other hand the traditional formulation of antidiabetic drugs must be researched and re-standardized by using new techniques and methods for managing the diabetes mellitus. Furthermore these drugs will be accessible to the people who are unable to purchase the costly synthetic drugs. Hence herbal drugs may be an emerging alternative of synthetic drugs to curing diabetes mellitus.

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