Review Article

Role of herbs in the amelioration of memory loss due to diabetis mellitus: A brief review

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Abstract

Present review gives emphasis on the role of herbal plant and polyherbal formulation in diabetes and associated CNS complication. Diabetes mellitus is categorized as a gathering of metabolic syndromes described via high blood sugar level (hyperglycaemia) and disturbances of carbohydrates and protein metabolism caused by deficiency of insulin release or insulin resistance or both. It is the most well-known endocrine issue and for the most part connected with high danger of delivering changes in different organs of the body, for example, kidney, liver, mind and heart. The negative impacts of diabetes on the focal sensory system have been accounted as a progression of neurochemical, neurophysiological and basic irregularities. Cognitive disturbances have likewise been perceived in diabetic patients. Diabetes additionally appears twofold the likelihood of building up Alzheimer's diseases and memory shortfalls. A few factors, for example, hyperglycaemia, expanded oxidative stress, brokenness of cholinergic framework and an irregularity in nitric oxide (NO) generation have been involved in CNS complication of diabetes. There has been expanded logical enthusiasm for therapeutic plants that have been accounted for to be utilized customarily to treat diabetes and complication in people. This is because of expanded adequacy of new plant-determined medications, developing interests in herbal medication and the presence of adverse reactions of synthetic drug. Herbal plants are useful in treatment of diabetes and associated CNS complication due to their antioxidant, antihyperglycemic and anti-inflammatory activity. Contrasted with the single herb, the polyherbal formulation has better and broadened restorative potential since it contain blend of different plant and indicated viability because of combined impact of these ingredients. In this way, present review provide information about the traditional medicinal antidiabetic plants, antidiabetic plants with CNS ameliorating effect, isolated constituents and polyherbal formulation in treatment of diabetes. And give peruses and specialists the essential ideas of understanding the neuroprotective and hypoglycemic impacts of herbal medicinal plants.

Keywords: Antidiabetic, hyperglycaemia, neuroprotective, insulin, antioxidant, anti-inflammatory

Introduction

Diabetes mellitus (DM) is ordered as a gathering of metabolic disorders described by high blood glucose level (hyperglycaemia) and aggravations of starches and protein digestion caused by insufficiency of insulin discharge or insulin resistance or both (Sharifzadeh M et al*.,* 2017; Afolayan et al*.,* 2010). It is the most well-known endocrine issue and connected with high danger of delivering changes in different organs of the body, for example, kidney, liver, brain and heart (Nishikawa et al*.,* 2000). Chronic hyperglycemia influences the focal sensory system and upgrades the likelihood of creating unsettling influences, for example, neurobehavioral changes, adjusted neuroendocrine capacities and neurotransmitter changes and hence, every one of these progressions were lead to end organ destruction (Brands et al*.,* 2004). Occurrence of each kind of diabetes shifts all through the world day by day. It was evaluated that in 2017 there are 451 million (age 18-99 years) individuals with diabetes around the world. These figures were relied upon to increment to 693 million by 2045 (Cho et al., 2018). In India, around 20 million people groups are influenced by diabetes mellitus and this figure is expected to reach to 57 million by 2025 (Arvind et al*.,* 2002; Seema et al*.,* 2014).

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Unending hyperglycemia in diabetes prompts an assortment of CNS entanglements. Neurological shortages in diabetes have been seen in both the peripheral and focal sensory system. Negative impacts of diabetes on the focal sensory system have been accounted for as a progression of neurochemical, neurophysiological and basic variations from the norm. Intellectual brokenness has likewise been perceived in diabetic patients (Tirgar et al., 2010; Sutalangka C et al., 2017). This in turn, leads to diabetic complications which may further enhance the diabetic conditions such as neurological, cardiovascular, renal and visual complications etc (Brownlee et al., 2001). In the event of diabetic patient, subjective brokenness has likewise been accounted for because of unending hyperglycaemia showed as shortfalls in learning and memory, diminished mental adaptability (Brands et al., 2007; Harten et al., 2006). Diabetic encephalopathy is also known as malfunction of brain. The complications associated with high blood glucose level include impaired spatial cognitive functions, memory loss, dementia, coma, seizures and death. Persistent high blood glucose level causes destruction of neurons (Chen et al., 2011). Chances of having Alzheimer's diseases and memory deficits are more in diabetes (Biessels et al., 2006). For example, in case of STZ induced diabetic rats cognitive impairments, memory deficits and passive avoidance learning have also been reported (Kuhad et al., 2008; Kucukatay et al., 2007). Hyperglycaemia initiated by diabetes is ordinarily connected with improved generation of free radicals and receptive oxygen species or hindered antioxidant defences in various areas of the mind (Mastrocola et al., 2005). Synthetic drugs (Table 1) such as insulin preparations, sulfonylureas, bigaunides etc. are currently available for the better management of DM. In spite of expected advancement made in the management of DM utilizing synthetic drugs, look for the natural prescription still proceeds because of antagonistic impacts of these customary medications (Mohammad et al., 2013).

