Journal of Cardiovascular Disease Research

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

Comprehensive study on reported medicinal plants with antidiabetic activity and various Antidiabetic polyherbal formulations.

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Abstract

Diabetes Mellitus is a common metabolic disorder in developing countries due to change in lifestyle i.e. food habit and lack of physical workout. The various synthetic drugs are available for its management. These drugs are associated with side effects. The alternative medicine preferred over synthetic drugs is herbal formulation due to lesser side effects. The vast number of medicinal plants has been reported by researcher showing antidiabetics. The use of polyherbal formulations with ant diabetic property is also preferred. The review paper highlights the plants having antidiabetic activity with their phytochemistry and possible mechanism of action.Additionally,the available polyherbal formulation with antidiabetic activity has been illustrated.

Keywords: Antidiabetic Activity,Medicinal plants, Phytochemistry, Polyherbal Formulation.

Introduction

Diabetes mellitus is a group of metabolic disorders resulting from defects in insulin secretion or reduced sensitivity of the tissues to insulin action or both. It is characterized through the chronic high blood glucose which causes the glycation of body protein and thus could lead to severe complications. Some of these complications are polyuria, polyphagia, polydipsia, ketosis, retinopathy as well as cardiovascular disorders. The classic symptoms of untreated diabetes are unintended weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger)[1]. Symptoms may develop rapidly (weeks or months) in type 1 diabetes, while they usually develop much more slowly and may be subtle or absent in type 2 diabetes. Other symptoms of diabetes include weight loss and tiredness[2].

The treatment convention requires a multimodal approach which ought to be customized with the goal that it changes from individual to individual. When all is said in done, DM is arranged into two classifications: Type 1 and Type 2. In sort 1 diabetes (T1DM), chemical insulin isn't created because of the obliteration of pancreatic β cells, while type 2 diabetes (T2DM) is portrayed by a reformist debilitation of insulin emission by pancreatic β cells and by a general diminished affectability of target tissues to the activity of this chemical. T2DM prompts other neurotic outcomes like cardiovascular issues, nephropathy, neuropathies and the patient gets inclined to various contaminations as well. The expanding clinical weight on patients with diabetes-related complexities additionally brings about a colossal monetary weight, which could seriously weaken worldwide financial development soon[3-4].

According to the Diabetes Atlas 2019, International Diabetes Federation most recent estimates indicate that 8.3% of adults, the majority of the 382 million people with diabetes are aged between 40 and 59, and 80% of them live in low- and middle-income countries[5]. All the three types of diabetes are on the increasing stage, on which type 2 diabetes in particular may increase upto 55% by 2035. Various synthetic drug namely Acarbose, Miglitol and Voglibiose, Sulphonylureas, Biguanides etc are used for the ailment of hyperglycemia. The synthetic drugs are associated with various side effects such as causing hypoglycemia at higher doses, dermatological reaction, liver problems, nausea and vomiting, generalized hypersensitivity reactions, lactic acidosis and diarrhea. The secondary complication of synthetic drugs leads to limitation in its use; and creating major medical issues in management of diabetes.

Additionally, most anti-diabetic drugs promote long-term weight gain. Thus, these drugs treat one of the key symptoms, hyperglycemia, but exacerbate weight gain and obesity which further contribute to the progression of type 2 diabetes. Therefore, while these drugs are beneficial over the short-term, they are not optimal for the long-term health of type 2 diabetic patients. The most desirable situation would be the development of new types of anti-diabetic drugs that are either hypoglycemic or anti-hyperglycemic without the side effect of promoting weight gain. Therefore, more research is required to develop new antihyperglycemic agents with high efficiency and low toxicity from traditional medicines.

