REVIEW ARTICLE

Effective use of Phytotherapy in the Management of Diabetes by Plant-based Medicine: A Review

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ABSTRACT

Objective: Herb-based restorative items have been recognized since prehistoric times, and a few therapeutic herbs and their active constituents were utilized for controlling diabetes in numerous people around the world. However, minimal toxicological data exist concerning conventional anti-diabetic plants. Several synthetic oral hypoglycemic agents are the essential treatment types for diabetes. As it may, apparent symptoms of similar medicament are the primary explanation behind an extended number of individuals looking for voluntary remedies that may have less severe or no reactions. This paper attempted to list the herbs with anti-diabetic and associated advantageous impacts from various parts of the world and polyherbal extractions. These herb's impacts can defer diabetic difficulties and give a more basis of antioxidants they are acknowledged for preventing/postponing diverse ailing states. The literature review was carried out in a scientific database using diabetes, anti-diabetic agents, and phytotherapy to manage diabetes by plant-based medicine as the keywords. To overcome the research gap, optimizing phytotherapy in the management of diabetes by plant-based medicine is regarded as a good target for anti-diabetic agents to design the treatment of type 2 diabetes mellitus (T2DM). Diabetes is the world's quick aborning emergent, and this disorder's information will increase similar additional acceptable therapies. Traditional plant medicines are used throughout the world for diabetes. Therefore, studying such drugs will provide the natural key to unlocking a scientist in the future.The review focused on alternative medicine to cure kinds of diabetes problems using herbal preparation.

Keywords: Diabetes mellitus (DM), Hypoglycemic and Medicinal herbs, Phytotherapy, Optimize

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INTRODUCTION.

Diabetes mellitus or hypoglycemia is a heterogeneous metabolic issue described by modifying sugar, lipid, and protein digestion by insulin insufficiency combined with insulin obstruction.[1] It is considered one of the five driving reasons for death on the planet.[2] According to WHO's report, 140 million people, are experiencing diabetes worldwide all over the world, and this figure might be multiplied continuously by 2030.[3]

According to studies, about 410 experimentally confirmed Indian medicinal plants with anti-diabetic activity, with 109 plants having the action elucidated or recorded. Hyperglycaemia happens because the yield of hepatic glucose is uncontrolled, and with reduced glycogen synthesis, glucose is decreased consumption by skeletal muscle. On the overreaching of the renal threshold's glucose reabsorption, there is a dropping of glucose into glycosuria (urine) as well as polyuria (Osmotic diuresis), resulting in polydipsia (increased drinking), dryness, and dehydration. Finally, deterioration is caused by insulin insufficiency through protein reduction and breakdown synthesis.[4,5]

Despite extensive advancement in diabetes treatment by oral hypoglycaemic agents, there is a need for more up-to-date therapeutic agents because the current engineered drugs have a few confinements.[4-7] Oral hypoglycaemic and insulin agents such as sulphonylurea and biguanides still affect the management, but there is a search for many efficient anti-diabetic agents. Natural medications with anti-diabetic action are yet to be industrially planned as present-day drugs, regardless of the point that it has been accolade for curative properties in medication's conventional frameworks.[1] Herb provided a possible source of hypoglycaemic medications

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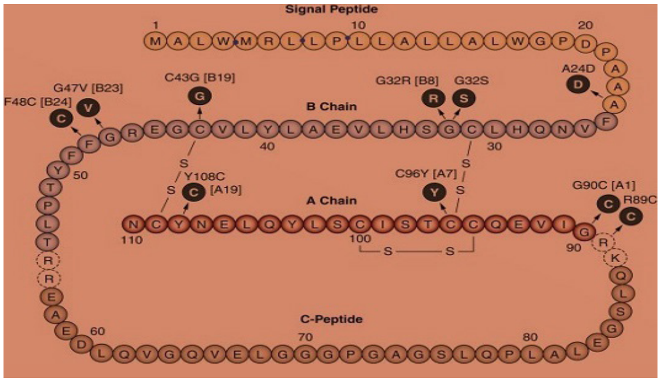
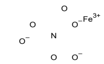
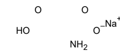
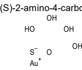
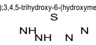
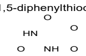
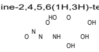