Types of Diabetes Mellitus (DM)

Diabetes is classified into two major categories i.e., insulin dependent diabetes mellitus or juvenile onset IDDM (Type-1 diabetes) and non-insulin dependent diabetes mellitus or adult onset NIDDM (Type-2 diabetes). Type-1 diabetes occurs due to an autoimmune destruction of beta cells (Islets of Langerhans present in pancreas) or any other unknown reason leading to absolute decrease in insulin secretion or insulin deficiency. In this kind of diabetes, flowing insulin level is low because of immune system pulverization of beta cells by body's own imuune system. Based on etiological factor, it has been additionally arranged into immune mediated and idiopathic types. In case of immune intervened DM, cell-mediated immune system decimation of beta cells happens by antigen counter acting agent response. Though in the event of idiopathic type-1, no counter acting agent aginst beta cell has been demonstrated (Wais et al., 2012). This type of diabetes is not connected with Histocampatibility antigen and absolutely inherited. While type 2 diabetes (T2DM) occours because of insulin obstruction and by dynamic hindrance of insulin discharge by pancreatic β cells. Insulin is secreted by β-cells of pancreas to maintain normal range of glucose in the blood. Generally, both types of diabetes have similar symptoms but they vary in degree and developement. There are some basic manifestations generally connected with diabetic patients, for example, blurry visions, polydipsia (a considerable measure drinking), fatigue, polyuria (a lot urine), polyphagia (a lot eating), weight reduction etc (Bharti et al., 2018). Diabetic Ketoacidosis (body produces abundance measure of blood acids normally ketone bodies found in the blood) is the real side effect of type 1 diabetes mellitus and caused by tireless hyperglycemic state and portrayed by nausea, vomiting and abnormal state of ketone bodies in blood (Ali et al., 2011).

Table 1. Currently available synthetic antidiabetic drugs along with side effects

Class of drug	Name of drug	Adverse effects
Insulin preparations	rapid or short acting (insulin lispro, insulin aspart, semilente) Intermediate acting (lente) slow or long acting include protamine, zinc insulin, insulin glargine	Hypoglycaemia is the most common side effect of insulin glargine
Meglitinides	Repaglinide Nateglinide	Weight gain, Arthralgia Dyspepsia
Sulfonylureas	Tolbutamide, chlorpropamide Glibenclamide, glimepride	Hypoglycaemia, weight gain
Bigaunides	Metformin Phenformin	Git disturbances, kidney complications
Thiazolidinedione's	Rosiglitazone Pioglitazone	Weight gain, fluid retention
α-glucosidase inhibitors	Acarbose, miglitol	Abdominal discomfort, loose stool

Etiology and Pathogenesis of Diabetes Mellitus

Type-1 diabetes mellitus (IDDM) involves autoimmune destruction of beta cells by its own body system. Pathogenesis of type 1 involves environmental factors that may activate autoimmune destruction of beta cell (antigen-antibody reaction) in genetically susceptible individuals, resulting in deficiency in insulin secretion and hence leads to a state of hyperglycemia (Harrison et al., 1999). Pathogenesis of type 2 diabetes mellitus (NIDDM) includes both insulin obstruction and impeded insulin discharge for the most part connected with obesity because of the arrival of free unsaturated fats (FFA) and incendiary cytokines by fat tissue. Beta cell dysfunction results in impaired secretion of insulin in the body. Insullin resistance is defined as a condition in which body produces enough insulin but body tissues show resistance to the insulin action, resulting in high blood glucose level (down regulation of insulin receptor). Instabilities of lipids metabolism in the body lead to expansion of insulin resistance (Ragheb et al., 2011) as mentioned in figure 1.

