Publisher
ADSRS EDUCATION AND RESEARCH
www.adsrs.net

E-ISSN:2583-4479

Global Journal of Novel Pharma and Paramedical Research

2022 Volume 1 Number 1 Jan-Jun

Research Article

Diabetes Mellitus

A review on current epidemiology and herbal approach towards the management of diabetes mellitus in India

Roy S.[1], Biswas S.[2], Das S.[3], Majumder S.[4], Ghosh P.[5], Choudhury S.[6], Bose A.[7], Mondal S.[8*]

DOI: https://doi.org/10.58260/j.ppmr.2202.0102

[1] Sukanta Roy, The Neotia University, Sarisha, West Bengal, India.

[2] Sudeepto Biswas, TAAB Biostudy services, Kolkata, West Bengal, India.

[3] Sourav Das, TAAB Biostudy services, Kolkata, West Bengal, India.

[4] Shramana Majumder, Covance India Pharmaceutical Services, Bengaluru, Karnataka, India.

[5] Parag Ghosh, The Neotia University, Sarisha, West Bengal, India.

[6] Sangeeta Choudhury, TAAB Biostudy services, Kolkata, West Bengal, India.

[7] Anirbandeep Bose, TAAB Biostudy services, Kolkata, West Bengal, India.

[8*] Subhasish Mondal, The Neotia University, Sarisha, West Bengal, India.

The article here is about the disorder Diabetes Mellitus (DM) and the various treatments from the herbal background more specifically in India. It has been found that DM is a very common disorder affecting people mostly from the Asian subcontinent. The most common form of diabetes is Non-insulin dependent Diabetes Mellitus (NIDDM) or Type 2 DM (T2DM) and although a number of treatment approaches have been taken for this, herbal drugs never stand apart. Herbal medicines have been the backbone of the entire medicinal system in India and hence this paper will specifically look into all the original, novel, and ancient ways to treat the disorder. Several plants have been found to have anti-diabetic effects like catechu, basil, ginko biloba, fenugreek, and much more. Also, there have been many marketed herbal products too like Bitter gourd powder, episulin, Dia care, and much more which have been discussed in detail in the paper. Interestingly, all of these herbal products have some mechanism of action which are quite varied and have been discussed here. So, the main approach behind this paper is to re-establish herbal drugs as effective ways of medication against the disorder of Diabetes Mellitus.

Keywords: Diabetes Mellitus, Herbal drugs, Metabolic disorder, Traditional plants

Corresponding Author

Subhasish Mondal, , , The Neotia University, Sarisha, West Bengal, India.

Email: subhasish.mondal@tnu.in

How to Cite this Article

Sukanta Roy, Sudeepto Biswas, Sourav Das, Shramana Majumder, Parag Ghosh, Sangeeta Choudhury, Anirbandeep Bose, Subhasish Mondal, A review on current epidemiology and herbal approach towards the management of diabetes mellitus in India. Glo.Jou.of.pharma.par.of.ADSRS.Edu.Res. 2022;1(1):13-27.

Available From http://ppmr.adsrs.net/index.php/ppmr/article/view/2

To Browse

Manuscript Received	Review Round 1	Review Round 2	Review Round 3	Accepted
2022-06-04	2022-06-07	2022-06-11	2022-06-23	2022-06-30

Conflict of Interest	Funding	Ethical Approval	Plagiarism X-checker	Note
Nil	Nil	Yes	17%	

Introduction

Diabetes mellitus (DM) is considered one of the oldest metabolic disorders notorious to society. It was initially stated about 3000 years ago in an Egyptian manuscript [1]. In the year 1936, two types of diabetes were found which further stated type 1 DM and type 2 DM. Depending upon their biological appearance they simultaneously phrase at Insulin-dependent Diabetes mellitus(IDDM) and Non- Insulin-dependent Diabetes mellitus (NIDDM) [2]. Type 2 DM NIDDM is the most abundant form of DM which is associated with hyperglycemia, insulin resistance, and relative insulin deficiency [3]. Type 2 DM results from the collaboration of various factors like genetic, behavioral, and environmental risk factors [4,5].