Herbal medicines were considered to be less toxic with fewer side effects than synthetic drugs. In the Ayurvedic system of medicine, as mentioned in ancient Indian books like Charak, Samhita, MahdhavNidan and AstangSanghra, there are about 600 plants, which are stated to have antidiabetic property. Wide arrays of plant

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

derived active principles representing numerous phytochemicals have demonstrated consistent hypoglycemic activity and their possible use in the treatment of diabetes mellitus. Indian plants which are most effective and commonly studied in relation to diabetes are namely *Allium cepa, Allium sativum, Aloe vera, Cajanus cajan, Coccinia indica, Caesalpinia bonducella, Ficus bengalenesis, Gymnemasylvestre, Momordica charantia, Ocimum sanctum, Pterocarpus marsupium, Swertia chirayita, Syzigiumcumini, Tinospora cordifolia, Trigonella foenum, Phyllanthus emblica, Annona squamosa* etc.

Currently, some restorative plants have been accounted for to be helpful in diabetes worldwide and have been utilized experimentally as antidiabetic and antihyperlipidemic cures. The medicinal plant demonstrated antidiabetic activity by decreasing the glucose -6 phosphates and fructose 1, 6 phosphatase enzymes activity, enhancing the secretion of insulin, regeneration of pancreatic β cells, inhibiting the α-glucosidase and amylase etc mechanism. It has been reported that more than 400 plant species having hypoglycemic action have been accessible in writing, notwithstanding, looking for new antidiabetic drugs from normal plants is as yet alluring in light of the fact that they contain substances which show option and safe impacts on diabetes mellitus[6].

Table: 1 Illustrated the scientifically reported antidiabetic plants with their possible mechanism of action along with phytochemicals:

Sl.No.	Plant Name	Parts Used	Phytochemical	Mechanism of Action	Ref.
1	Acanthopanax senticosus (Arapiaceae)	Whole Plant	Polysachharide,Flavonoid, Polyphenol	Antidiabetic by antioxidant activity	7
2	Acorus calamus (Acoraceae)	Rhizome	Phenylpropanoids,Sesquiterpenes, monoterpenes,xanthoneglycosides,flavonessteroids,lignans, triterpenoids &saponins.	It lowers Glucose-6-Phosphates and Fructose1,6-phosphatase enzymes activity	8
3	Adina cordifolia(Rubiaceae)	Leaves	Flavonoid, Polyphenol,saponins,tannin and terpenoids	It enhances the secretion of Insulin	9
4	Afzelia Africana (Fabaceae)	Stem Bark	Flavonoids,proanthocyanidins,tannins,phenols and flavonolos	Enhancing secretion of Insulin from pancreatic cells or by increasing peripheral glucose uptake	10
5	Ginkgo biloba (Ginkgoaceae)	Leaves	Ginkgolides	Insulin secretion	11
6	Gymnema sylvestre (Apocynaceae)	Leaves	Gumarin,betaine,Choline, trimethlyamine	Regeneration of pancreatic β cells and insulin secretion	12
7	Ocimum Sanctum (Lamiaceae)	Leaves	Flavonoid, Polyphenol,saponins and steroids	Insulin secretion,Carbohydrate digestion and absorption	13
8	Phyllanthus amarus (Euphorbiaceae	Leaves	Brevifolin carboxylic acid, ethyl brevifolin carboxylate	Carbohydrate digestion and absorption	14
9	Salvia officinalis (Lamiaceae)	Leaves	Alkaloids, saponin, tannin, terpenoid	Bring serum glucose and insulin towards normal values	15
10	Trigonella foenum graecum (Fabaceae)	Seeds, tuberous	Alkaloids, steroids, carbohydrates	Glucose transport,	16