Table 2. List of medicinal plants traditionally used to treat diabetes

S. No.	Name of plants	Family	Common name	Parts used
1.	*Acacia arabica* Willd.	Mimosaceae	Babul, Kikar	B
2.	*Acacia senegal* Willd.	Mimosaceae	Gum acacia, Kher	G
3.	*Aconitum ferox* Wall.	Ranunculaceae	Indian aconite	TR
4.	*Alpinia galangal* Willd.	Zingiberaceae	Blue ginger	Rh, F
5.	*Anacylus pyrethrum* Linn.	Asteraceae	Mount atlas daisy	R
6.	*Andropogen muricatus* Linn.	Poaceae	Beard grass	R
7.	*Arachis hypogaea* Linn.	Papilionaceae	Peanut	S
8.	*Benincasa cerifera* Savi.	Cucurbitaceae	Wax gourd	S, FJ
9.	*Casearia esculent* Roxb.	Samydaceae	Chinese salacia	R, B
10.	*Cassia fistula* Linn.	Caesalpiniaceae	Golden rain tree	Pu
11.	*Cephalandra indica* Linn.	Cucurbitaceae	Kundru ki bail	L, RB, F
12.	*Citrus aurantium* Linn.	Rutaceae	Bitter orange	F
13.	*Cocculus cordifolius* DC.	Menispermaceae	Moonseed	S, L, R
14.	*Eleusine coracana* Gaertn.	Poaceae	Finger millet	S
15.	*Emblica officinalis* Linn.	Euphorbiaceae	Anwla	F, L , R , S
16.	*Eriodendron afractuosum* Linn.	Bombacace	White silk cotton tree	G
17.	*Erythrina indica* Lam.	Papilionaceae	Indian coral tree	B, L, J
18.	*Eugenia jambolana* Lam.	Myrtaceae	Java plum, Black plum	F, L, S, B
19.	*Ficus bengalensis* Linn.	Moraceae	Banyan	B
20.	*Geranium wallichianum* Oliv.	Geraniaceae	Lal jari	RH
21.	*Gymnema sylvestre* Retz.	Asclepiadaceae	Gurmar	R, L
22.	*Hemidesmus indicus* Linn.	Asclepiadaceae	Indian Sarsaparilla, Anantamul	R, RB
23.	*Hydrocotyle asiatica* Linn.	Umbelliferae	Indian Pennywort	WP, L, F
24.	*Juneperus communi* Linn.	Coniferae	Juniper	F
25.	*Linaria cirrhosa* Linn.	Scrophulariaceae	Toadflax	WP
26.	*Linaria ramosissima* Wall.	Scrophulariaceae	Linaria	WP
27.	*Melia azadirachta* Linn.	Meliaceae	China berry tree	WP, RB, L
28.	*Musa sapientum* var.syalvesteris.	Musaceae	Banana	F, L, S
29.	*Nymphaea lotus* Linn.	Nymphaeceae	Blue lotus	S, F
30.	*Orchis mascula* Linn.	Orchidaceae	Orchis	RP
31.	*Oryza sativa* Linn.	Gramineae	Rice	WP
32.	*Pandanus adoratissimus* Willd.	Pandanaceae	Kewda	R
33.	*Papaver somniferum* Linn.	Papaveraceae	Opium poppy	C, P, S
34.	*Phaseolus roxburgii* Linn.	Papilionaceae	Vigna mango	WP
35.	*Phyllanthus niruri* Linn.	Phyllanthaceae	Gale of the wind	WP
36.	*Physalis alkekenji* Linn.	Solanaceae	Strawberry groundcherry	WP
37.	*Prunus amygdalus* Baill.	Rosaceae	Sweet almond	S
38.	*Psidium guyava* Linn.	Myrtaceae	Guava	B, F, L
39.	*Rourea santaloides* Gaertn.	Connaraceae	Vardhara Mool	R
40.	*Striga orboanchoides* Benth.	Scrophulariaceae	Witchweed	R
41.	*Terminalia chebula* Retz.	Comberetaceae	Myrobalan	F
42.	*Tribulus terrestris* Linn.	Zygophyllaceae	Bindii	F, R, WP

Table 2. Continue.....

S. No.	Name of plants	Family	Common name	Parts used
43.	*Trigonella foenum graecum* Linn	Papilionaceae	Fenugreek	S, L
44.	*Vitis vinifera* Linn	Vitaceae	Grape vine	F, L
45.	*Tinospora cordifolia* Willd.	Menispermaceae	guduchi, giloy	SJ
46.	*Ceiba pentandra* Linn.	Bombaceae	kapok, white silk cotton tree	R
47.	*Boswellia serrata* Roxb.	Burseraceae	Indian Olibanum	G
48.	*Sesbania aegyptiaca* Pers.	Leguminosae	Sesbania	R
49.	*Pongamia glabra* Vent.	Leguminosae	Karanj	F
50.	*Cassia sophera* Linn.	Fabaceae	Kasaundi	B
51.	*Cassia auriculata* Linn.	Fabaceae	Matura tea tree	F
52.	*Cassia glauca* Linn.	Fabaceae	Cassia glauca	B, L
53.	*Acacia arabica* Willd.	Fabaceae	Babool	L, G
54.	*Acacia Senegal* Willd.	Fabaceae	Gum acacia Kher	G
55.	*Pithecellobium bigeminum* Linn	Fabaceae	Kalitiya	S
56.	*Rhizophora mucronata* Lam.	Rhizophoraceae	Red mangrove	B
57.	*Kandelia* rheedii Linn.	Rhizophoraceae	Pisang pisang	B
58.	*Eugenia jambolana* Linn.	Myrtaceae	Java plum	S
59.	*Casearia esculenta* Roxb.	Salicaceae	Saptrangi	R
60.	*Coccina indica*	Cucurbtaceae	Baby watermelon	WP
61.	*Jasminum officanale* Linn.	Oleaceae	Jasmine	F
62.	*Strychnos potaorum* Linn.	Loganiaceae	Clearning nut tree	F, S
63.	*Premna integrifolia* Linn.	Verbenaceae	Agia, Arni	R
64.	*Actinodaphne hookeri* Meissn.	Lauraceae	Pisa	L
65.	*Ficus bengalensis* Linn.	Moraceae	Bar	B
66.	*Ficus glomerata* Roxb.	Moraceae	Cluster fig tree	R
67.	Alpinia galangal Roxb.	Zingiberaceae	Thai ginger	Rh
68.	*Musa sapientum* Linn.	Musaceae	Banana	R, F
69.	*Borassus flabellifer* Linn.	Arecaceae	Palm tree	WP