Till now, Type 2 DM is considered to be the utmost form of DM, which occurs in 85 to 95% of the nations that are developed and with more incidence in the nations which are developing, as per the International Diabetes Federation. This disease generally takes years or even decades to mature. Diabetes starts off with pre-diabetes at first, in which the levels of glucose (blood sugar) are mostly within the normal range but not as much high as to be eligible for the diagnosis of diabetes. Normal but not high enough yet for a diagnosis of diabetes. People with prediabetes can often delay or prevent the escalation to type 2 diabetes by losing weight through improvements in exercise and diet, like the Diabetes Prevention Program.

The existing therapies against DM mainly mostly contain oral hypoglycemic or anti-hyperglycemic agents and insulin. The anti-DM drugs generally work by the mechanism of acting on a particular metabolic pathway to control hyperglycemia and are so associated with a number of side effects. The search for a better remedy starts with this realization that focuses on other metabolic pathways apart from just carbohydrate, protein, or fat metabolism.

The herbal drugs come into existence here, the preparations are made from more than 800 traditional plants and the active constituents are supposed to have antidiabetic activity as it is proved by the in-vivo and in-vitro studies. The extracts act at various levels like inhibition of glucose absorption from the intestines, increasing insulin secretion from the pancreas, increasing

The glucose uptake through the adipose and muscle tissues, or inhibition of glucose formation from the hepatocytes. The best part about the herbal extracts is that along with their unique mechanism of action they have very less side effects as compared to synthetic drugs and are of natural origin. So, for the treatment of diabetes, the significance of herbal medicines can be considered well. The only challenge is there is very limited research on the therapeutic use of the extracts.

Epidemiology: Diabetes is about to become a pandemic in India with over 62 million diabetic patients currently identified with it [6, 7]. In the year 2000, India became the maximum number (31.7 million) of individuals with DM in the world. Meantime, China with 20.8 million and the United States with 17.7 million are gaining second and third place respectively [8]. By the year 2030, it is assumed that DM may affect up to 79.4 million people in India, whereas China with 42.3 million, and the United States with 30.3 million will also observe a noticeable increment in those affected by the disease [8, 9]. The causality of DM in India is involved several factors as well as it includes environmental influenced genetic factors like obesity associated with growing living standards, high rate of urban migration, and evolving lifestyle [10].

The diabetes prevalence in India can be drawn into a pattern that is related to the demographical distribution of DM countrywide. A rough estimation shows that the occurrence of DM in rustic populations is one-fourth that of the urban population of India including other Indian subcontinent countries like Bangladesh, Nepal, Bhutan, and Sri Lanka [8, 11].

A large community study led by the Indian Council of Medical Research (ICMR) from which the initial results revealed that a lesser percentage of the population is undertaken by diabetes in North Indian states like Chandigarh with 0.12 million, Jharkhand with 0.96 million as compared to Maharashtra with 9.2 million and Tamil Nadu with 4.8 million[11]. The National Urban Survey steered all the metropolitan cities of India which revealed a similar trend: 11.7% in Kolkata (East Indian), 6.1% in Kashmir Valley (North Indian), [12] 11.6% in New Delhi (North Indian), and 9.3 % in West Indian (Mumbai) compared with (13.5% in Chennai (South Indian), 16.6% in Hyderabad (south Indian), and 12.4% Bangalore (South Indian) [13].

In conclusion, the different states that the north Indians are migrated populations from throughout Asia and south Indians are termed as host populations [14].

Current western method of diabetes management and mechanism of action:

- T2DM or NIDDM is considered a chronic metabolic disorder. By DM millions of people are affected globally and are accompanied by several comorbidities and micro/macrovascular difficulties. DM management is a complex process and must be designed personalized to the individual. Physicians and paramedics like nurses, pharmacists, and dieticians are usually employed as a well-adjusted healthcare team in the management of a diabetic individual. The American Diabetes Association (ADA) encourages diabetes self-management education, an arrangement in which the patient associated with DM is fortified with enough knowledge and skills to afford self-care, manage emergency (severe hyperglycemic and hypoglycemic events), and introduce a healthy lifestyle [15, 16].
- Primarily non-pharmacological management of T2DM includes suitable diet and exercise. Diet should be maintained in such a way that does not involve in weight gain. Minimum30 minutes of moderate to intense physical activity can recover T2DM and weight supervision. Intense lifestyle modifications (LSMs) are the topmost choice of all disease management models and must be stimulated in both individuals who are at risk for developing DM (pre-diabetic) and individuals who are already associated with DM.
- For individuals necessitating medical assistance for T2DM, metformin, **a biguanide**, is cast off as a first-choice treatment for most patients who are not able to maintain their glycemic level within the desired limits with LSM. Metformin intensifies the glucose uptake by the skeletal muscles [17], constrains gluconeogenesis in hepatic cells [18], as well as facilitates insulin sensitivity towards its receptor [19] (summarized in Table1). Metformin is not only the first choice for the treatment of T2DM but also helps in the prevention of high-risk populations towards T2DM [20].
- **Sulfonylureas** are used as a second choice of Oral hyperglycemic agents which surges insulin discharge by coupling to K+/ATPase (potassium) channels in the β-cells present in Islets of Langerhans in the pancreas [21]. Second-generation sulfonylureas are extensively used because of their acute pharmacological action, lesser drug interactions, and lesser severe adverse drug reactions [22]. Insulin, which is more often stated as the last choice of therapy in the treatment of T2DM and is the compulsory treatment of Type 1 DM (T1DM, IDDM), is now considered an effective combination in association with metformin as a second choice of treatment instead of sulfonylureas [22,23]. Insulin is highly efficient in controlling blood glucose and glycosylated hemoglobin (HbA1C). Insulin routines are varying depend upon the individual patient and can be used in various combinations.
- Further, less corroborated classes of a hyperglycemic agents which are used along with metformin are **thiazolidinediones** (TZDs) and **GLP-1 analogue** (glucagon-likepeptide-1). TZDs (pioglitazone, rosiglitazone) control peroxisome proliferator-activated receptor γ (PPARγ), a nuclear receptor that modulates glucose and lipid metabolism up to a certain level. Stimulation of PPARγ directed to the primary enhancement of insulin sensitivity in adipose tissue and also imparts an effect on skeletal muscle and liver [24]. TZDs are found to be responsible for amplifying cardiovascular events due to a trial that confirmed the myocardial events with rosiglitazone [25]. GLP-1 analogues (exenatide, liraglutide) are peptides derivative that are incretin hormones released from the small intestines after meals [26]. It imparts the action by binding to the GLP-1 receptors which are situated in the pancreas and help to trigger the insulin release and deplete glucagon release. The **meglitinides** class (repaglinide, nateglinide) shows identical pharmacological activity to sulfonylureas [27] but coupled to the SUR-1 site on the K+/ATPase pump of the β-islet cells in the pancreas, which further trigger the insulin release. There is an improved risk of lower glycemic condition of hypoglycemia associated with the meglitinides.
- **α-Glucosidase inhibitors** (acarbose, miglitol) show pharmacological effects initially by constraining the effect of α-glucosidase

- enzymes on the intestinal brush border in the gut wall. α-Glucosidase is considered a key enzyme that leads to the breakdown of carbohydrates to lower molecular weight carbohydrates like starch, dextrin, and disaccharides for systemic absorption [28]. α-Glucosidase inhibitors could also have a synergistic effect to stimulate GLP-1 secretion. A protease enzyme called Dipeptidyl peptidase-4 (DPP-4) is accountable for the deactivation of hormones GLP-1 and GIP (gastric inhibitory peptide) [29].

Table-1: Mechanism of action of western and herbal medicine mechanism upon different area in management of diabetes control (figure- 1)

Drug used	Carbohydrate uptake inhibition (1)	Increment of Peripheral glucose uptake (2)	PPARγactivation (3)	Modulation of expression in insulin receptor activity (4)	Insulin receptor response improvement (4)	Reduction of natural cell death (apoptosis) (5)	Increase insulin secretion (6)	Reduced glucon eogenesis/glycogenolysis (7)	reduction of glucagon activity (8)
Biguanides		ü			ü			ü	
Sulfonylureas			ü						
Thiazolidinediones							ü		ü
GLP-agonists							ü		
Meglitinides							ü		
α-glucosidase inhibitors	ü								
DPP-4inhibitors							ü		ü
Herbal medicine									
G.sylvestre							ü		
M.charantia	ü	ü	ü			ü		ü	
F.Mori	ü	ü							
T.foenum-graecum		ü					ü	ü	
RidixRehmanniae							ü	ü	
S.tetrandra							ü		
Rhizomacoptidis	ü			ü	ü				
Radixastragali					ü		ü		
E.japonica							ü		
G.biloba	ü	ü							
Radixginseng		ü	ü			ü	ü		
Fructusschisandrae	ü		ü		ü	ü	ü		
P.lobata	ü	ü	ü			ü			
C.officinalis	ü	ü			ü	ü		ü	
B.racemosa	ü								
S.cumini	ü							ü	
T. cordifolia	ü						ü	ü	
O. basilicum	ü								
B. aristata								ü	

- DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin) help to intensify the endogenous GLP-1levels.