Figure 1: All forms of diabetes are affected by insulin deficiency (low insulin-flowing concentration) and a weakening of the peripheral tissues' response to insulin resistance

Figure 2: Structures of compounds

S. no.	Compound name	Structure
a	Ferric nitroacetate	 2-[bis(2-oxido-2-oxoethyl)amino]acetate iron 3+
b	Monosodium glutamate	 sodium (S)-2-amino-4-carboxybutanoate
c	Gold thioglucose	 gold(1+);3,4,5-trihydroxy-6-(hydroxymethyl)oxane-2-thiolate
d	Dithizone	 (E)-1,5-diphenylthiocarbazone
e	Alloxan	 pyrimidine-2,4,5,6(1H,3H)-tetraone
f	Streptozotocin	 1-methyl-1-nitroso-3-[(2S,3R,4R,5S,6R)-2,4,5-trihydroxy-6-(hydroxymethyl)oxan-3-yl]urea

and was utilized in diabetes treatment. Examination of many Indian plants was performed for their valuable utilization in various kinds of diabetes, and various scientific journals have also reported it.[2] The conventional therapeutic practice like Ayurveda for diabetes remedies characterizes some plants that can be used as herbal drugs. So, they play a significant part as a natural medicine because of their fewer side effects. The chemical constituents in herbal plants influence the fighting of the insulin resistance issue and regeneration of pancreatic beta cells. Furthermore, hypoglycaemic herbs inhibit intestine glucose absorption and the production of glucose from the liver, increase glucose intake by muscle tissues or adipose, and increase insulin secretion.[4]

Alternative medicine (AM) has grown in popularity in recent years, attracting many researchers worldwide.[8-11] This interest has been considered due to their apparent innocuousness; such care could be harmful to patients.[8] Alternative medicine covers all treatments or practices that are not regulated by traditional medicine. Alternative medicine is a general concept that incorporates all clinical treatments or methods that are not part of conventional medical practice.[12] They may categorize as pharmacological (herbal therapies or homeopathy), physical (acupuncture or chiropractic), nutritional (macrobiotics or vegetarianism), or cognitive (cognitive therapy/hypnosis). There is no question about it.

Phytotherapy has long been a source of medicinal drugs, and there have been many attempts over the years to use herbal medicines to cure diabetes.[13,14] Scientific reports on herbal medicine and type 2 diabetes (T2D) are continuously rising.[15] Despite an abundance of literature available, the therapeutic effect of medicinal plants is still uncertain. Furthermore, better evidence-based data is essential.[16] Indeed, despite a long history of folk medicine, most common species used are clinically inconsistent, mainly because of the low quality of clinical studies.[17] The variability of the raw herbal materials and preparations used, which can contribute to the results' non-reproducibility, is another factor to be considered.[18] This review aims to provide an overview of the use of medicinal plants