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				carbohydrate metabolism, stabilizing agents	
11	Morus alba (Moraceae)	Root barks	Flavonoids, steroids, carbohydrates	Decrease serum glucose level	17
12	Tinospora cordifollia (Menispermacea)	Leaves	Tinosporine, cordifolide, tinosporide, cordifole, columbin	Cholesterol synthesis, glycolysis, DPP-IV inhibition	18
13	Zingiber officinale (Zingiberaceae)	Root	Gingerols, shogaols	Effective in lowering serum glucose, cholesterol and triacylglycerol levels	19
14	Nigella sativa (Ranunculaceae)	Seeds	Thymoquinone	Assessing the antihyperglycemic potential	20
15	Panax quinquefolium (Araliaceae)	Leaves	Quinquenoside L3 and L9	Regeneration of pancreatic β cells and insulin secretion	21
16	Curcuma longa (Zingiberaceae)	Rhizome	Soy isoflavones (genistein, diadzein)	Lipid and glucose metabolism, PPAR activation	22
17	Silybum marianum (Poaceae)	Whole Plant	Silymarin, silybin, silychristin, silidianins	HMG Co A suppression	23
18	Eclipta alba (Asteraceae)	Leaves	Wedelolactone, dimethyl wedelolactone	Insulin secretion, carbohydrate digestion and absorption	24
19	Xanthocerciszambesiaca (Ganodermataceae)	Leaves, twig, flower	Castanospermine, epifagomine, fagomine	Carbohydrate digestion and absorption, insulin secretion	25
20	Citrus paradisi Macfad. (Rutaceae)	Grape fruit peels	Limonin, bergamottin	inhibited α-amylase, α-glucosidase and ACE enzyme activities	26

Phytochemicals having antidiabetic activity:

The detection of novel herbal antidiabetic drugs has great importance due to their minimum side effects and safety concerns. In this connection, the examination of phytochemicals answerable for antidiabetic impacts has advanced over the most recent couple of many years. The antidiabetic impact of plant materials has been credited to the combination of phytochemicals or a solitary part of plant extract. Restorative plants produce a wide assortment of phytochemicals, incorporate alkaloids, phenolic acids, flavonoids, glycosides, saponins, polysaccharides, stilbenes, and tannin, which are seriously explored for their antidiabetic impacts table 2 demonstrated the phytochemical obtained from the plants having antidiabetic activity:

Table 2: Phytochemicals having antidiabetic activity with possible mechanism of action :

Sl.No.	Phytochemical	Source	Mechanism of action	Ref. No.

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	Alkaloids			
1	Berberine	Berberis sp.	It declines the absorption of glucose Inhibition of α-glucosidase and declined the glucose passage through the intestinal epithelium	27,28
2	Boldine	Peumus boldu	Betterment of endothelial function in diabetic db/db mice by inhibiting the angiotensin II-mediated BMP4 oxidative stress cascade	29
3	Lupanine	Lupinus sp.	Increases the insulin secretion Expands glucose homeostasis by prompting ATP-sensitive potassium (KATP) channels and insulin genes	30
4	Neferine	Nelumbo nucifera	It lessened the expression of CCL5 and CCR5 mRNA in the superior cervical ganglion of T2DM rats	31
5	Oxymatrine	Sophora flavescens	Decreased blood glucose, urinary protein and albumin excretion, serum creatinine, and blood urea nitrogen in a T2DM high-fat diet streptozotocin	32
	Flavonoids			
6	Naringenin	Various plant sp.	Glucose adsorption decreased by the intestinal brush border, diminish renal glucose reabsorption, and proliferation of glucose uptake and use by muscle and fat tissues.	33
7	Catechins	Tea and cacao	Antioxidant activity	34
8	Fisetin	Various plant sp.	Reduces blood glucose, improves glucose homeostasis through the inhibition of gluconeogenic enzymes, and increases the level and activity of glyoxalase	35
9	Kaempferol	Various plant sp.	Improves insulin sensitivity and preserves pancreatic β-cell mass	36
10	Luteolin	Aromatic flowering plants	Enhances cardiac failure in T1DM cardiomyopathy	37
11	Naringenin	Grape fruit	Attenuates diabetic nephropathy via its anti-inflammatory and anti-fibrotic activities	38
12	Quercetin	Fruits & vegetables of various plants	Decreased the cell percentages of G(0)/G(1) phase, Smad 2/3 expression, laminin, and type IV collagen and TGF-β (1) mRNA levels	39
13	Rutin	Fruits & vegetables of various plants	Improves glucose homeostasis by altering glycolytic and gluconeogenic enzymes. Stimulatory effects on glucose uptake. Improves insulin-dependent glucose transporter and potentiates insulin receptor kinase	40-43
14	Silymarin	Silybum marianum	Ameliorates diabetic cardiomyopathy through the inhibition of TGF-β1/Smad signaling, suggesting that silymarin could have a potential role in diabetic cardiomyopathy treatment	44
15	Chrysin	Passiflora sp.	Reduced the serum levels of pro-inflammatory cytokines, interleukin-1beta (IL1β), and IL-6	45
	Triterpenoid			
16	Boswellic acids	Boswellia sp.	Attributed to stimulating β cells to release more insulin. They are used for the prophylaxis and treatment of damage and inflammation of the islets of Langerhans.	46,47
17	Celastrol	Tripterygium wilfordii, Celastrus	NF-kB inhibitor, improves insulin resistance, and attenuates renal injury	48, 49