Abbreviation used: Type of part used: Rh-Rhizome; SB-Stem bark; B-Bark; L-Leaves; S-Seeds; R-Root; WP-Whole plant; F-fruit; ST-Stem; Po-Pods; P-Petals; C-Capsules; TR-Tuberous Root; RJ-Root juice; FJ-Fruit Juice; RB-Root bark; Pu- Pulp; G-Gum

Despite appreciable progress made in the management of DM using synthetic drugs, search for the herbal medicine still continues due to adverse effects of these conventional drugs. Synthetic drugs (Table 1) such as insulin preparations, sulfonylureas, bigaunides etc. are currently available for the better management of DM (Mohammad et al., 2013). Treatment of diabetes and related intricacies is more troublesome because of the absence of medications with security and viability. Despite the fact that a few medications are not capable for managed clinical, biochemical and histological fix. Unexpectedly, the herbal drugs and plant based pharmaceutical have developed broad significance around the world, for the most part because of higher security, less number of antagonistic impacts, effective cost and consistent blood glucose lowering capacity and also shown effectiveness in treatment of diabetes related complications (Modak et al., 2007). Hence, in the developed countries, use of herbal drugs and plant based formulations has been increased due to the beneficial effect of these preparations in comparision with synthetic drugs (Seyed et al., 2015). Bioactive consistuents of herbal drugs such as alkaloids, peptidoglycan, glycosides, steroids, glycopeptides, terpenoides, amino acid, guinindine and inorganic ions etc. have also gained effectiveness in the treatment of DM and associated complications. According to ethno-botanical survey, there are about 800 plants which have shown antidiabetic potential. Bioactive consistuents of natural medications, for example, alkaloids, peptidoglycan, glycosides, steroids, glycopeptides, terpenoides, amino acid, guinindine and inorganic particles and so on have additionally picked up adequacy in the treatment of DM and related complications. As per ethno-plant study, there are around 800 plants which have demonstrated antidiabetic potential. Thus, many plants and plants based medicines alone and in combination have been used for diabetes and its management (Alarcon et al., 1998). Medicinal plants used in treatment of diabetes and antidiabetic plants ameliorating CNS functions have been listed in table 2 (Kiritikar et al., 1991; Nandkarni et al., 1976).

Plants with Antidiabetic and CNS activity

***Zingiber officinale* Rosace [ZO]**

ZO is commonly known as Ginger; belonging to family Zingiberaceae. Ginger and its active constituent such as gingerol also exhibit hypoglycaemic effect and play a significant role in controlling of diabetes related complications (Wattanathorn et al., 2011). A study on antidiabetic activity showed that administration of ethanolic

extract of ginger by oral route at a dose of 200 mg/kg significantly decreased fasting blood glucose, cholesterol, triglycerides level in STZ induced diabetic rats (Bhandari et al., 2005). In another study it has been investigated that ginger (500 mg/kg/day) showed neuroprotective effect in the brain of streptozotocin induced diabetic rats via reducing oxidative stress and reducing AChE expression (EL- Akabawy et al., 2014). Recent evidence shows that ginger has neuroprotective effect by increasing brain antioxidant level and reducing the malondialdehyde (MDA) level. In case of diabetic rats, a marked decrease in activities of antioxidant enzymes such as catalase (CAT), glutathione reductase (GR), reduced glutathione (GSH), superoxide dismutase were observed. These results provide signal for the neuroprotective effect of ginger on CNS and in treatment of diabetes related central nervous system complications (Kondeti et al., 2011).