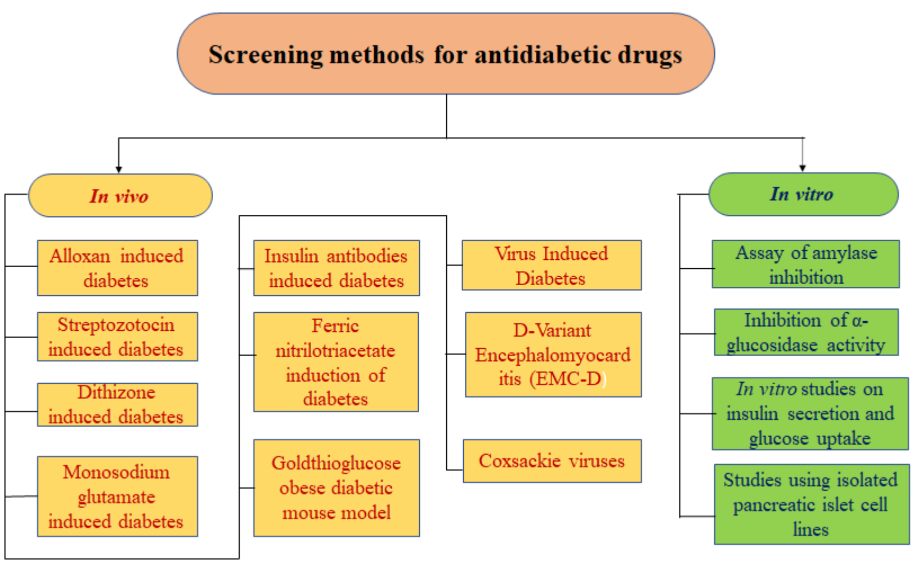


Figure 3: Screening methods of anti-diabetic agents.

Table 1: Anti-diabetic plants are conventionally believed to be efficacious in diabetes-associated complications treatment.[28]

S.no	*Complications*	*Medicinal Plants*
1	Polydipsia	*Polygonatumhumile, Polygonatummacropodum, Panax ginseng, Polygonatumofficinale*
2	Emaciation	*Allium sativum, Cichorumintybus*
3	Atherosclerosis	*Allium cepa, Allium sativum, Lyciumchinensis, Panax ginseng, Taraxacumofficinale, Trigonellafoenumgraecum*
4	Retinopathy	*Daucus carrota, Lyciumchinensis, Taraxacumofficinale, Vacciniummyrtillus*
5	Nephropathy	*Lycium chinensis*
6	Impotence	*Papaver somniferum, Panax ginseng, Crocus sativa, Coriandrum sativum, Ceiba petandra*

in diabetes management, focusing on species endorsed by authoritative documents such as World Health Organization monographs (WHO). Also, there is a focus on some of the most promising species that draw the scientific community's attention.

All forms of diabetes are affected by insulin deficiency (low insulin-flowing concentration) and a weakening of the peripheral tissues' response to insulin (Figure 1) resistance. As a result of osmotically active sugar alcohols such as sorbitol in tissues and non-enzymatically glycosylated compounds, the glucose effect on cellular metabolism is accountable.[19] Diabetes ketoacidosis is a severe complication that occurs in the absence of insulin due to a faster breakdown of fat into acetyl Coenzyme A, which in the absence of aerobic carbohydrate metabolism transforms to aceto-acetate hydroxybutyric acetone, which induces acidosis.[20]

Disorder Complications

Majority of diabetes complications are caused by tissues being exposed to high glucose levels for an extended period. Such metabolic disorientation issues arise during the consequences of diabetes, often in several years. These findings are abundant in blood vessel disorders, other small (microangiopathy) or large (microangiopathy) (macrovascular disease). In patients with diabetes, the macrovascular disease requires accelerated atheroma that is extraordinary and serious. Microangiopathy is a DM symptom affecting the retina, kidneys, and peripheral nerves. NIDDM or IDDM is a common complication of chronic nephritic failure, a significant and increasingly deteriorating complication with exorbitant costs to society and independent victims. Concurrent hypertension promotes increasing nephropathy of nephritic injury and decreases the risk of myocardial infarction.[21]

Screening Methods of Anti-diabetic Agents

Before introducing insulin and oral hypoglycaemic drugs, the most common treatment choice was the use of plants. More than four hundred plants have been proposed, and recent