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		orbiculatus, C. aculeatus, C.reglii, C.scandens		
18	Oleanolic acid	Fruits, herbs & vegetables	Reduces hyperglycemia beyond the treatment period with Akt/FoxO1-induced suppression of hepatic gluconeogenesis in T2DM mice	50
19	Triptolide	Tripterygium wilfordii	Reduced the levels of phosphorylated protein kinase B & phosphorylated inhibitor of kappa B & increased caspases 3, 8, and 9	51
20	Galactomannan	Tubers of Amorphophallus konjac & seeds of Cyamopsis tetragonolobus	Delay the rate of glucose absorption and, thereby, helps to reduce postprandial hyperglycemia	52,53
	Miscellaneous			
21	Piceatannol	Various plant sp.	Promotes glucose uptake through glucose transporter 4 translocation to the plasma membrane in L6 myocytes and suppresses blood glucose levels in T2DM model db/db mice	54
22	Butein	Various plant sp.	Inhibits central NF-kB signalling and improves glucose homeostasis	55
23	Embelin	Various plant sp.	Elevated plasma glucose, glycosylated hemoglobin, and pro-inflammatory mediators (interleukin 6 and tumor necrosis factor α)	56-57
24	Erianin	Dendrohium sp.	Inhibits high glucose-induced retinal angiogenesis via blocking the ERK1/2- regulated HIF-1α-VEGF/VEGFR2 signaling pathway	58
25	Gambogic acid	Garcinia sp.	Ameliorates diabetes-induced proliferative retinopathy through inhibition of the HIF-1α/VEGF expression via targeting the PI3K/AKT pathway	59
26	Garcinol	Garcinia sp.	Reductions of plasma insulin, homeostasis model assessment of β-cell function (HOMA-β-cell) functioning index, glycogen, high-density lipoprotein cholesterol, body weight, and antioxidant enzyme activities. Decreases elevated levels of blood glucose, glycosylated hemoglobin, and lipids	60-61

Polyherbal Formulation (PHF):

Polyherbal formulation has been used all around the earth due to its medicinal and therapeutic application. It has also recognized as polyherbal therapy or herb-herb combination. The active phytochemical constituents of individual plants are inadequate to attain the desirable therapeutic effects. When polyherbal formulations combining the multiple herbs in a meticulous ratio, it will give an enhanced therapeutic effect and decrease the toxicity. The active constituents used from individual plant are inadequate to provide attractive pharmacological action. There are evidences that crude plant extracts often have greater potency rather than isolated constituents. In traditional medicine whole plants or mixtures of plants are used rather than isolated compounds. Due to synergism, polyherbalism confers some benefits which are not accessible in single herbal formulations. Polyherbal formulations express high effectiveness in numerous diseases with safe high dose. Based on the nature of the interaction, there are 2 mechanisms on how synergism acts (i.e., pharmacodynamics and pharmacokinetic). In words of pharmacokinetic synergism, the capacity of herb to ease the absorption, distribution, metabolism and elimination of the other herbs is focused. Pharmacodynamics synergism on the other hand, studies the synergistic effect when active constituents with similar therapeutic activity are targeted by diverse mechanism of action. Hence it is assumed that similar findings will be obtained from present study.