***Embelica officinalis* Linn. [EO]**

Embelica officinalis Linn. (Euphorbiaceae) is commonly known as Indian Gooseberry or Amla. The plant parts such as fruits, roots and leaves are commonly used as important herbal medicines in Unani and Ayurvedic system of medicines. Various studies showed that fruit of EO have potent antioxidant, anti-inflammatory, hepatoprotective and antiulcer property. It is also used as stimulant for the brain in Unani system of medicine. It is the main ingredient of chyawanprash that affords protection to brain and increases coordination and memory (Vasudevan et al., 2007). Earlier study demonstrated that upon oral administration of hydro-methanolic leaves extract in STZ induced diabetic rats, hypoglycaemic effect was observed on various doses (100-400 mg/kg b.w.). The extract also helps in inhibition of diabetic complications by its antioxidant potential (Nain et al., 2012). It has also been studied that EO and its active constituents such as gallic acid, ellagic acid possess antidiabetic effect and avoid diabetic complications through their antioxidant, free radical scavenging potential (Tirgar et al., 2010).

***Cyperus rotundus* Linn. [CR]**

A study showed that *Cyperus rotundus* Linn. (Cyperaceae) exhibits neuroprotective and cognitive enhancing effects. Its chemical constituent such as quercetin, tannins, starch, gallic acid and p-coumaric acid are reported to produce antioxidant, neuroprotective, anticholinesterase activity (AchEI) and memory enhancing effect (Kilani et al., 2014). It has also been explored that administration of ethanolic extract of CR rhizomes at doses of 250 and 500 mg/kg b.w. possess antidiabetic activity (Sutalangka et al., 2017).

***Alpinia galangal* Willd. [AG]**

Alpinia galangal [AG] belonging to family Zingiberaceae, is commonly known as Blue ginger. Prior examination reveales that AG indicates neuroprotective impact by diminishing free radicals generation and expanding action of antioxidant enzymes on odministration of extract at 200 and 400 mg/kg for 14 (Hanish et al., 2011). Methanol and aqueous extracts of AG rhizome significantly reduce the blood glucose levels (Akhtar et al., 2002). Further, oral administration of methanol concentrate of AG (200 and 400 mg/kg) in Streptozotocin induced diabetic rats was compelling in controlling blood glucose levels and advancement lipid profile in diabetic rats (Verma et al., 2015).

***Terminalia Chebula* Retz. [TC]**

Terminalia Chebula Retz. (Comberetaceae) is commonly known as myrobalan. Active constituent (chebulic acid) from the fruit of TC exhibits antihyperglycemic effect on oral administration at a dose of 100 mg/kg b.w. (Huang et al., 2012). It has also been explored that hydro-alcoholic fruit extract of TC at a dose of (250, 500 and 1000 mg/kg) in wistar rats, exhibits antioxidant, anticonvulsant and protective effect against cognitive impairment (Kumar et al., 2018).

***Mangifera indica* Linn. (MI)**

Mangifera indica (Anacardiaceae) is commonly known as mango. Its fruit extract upon oral administration in male wistar rats (180-200 g) at various doses 15, 50 and 200 mg/kg b.w. exhibited protective effect against mild cognitive impairments. Oxidative stress also play important role in pathology of cognitive impairement. Thus, result gives suggestion for the potential protective effect against oxidative stress which in turn improves memory (Areekul et al., 2014). It has also been inspected that MI exhibits antidiabetic effect in STZ induced diabetic rats due to presence of flavonoids and phenolic acid (Irondi et al., 2016).

***Centella asiatica* Linn. [CA]**

CA (Umbelliferae) is most commonly known as Indian pennywort. Recent, study reveales that its active constituent (asiatic acid) possesses neuroprotective effect in aluminium chloride induced rat model of Alzheimer's diseases (Ahmad et al., 2018). It has also been used for the enhancement of memory and intellectual function from ancient times. A study recommends that water extract from the plant exhibits neuroprotective effect in cognitive impairment in rat model of Alzheimer's diseases (Defillipo et al., 2012). It has also been reported that CA extract possesses defence to the hippocampus against diabetic induced dysfunction which may further support in enhancement of memory (Giribabu et al., 2014).

***Punica granatum* Linn. [PG]**

Punica grantum Linn. (Lythraceae) is commonly known as Anar. It has been investigated that pomegrante flower recovers learning and memory in STZ induced diabetic rats by reducing oxidative stress due to its antioxidant activity. PG flower supplementation expressively decreases oxidative stress,

glutathione (GSH) content, glial-fibrilan acidic protein. When administered at doses of (300, 400 and 500 mg/kg/day) in STZ induced diabetic rats, it showed improvement in learning and memory. Thus, results show that PG administration may be significantly useful in treating learning and memory deficit in diabetic patients (Combay et al*.,* 2011).

***Calendula officinalis* Linn. [CO]**

Calendula officinalis Linn. (Asteraceae) is regularly known as normal marigold. It has been accounted for that oral administration of hydro alcoholic concentrate of CO at a measurement of 300 mg/kg essentially enhances learning and memory in STZ induced diabetic rats. CO extract has significant antioxidant, anticholinergic and antidiabetic activities (Mordkhani et *al.,* 2015).