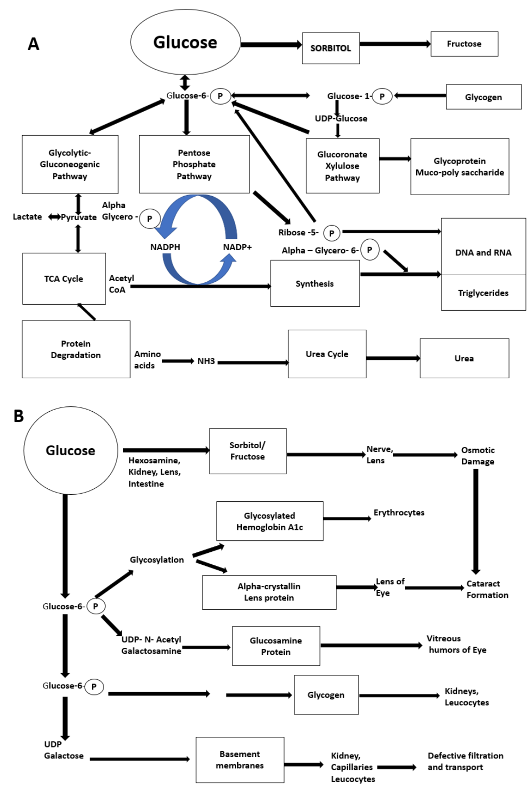


Figure 4: MOA of antidiabetic drug

research has thoroughly raised the potential worth of various treatments. The hypoglycaemic and anti-hyperglycemic effects of several plants used as anti-diabetic remedies were identified, and the mechanisms of their behaviors were also investigated. Chemical studies directing the detection, purification, and isolation of substances responsible for anti-diabetic activities are being performed in different diabetogenesis.[22-24] Alloxan and streptozotocin are the most widely used diabetogenic agents (Figure 2), and inducing experimental diabetes in rats by substantially killing pancreatic beta cells is the most convenient technique used today Screening methods of anti-diabetic agents Figure 3.

Herbal Drugs Used in the Treatment of Diabetes

Recently, in animal studies, several researchers verified many conventionally used medicinally important plants for their anti-diabetic ability. Several artificial oral hypoglycaemic agents used as a standard medical practice were extracted from natural plants, such as the plant *Galega officinalis* (Goat's Rue or French Lilae) used to produce metformin, an anti-diabetic drug.[25,26] In clinical procedures often use synthetic hypoglycaemic agents; some significant side effects have been observed, such as disruption of kidney and liver functions, coma, and hematological effects. Besides, it was recommended that they should not be used at times of pregnancy. Medicines extracted from plants are also thought of as being less hepatotoxic relative to synthetic medicines. Therefore, the active research area is known to be where more effective and safer drug agents are being searched for.

Table 2: List of reported effective anti-diabetic medicinal plants.

S. no	Crude drug name	Ref.	S.no	Crude drug name	Ref.	S.no	Crude drug name	Ref.
1	Abelmoschus moschatus Medik	[29]	17	*Artemisia herba-alba Asso*	[43]	33	*Cuminum cyminum L*	[60]
2	*AbrusprecatoriusL.*	[30]	18	*Astragalus membranaceus Bunge*	[29]	34	*Dioscorea dumetorum*	[61]
3	*Acacia arabica*	[30]	19	*Averrhoa bilimbi*	[44]	35	*Emblica officinalis*	[62]
4	*Achyranthes aspera* L	[29]	20	*Azadirachta indica*	[45]	36	*Ficus bengalensis* L	[63]
5	*Achyrocline satureioides*	[31]	21	*Barleria lupulina*	[46]	37	*Ficus hispida*	[64]
6	*Acosmium panamense* Schott.	[29]	22	*Bauhinia candicans*	[47]	38	*Gongronema latifolium*	[65]
7	*Adenanthera pavonine L*	[32]	23	*Berberis aristata*	[48]	39	*Gymnema Sylvestre*	[66]
8	*Aegle marmelos*	[32]	24	*Biden spilosa L*	[49]	40	*Helicteres isora* L	[67]
9	*Aervalanata*	[34]	25	*Biophytum sensitivum*	[50]	41	*Holostemma ada kodien*	[68]
10	*Agrimony eupatoria L.*	[35]	26	*Bixa orellana L*	[51]	42	*Jatropha curcas*	[69]
11	*Ajuga iva* L. Schreberr	[29]	27	*Boerhaavia diffusa*	[52]	43	*Lawsonia inermis*	[70]
12	*Allium cepa*	[36]	28	*Boswellia glabra*	[53]	44	*Lepidium sativum* L	[71]
13	*Allium sativum*	[37]	29	*Bougainvillea spectabillis*	[54]	45	*Momordica charantia*	[72]
14	*Alpinia galangal*	[38]	30	*Brassica nigra* (L)	[55]	46	*Nigella sativa L*	[73]
15	*Andrographis paniculate Burm*	[39]	31	*Caesalpinia bonducella*	[56]	47	*Ocimum gratissimum*	[74]
16	*Annona squamosa L*	[40]	32	*Cassia auriculata L*	[57]	48	*Ocimum sanctum* L	[2]
17	*Aporosalindleyana*	[41]	33	*Combretum lanceolatum*	[58]	49	*Ocimum canum*	[75]
18	*Artemisia dracunculus L*	[42]	34	*Coriandrum sativum L*	[59]	50	*Operculina turpethum*	[76]
51	*Origanum vulgare* L	[77]	56	*Retama raetam*	[82]	61	*Terminalia catappa*	[86]
52	*Panax ginseng*	[78]	57	*Salacia reticulate* W	[83]	62	*Tinospora cordifolia*	[87]
53	*Passiflora glandulosa* cav	[79]	58	*Syzygium cumini*	[84]	63	*Urtica dioica*	[88]
54	*Phyllanthus amarus*	[80]	59	*Talinum cuneifolium*	[85]	64	*Vinca rosea*	[89]
55	*Psidium guajava* L.	[81]	60	*Telfaria occidentalis*	[29]	65	*Zizypus jujube*	[90]