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Table:3
Marketed Poly Herbal Formulation with dosage form having antidiabetic activity:

Sl.No.	PHF (Company)	Composition	Dosage Form
01	**MADHUNASHINI VATI (Divya Pharmacy)**	Tinospora cordifolia Momordica Charantia Aegle marmelos Gymnemasylvestre Terminalia chebula Tribululsterrestris Ficus bengalensis Withaniasomnifera.	Tablet (Prepared from Wet Extracts)
02	**MADHUGRIT (Divya Pharmacy)**	**Powder:** ChandrapbhaVati 200mg Asphaltumpunjabianum 50mg **Extract of:** Tinospora cordifolia 50mg Citrullus colocynthis 10mg Momordica Charantia 50mg Swertia chirata 50mg Asparagus racemosus 25mg Withaniasomnifera 25mg	Tablet (Powders & Extract)
03	**MEHANTAKA VATI (Sri Sri Tattva)**	Chandrika 170 mg Ashwagandha 60 mg Laksha 10 mg Lavang 10 mg Amarbel 10 mg BidhariKand 50 mg Sitawar 10 mg Karu 10mg Babool 40 mg Soomlata 03 mg Chkramard 32 mg Sonapatha 15 mg Konch Beej 20 mg LohBhasm 10 mg	Capsule
04	**MADHUMEH MANTRA Capsule (Tansukh)**	Acacia Arabica 50 mg Swertia chirata 50mg GymnemaSylvestre 50 mg Syrzygium Cumin 50 mg TregonellaFoenum Graecum 50 mg Azadirachita Indica 50 mg Cinnamomum Tamala 50 mg Shilagit 50 mg	Capsule

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05	**MADHUMEH MANTRA Granules (Tansukh)**	**Each 10 gm contains:** Acacia Arabica 01 g Swertia chirata01gGymnemaSylvestre01 g Syrzygium Cumin 01 g TregonellaFoenum Graecum 01 g Azadirachita Indica 01 g Tinospora Cordifolia 01 g Pterocarpus marsupium 01 g Momordica charantia 01 g Curcuma longa 01 g	Granules
06	**DIABECON (Himalaya Herbal Healthcare)**	GymnemaSylvestre 30mg Pterocarpus marsupium 20 mg Glycyrrhiza glabra 20 mg Casearia esculenta 20 mg Syzygiumcumini 20 mg Asparagus racemosus 20 mg Boerhaviadiffusa 20 mg Sphaeranthus indicus 10 mg Tinospora Cordifolia 10 mg Swertia chirata 10 mg	Tablet
07	**MADHUMEHARI YOG WITH GOLD (Baidyanath)**	Bang Bhasm, Nag Bhasm, YasadBhasm each 2.564 mg GymnemaSylvestre 23.077 mg Azadirachita Indica 23.077 mg Syzygiumcumini 23.077 mg Shilazit 46.153 mg SwarnBhasam 1.923 mg Ficus glomerata q.s. Tinospora Cordifolia q.s. Pterocarpus marsupium q.s.	Tablet
08	**EVER HERB (Anti Diabetic)**	GymnemaSylvestre 100mg Pterocarpus marsupium 95mg Emblicaofficianlis 75mg Enicostemma littorale 50mg SyzygiumCumini 30mg	Tablet

Conclusion:

Diabetes is one of the common metabolic disorder and widespread all over the country. The complication is alarming day by day if untreated or uncontrolled. There are various synthetic and herbal medicine available. The review paper highlighted the various medicinal plants having antidiabetic activity with mechanism of action. Similarly, Mode of action of the phytochemicals such as alkaloids,flavonoids etc showing antidiabetic activity. It illustrates the essential data to the researcher pursuing research work in the field of Pharmacology and Therapeutics to develop polyherbal formulation with benefits of additive antidiabetic effect and minimising other after effects.

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