***Glycyrrhiza glabra*l Linn. [GG]**

GG belonging to family Leguminosae is known as Liquorice. Early study, reveals that glabridin, a major active flavonoids in GG at different dose levels (5, 25 and 50 mg/kg, p.o) improves learning and memory dysfunction in STZ induced diabetic rats. GG possesses antioxidant, neuroprotective and anticholinesterase effects that may be responsible for amending effect in learning and memory impairments (Hasanein et al., 2011).

There are wide ranges of herbal plants that have been utilised for the diabetic treatment. Various herbal plants have been explored with reported antidiabetic activity (as mentioned in table 4).

Marketed herbal formulation

Many herbal formulations (as mentioned in Table 5) available in the market are used for the effective treatment of diabetes such as diabecon, diabeta, epiinsuluin, gurmar powder and Chandraprabha vati etc (Modak et al., 2007; Suresh et al., 1995).

(i) Diabecon is an herbal formulation manufactured by Himalaya, it contains combination of many Indian herbs and plants such as *Gymnema sylvestre, Glycyrrhiza glabra, Asparagus racemosus, Tinospora Cardifolia, Aloe Vera, Curcuma longa, Momordica charantia, Piper nigrum, Triphala, and Phyllanthus amarus* etc. Diabecon demonstrated its antidiabetic action by means of expanding peripheral usage of glucose, hepatic and muscle glucagon substance, additionally advance beta cells recovery and increment C-peptide level. It has been reported that diabecon protects beta cell from oxidative stress reaction via its antioxidant potential. It produces insulin like action by decreasing the glycated haemoglobin levels, and modifies the fatty acid profile. Hence, it reduces the long term effect of diabeties and its complications. Some of these plants have also been traditionally used in memory improvement (Modak et al., 2007).

(ii) Diabeta is also well known marketed herbal formulation available in the capsule form manufactured by Sanofi-Aventis. It contains many ingredients such as *Curcuma longa, Momordica chirantia, Acacia Arabica, Tinospora cardifolia, Zingiber officinale* etc. It is used as an antidiabetic drug, as well as also also correct the deteriorating complications associated with diabetes mellitus. It is safe and effective in controlling of DM and associated complications and had shown fewer side effects in comparision of synthetic antidiabetic drugs. It is effective in controlling of blood glucose level via acting different sites and pathways that act as activator of diabetic condition. *Zingiber officinale* belonging to family Zingiberaceae has been explored for its neuroprotective effect in STZ induced diabetic rats (Modak et al*.,* 2007).

(iii) Epinsulin is an Ayurvedic marketed herbal formulation manufactured by Swastik formulations, contains epicatechin, an active constituent. Epicatechin act as an insulin enhancer via increasing the cAMP content of the Islets of Langerhans present in pancreas. It acts via increasing cathepsin activity which in turn enhances insulin secretion by converting proinsulin to insulin. Additionally it has been reported that it also possesses neuroprotective effect and correct diabetic complications such as retinopathy and disturbed metabolism of glucose and lipids. Hence, it is useful in treatment of diabetes and associated complications (Modak et al., 2007).

(iv) Gurmar powder is also a well known Herabl antidiabetic drug, manufactured by Garry and Sun Pharmaceuticals. It helps in reducing blood glucose level via decreasing the intestinal absorption of sacharides, also maintain metabolic activities of liver, kidney.It act as an insulin secretion enhancer and prevent hyperglycemic state (Modak et al., 2007).

(v) Chandraprabha vati (CPV) is an Ayurvedic formulation available in classical Vati form. It contains 37 herbomineral ingredients. The ingredients like *Acorus calamus, Cyperus rotundus, Tinospora cordiofoli, Curcuma longa, Berberis aristata, Piper longum, Coriandrum sativum, Terminalia chebula, Terminalia belerica, Embelica officinalis, Zingiber officinale, Piper nigrum* and so on have been assessed for their antidiabetic and memory upgrading impacts in a few animals considers by means of alloxon model. It acts by means of lessening blood glucose and lipid profile (Wanjari et *al.,* 2016)**.**

Isolated constituents having antidiabetic potential

There are wide varities of phytoconstituents valuable in treatment of diabetes. These incorporate alkaloids, glycosides, peptidoglycan, hypo-glycan, steroids, guanidine, glycopeptides, terpenoides, amino acids and inorganic particles. Chemical structure of isolated constituents having antidiabetic activity has been shown in figure 1.