Additional sweeteners such as barley malt, honey, rice syrup, fructose (fruit sugar), and thus herbal stevia are used these days to impart natural sweetener alternatives to table sugar. Stevia is a natural sweetener that is a perfect alternative to artificial sweeteners. It is incredibly targeted, but only a small amount is used, and it has the side effects that artificial sweeteners have.[27] Table 1 lists the most widely used plants in herbal formulations for diabetes care. Table 2 lists herbal plants that have reported anti-diabetic activity in various reputed journals. Table 3 lists medicinal plants used in the management of diabetes, and Table 4 provides a list of polyherbal formulations of ayurveda used in diabetes.

The Mechanism Involved in Diabetes Treatment

The current diabetes treatment focuses on lowering and controlling glucose to a conventional level. The mechanisms may be (Figure 4).

- A stimulating cell of the duct gland island unleashes insulin
- Resisting blood glucose rising hormones
- Increasing the insulin receptor sites quantity or raising the efficiency as well as sensitivity to insulin
- Decreasing the glycogen's leading-out.
- Enhancing the glucose use within the organs and tissues
- Taking away free radicals, upsetting of proteins and lipids, and resisting lipids per chemical reaction
- Improving microcirculation within the body.

Table 3: List of medicinal plants used in the management of diabetes mellitus

Scientific Name	Family	Parts Used	Active Ingredient	Probable Mechanism of action	References
Acantho panax senticosus	Araliaceae	Whole plant	Polysaccharide.	Potent antioxidant activity leads to anti-diabetic activity.	[91]
Acorus calamus	Acoraceae	Rhizome	Phenylpropanoids, sesquiterpenes, monoterpenes, xanthone glycosides, flavones, steroids, lignans, triterpenoid and saponins.	Decrease the activity of glucose -6 phosphates and fructose 1, 6 phosphatase enzymes.	[92]
Adina cordifolia	Rubiaceae	Leaves	Tannins, saponins, and flavonoids.	Increase the insulin secretion or inhibit the intestinal absorption of glucose.	[93]
Afzelia africana	Fabaceae	Stem Bark	Flavonoids, proanthocyanidins, tannins, phenols and flavonols.	Potentiating of insulin from β cells or by increasing peripheral glucose uptake.	[94]
Alangium lamarcki	Alangiaceae	Leaves	Alkaloid, terpenoids, steroids, tannins and phenol.	Improvement in glucose tolerance, restoration of liver glycogen, and antioxidant activity to reduce the risk of secondary complications associated with diabetes.	[95]
Albizia odorless ima	Mimosaceae	Bark	Bi flavonoids, Triterpene glycosides, saponins, sapogenins and fatty acids.	Insulin secretion and improvement of glycogenesis process.	[96]
Bauhinia vahlii	Fabaceae	Stem bark		Increases the level of insulin secretion.	[97]
Bougain villea spectabilis	Nyctaginaceae	Stem Bark		Hypoglycemic activity due to flavonoids.	[98]
Caesalpinia digyna	Leguminosae	Root	Tannins phenolics and triterpenoids.	Overproduction and decreased utilization of the tissues.	[99]