Mangiferin is an active constituent isolated from

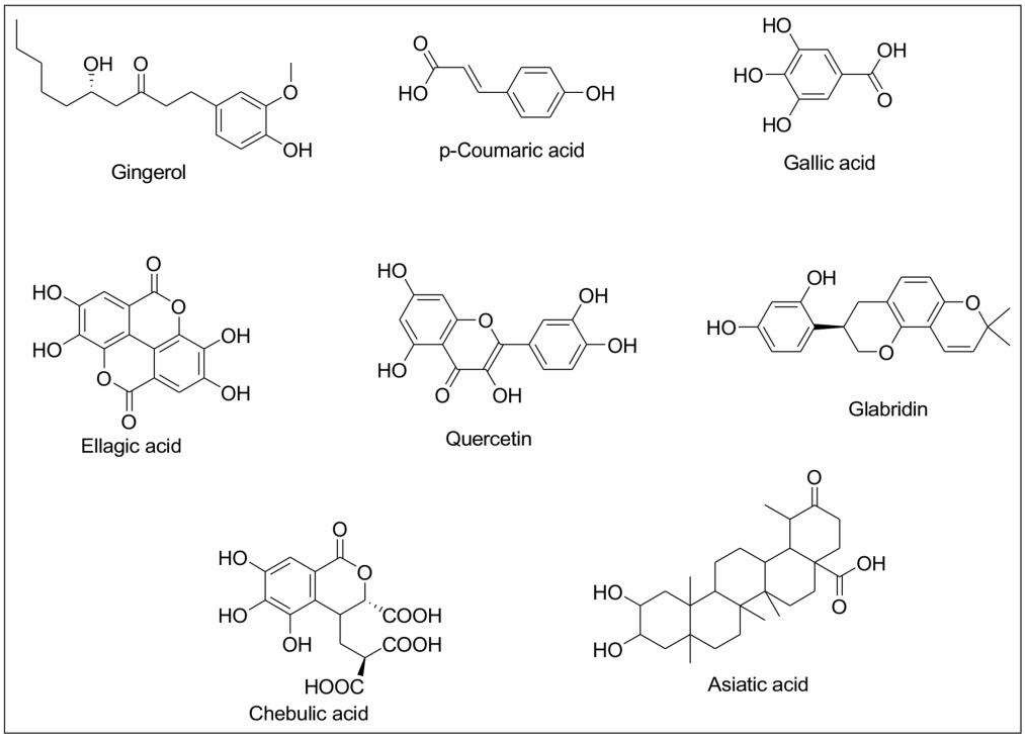

Figure 1. Chemical structure of isolated constituents having antidiabetic activity

Anemarrhena asphodeloides (Asparagacea). It showed significant antidiabetic activity after oral administration at a dose level of 30 mg/kg b.w for 3 weeks in KK-Ay mice. It showed significant reduction in blood glucose level and prevent hyperglycemic state in case of diabetic rats. It also showed significant improvement in hyperinsulinemia when subjected to insulin tolerance test (Miuri et al., 2001).

Stevioside is an active constituent isolated from the leaves of *Stevia rebaudiana* Bertoni (Asteraceae). Stevioside showed significant decrease in blood glucose level and act as insulin secretogoges by enhancing insulin secretion in the body and also inhibit the secretion of glucagon hormone. Stevioside at a dose of 0.2 g/kg b.w. indicated antihyperglycaemic, insulinotropic, and glucagonostatic activities in diabetic Goto-Kakizaki (GK) rats. Hence, stevioside possesses significant antihyperglycaemic, insulinotropic activity (Jeppesen et al., 2002).

Mycaminose is also an active moiety of *Syzygium cumini* which is commonly known as jamun (Myrtaceae). It has been investigated that mycaminose showed significant antidaibetic activity after oral administration at a dose of 50 mg/kg b.w for 15 days in STZ induced diabetic rats. It posseses significant antidiabetic activity by enhancing insulin secretion from the beta cell of pancreas (Kumar et al., 2008).

Ficanone is an active principal isolated from the bark of Ficus *arnottiana* which is commonly known as Indian Rock Pig (Moraceae). It has been investigated that significant reduction in fasting blood glucose level was found upon oral administration of metanolic, ethanolic extract of ficanone at a dose level of 50 mg/kg for 21 days. Ficanone posseses antidiabetic and antioxidant activity by reducing fasting blood glucose and significantly reduced glutathione, catalase and superoxide dismutase level. Histopathological study also showed significant increase in beta cell mass (Mazumder et al*.,* 2008).

Subcoriacin (3-aryl-6-prenylcoumarin) is also an active constituent isolated from the plant *Eysenhardita subcoriacea* (Leguminosae). It has been investigated that Subcoriacin shows significant antidiabetic and antioxidant activity after 5 days treatment at a dose level of 100 mg/kg by intraperitonial route in STZ treated diabetic rats. It showed significant decrease in blood glucose level and increase activities of antioxidant enzyme suc as superoxide dismutase (SOD) and catalase (CAT) etc (Mastache et al., 2010).