Callistemon lanceolatus DC	Myrtaceae	Leaves	Flavonoids	Blood glucose lowering by the regeneration of pancreatic islets and probably insulin release.	[100]
Camellia sinensis L.	Theaceae	Leaves	Poly phenols, caffeine, theaflavins and the arubigins.	Increasing the Insulin /glucose ratio.	[101]
Carissa carandas Linn	Apocynaceae	Fruits	Polyphenolic, flavonoid and flavanone.	Increase in degree of polymerization and segregation of secondary metabolites.	[102]
Catathelasma ventricosum	Tricholomatac eae		Polysaccharides.	Polysaccharides may stimulate pancreatic release of insulin and/or reduce insulin metabolism.	[103]
Chaenomeles sinensis	Rosaceae	Fruits	Bioactive triterpenes such as oleanolic acid and ursolic acid. Bioactive phenolic acids vitamin and flavonoids.	Inhibition of glucose transporter, α- glycosidase, α- amylase, lipase and strong antioxidant potential.	[104]
Merremia emarginata Burm. F	Convolvulaceae	Whole plant		Stimulates insulin secretion from remnant β-cells or regenerated β- cells.	[105]
Merremia tridentat a (L.)	Convolvulaceae	Root		Potentiating the pancreatic secretion of insulin from existing β- cells of islets by increasing the level of insulin.	[106]

Anti-diabetic medicative plants, without a doubt, have a significant impact on reducing blood sugar. However, the action mechanism still needed to be clarified. Halpern and Glazer, in 1929, reported that insulin-potentiating activity was observed in natural products and was the first proof of it. Furthermore, glucose levels can be managed by these herbs through various mechanisms. These are considered additional or less similar actions to the artificial medication. Also, herbal's anti-diabetic

Table 4: Polyherbal formulations used in the treatment of diabetes mellitus [110]

Formulations			
1	Amree Plus	19	D-nil
2	Apenia churna	20	DRF/AY/5001
3	Cogent db+	21	D-Tone
4	Daibitol	22	Glucomap
5	DBT	23	Glycoherb
6	Debix	24	Hyponidd
7	D-Fit Capsules	25	Jambrulin
8	Diabecom	26	Jambvasana
9	Diabet	27	Karela cap.
10	Diabrid	28	Karnim
11	Dia-care	29	Lokmanya churna
12	Diakyur	30	Madhumardan churna
13	Diamed	31	Madhumehari dane
14	Dianex	32	Madhurim powder and pills
15	Diashis	33	Mamejava ghanavati
16	Diasol	34	Mehasudanamrut
17	Diasulin	35	Tribangasheela
18	Dihar	36	Vasant kusumakar rasa

action mechanism can be classified as:

Insulin secretion stimulation (*Allium sativum* [37], *Allium cepa [36], Panax ginseng* [78])

Inhibition in renal glucose reabsorption (*Fraxinus excelsior* [107])

Hepatic glycolysis and glycogenesis stimulation (*Momordica charantia [72]*)

Digestion improvement and urea and blood sugar reduction (*Aegle marmelos* [33])

Glucose use increased by tissues and adrenergic receptors effect (*Allium cepa* [36]*, Allium sativum* [37]*, Panax Ginseng [78]*) Potentiates the exogenously injected insulin's action (*Rubia cordifolia* [108]**)** Cortisol lowering activities (*Ocimum sanctum* [2], *Boerhaavia diffusa* [109]).