Thymoquinone is an isolated constituent of plant *Nigella sativa* (Ranculaceae). It showed significant antidiabetic and antioxidant activity at doses (2.5 and 5 mg/kg) by intraperitonial route in STZ induced diabetic rats. It showed significant improvement in spatial learning and memory by reducing oxidative stress and blood glucose level (Saheli et al., 2012; Vafee et al., 2015). Quinone constituent of plant seed *Nigella sativa* (NS) has been reported to possess beneficial effect in the treatment of diseases such as immunopotentiation, and antidiabetic and gastroprotective. Thymoquinone has been reported for its neuroprotective effect in STZ induced diabetic rats. It prevent cognitive

decline associated with diabetes mellitus by reducing oxidative stress. In another study it has also been reported that thymoquinone have potential to restore the normal oxidative balance, inhibition of cholinesterase activity and mitochondrial dearrangement (Sahak et al., 2016).

Glabridin (major flavonoid) is an active constituent of *Glycyrrhiza glabra* L. (Fabaceae). Glabridin has been investigated for its antidiabetic effect in STZ induced diabetic rats. Administration of glabridin at doses 25 & 50 mg/kg in STZ induced diabetic rats showed significant reduction in blood glucose, lipid profile, LDL, triglycerides, cholesterol level and improvement in body weight, HDL Level and antioxidant enzyme level (EI Ghffar et al., 2016).

Gingerol isolated constituent of *Zingiber officinale* (Zingiberaceae), was already reported to decrease blood glucose level in type 2 diabetic mice. Endocrine signaling is usually associated with insulin discharge and is irritated in db/db Type-2 diabetic mice. [6]-Gingerol increased glucose-stimulated insulin secretion and improved glucose tolerance after 4 week treatment of diabetic mice. Plasma GLP-1 was observed to be essentially elevated in the treated mice (Samad et al., 2017).

Quercetin isolated constituent of *Phyllanthus emblica* L. fruit (Phyllanthaceae). Administration of quercetin at a dose of 75 mg/kg b.w in STZ induced diabetic rats showed significant decrease 14.78% in blood glucose levels in the diabetic rats after 7 days of treatment. It showed significant improvement in profiles of triglycerides, LDL, HDL, VLDL and total cholesterol at doses of 50 and 75 mg/kg in STZ induced diabetic rats (Srinivasan et al., 2018).

Gallic acid isolated constituent present in various plants such as *Zingiber officinale*, *Punica grantum* showed significant antidiabetic and antioxidant activity in alloxon induced diabetic rats. It has been investigated that administration of gallic acid at doses of 5, 10, and 20 mg/kg b.w. for 45 days showed significant reduction in blood glucose level and increase antioxidant enzyme level in alloxon induced diabetic rats (Ramkumar et al., 2014).

Chebulic acid isolated constituent of *Terminalia chebula* Retz. (Comberetaceae). Active constituent (chebulic acid) from the fruit of *Terminalica chebula* exhibits antihyperglycemic effect on oral administration at a dose of 100 mg/kg b.w. The outcome demonstrated that the maltose-hydrolysis action was down-directed by chebulagic acid, which turned out to be a reversible inhibitor of maltase in Caco-2 cells (Huang et al., 2012).

Ellagic acid isolated constituent of Embelica officinalis Linn. (Euphorbiaceae) is commonly known as Indian Gooseberry or Amla. Administration of methanolic exract of Ellagic acid at doses 250 and 500 mg/kg b.w. showed significant decrease in fasting blood glucose level after 28 days of treatment in diabetic rats. It produces significant increase in plasma antioxidants level, Liver GSH and decrease in Liver TBARS level (Fatima et al., 2017).

Chlorogenic acid showed significant antidiabetic activity in STZ induced type 2 diabetic rats. Administration of extract of Mulberry leaves at doses 250 and 750 mg/kg b.w. showed significant dose dependent decrease in blood glucose level after 11 days. Chlorogenic acid showed significant antidiabetic activity in type 2 diabetic rats.

Valoneic acid dilactone isolated constituent of *Punica grantum* Linn. (Lythraceae) showed significant antidiabetic activity in alloxon induced diabetic model of rats. Oral administartion of valoneic acid dilactone at doses of 10, 25 and 50 mg/kg showed significant dose dependent decrease in blood glucose level in alloxon induced diabetic rats (Jain et al., 2012).

Coagulanolide, a withanolide isolated from *Withania coagulans* fruits and showed significant antidiabetic activity by inhibiting postprandial increase in blood glucose level and significant inhibitin of post-sucrose load in normal rats as well as STZ induced diabetic rats (Mayur et al., 2008).

Conflicts of interest: Not declared.

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