Toxic Effects of Herbs

There is a lack of toxicological data on ancient anti-diabetic plants. Through the accumulative knowledge of private interactions, it is fair to assume that the plants' use over many centuries and as daily constituents of the diet would show any apparent adverse side effects. Patients are also at risk of ingesting herbal drugs, believing their efficacy credibility to be valid. Patients are still at risk of consuming herbal treatments, mistaking their effectiveness for safety; nevertheless, repeated ingestion of copious quantities of conventional medicines should still be treated cautiously. Many major alkaloids isolated from this plant, such as leurosine, vindoline, vindolinine, and catharanthine, developed a mild hypoglycemic response in healthy rats at intervals of 2–5 hours. However, none were sufficiently potent to prove further investigation due to the cytotoxic and neurologic effects of *Catharanthus* alkaloids [111].

Ficus bengalensis (banyan tree), used in Asia to treat diabetes for centuries, has been linked to gross behavior, neurologic, and autonomic harm in rats.[63] The central nervous system stimulation and hypertensive effect of ephedrine from shrub species and central nervous stimulation by Panax species have limited their use in diabetes treatment.[78, 111] Ackee fruits that are not entirely ripe (ackee fruit) in Central America and Africa are a standard diabetes herapy. Homoglycans (aminopropyl propionic acid derivatives) facilitate glucose use and inhibit gluconeogenesis by inhibiting long-chain fatty acid oxidation in healthy and diabetic animals and humans. However, research has paused further because of their poisonous effects, which cause neuroglycopenia.[112] Other non-cultivated conventional anti-diabetic mushrooms, such as *C. comatus*, can accumulate dangerous metals if ingested in substantial amounts. When hepatic glycogen depletion and hepatic necrosis occur, the toxic effects of *A. phalloides* are most likely due to neuroglycopenia.[113]

Using herbal medicines such as *Adenia gummifera* (fulwa), Chenopodium*, Ambrosioides*, *Spilanthus Mauritania,* and *Ibozariparia*, a study in South Africa found cases of spontaneous hypoglycemia, hepatic and renal necrosis,[114] according to a case-study document, *M. charantia's* hypoglycemic effect was additive to that of chlorpropamide and *V. myrtillus*, and synthalin tended to lower insulin levels.[115-117]

CONCLUSION

Diabetes mellitus is the most common world's fastest-emerging endocrine disorder, affecting millions of people worldwide. It is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The increase in resistance and populations of patients at some risk, in conjunction with the restricted number of commercially available drugs for diabetes that still present, have many side effects and problems like unwanted hypoglycaemics effect are the cause to shift the research towards traditionally available medicine which have low side effect and wide range of bio activity and do not need laborious pharmaceutical synthesis seems highly attractive. This review article may be useful to health professionals, scientists, and scholars to develop evidence-based alternative medicine to cure different kinds of diabetes problems using herbal preparation. Substances and extracts isolated from different natural resources play a key role in designing medicine and treating hyperglycemia problems in diabetes mellitus. Consequently, an analysis of such drugs could offer a natural key to unlocking a scientist in the future.

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LIST OF ABBREVIATIONS

ACE = Angiotensin-Converting Enzyme
AT1 = Angiotensin-I
CoA = Coenzyme A
CVD = Cardiovascular Disease
DCCT = Diabetes Control and Complications Trial
DM = Diabetes Mellitus
DME = Diabetic Macular Edema
DMI = Diabetic macular ischemia
DM1 = Diabetes mellitus 1
DM2 = Diabetes mellitus 2
DR = Diabetic Retinopathy
DRS = Diabetic Retinopathy Study
IDDM = Insulin Dependent Diabetes mellitus
MIDD = Maternally Inherited Diabetes and Deafness
MODY = Maturity Onset Diabetes of the Young
NCD = Non-Communicable Disease
NIDDM = Non-Insulin Dependent Diabetes mellitus
PDR = Proliferative Diabetic Retinopathy
PVS = Posterior Vitrectomy Surgery (PVS)
T1DM = Type 1 Diabetes mellitus
T2DM = Type 2 Diabetes mellitus
t–RNA = transfer Ribo Nucleic Acid
VEGF = Vascular Endothelial Growth Factor

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