- An endogenous enzyme called amylin and its analogs (pramlintide) further facilitate endogenous amylin secretion along with insulin from pancreatic β-islet cells by binding to amylin receptors present in the brain as well as reducing gastric emptying, reducing post prandial glycemic levels [30,31].

- Table -1 contains the different mechanisms of action by western medicine as well as medicine used in Chinese and Indian traditional herbal systems to manage the diabetic condition.

Herbal medications for treatment and prevention of diabetes in India and China:

Around 800 plants are identified which have been found to possess a key role in the prevention and treatment of T2DM in the traditional Chinese and Indian herbal medicinal cultures. Ancient traditional herbal medicine provided the foundation for the prevention and treatment of numerous diseases. Out of them, several herbal preparations are present as a unit of herbal extract or in a mixture of herbal extract formula. Over 400 herbal extracts were found to be a positive effect in In-vitro or In-vivo while treating T2DM or NIDDM [32].

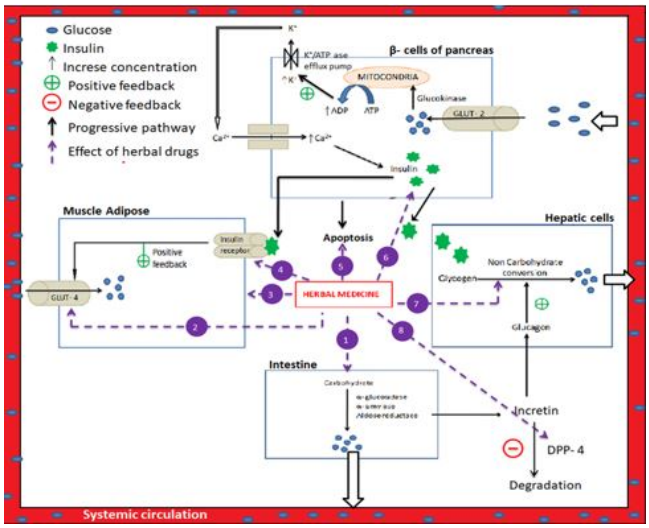

Fig. no. 1: Different mechanisms of action of herbal (1. Inhibition of carbohydrate absorption. 2. Insulin sensitivity improvement of insulin-resistant cells. 3. Rising glucose uptake by peripheral cells. 4. Modulating insulin release. 5. Improving endogenous incretins activities. 6. Exercising anti-oxidant effects and constraining cell apoptosis. 7. Triggering the glycogenesis or suppressing hepatic glycogenolysis).

The medicinal activity of the herbal extract can be differentiated as (Figure1) [32-34].

1. Inhibition of carbohydrate absorption.

2. Insulin sensitivity improvement of insulin-resistant cells.

3. Rising glucose uptake by peripheral cells.

4. Modulating insulin release.

5. Improving endogenous incretins activities.

6. Exercising anti-oxidant effects and constraining cell apoptosis.

7. Triggering the glycogenesis or suppressing hepatic glycogenolysis.

- **Gymnema sylvestre Schult** (synonym. Periploca sylvestris Retz, **Gurmar in Hindi**), belongs to the genus Gymnema and the family of Apocynaceae, mostly found in the tropical forests present beneath the equator as southeast Asian countries like the central portion of India, the southern part of China and Vietnam. It is also found in countries like Australia, and the African continent. In India and China as an herbal medicine practice the leaves of sylvestre are mostly used in several treatment regimens for conditions like diabetes, hypercholesterolemia, joint pain, and snake bites [35, 36]. The chemical constituents which are present in higher amounts within the leaves of G. sylvestre are gymnemic acids I-VII, conduritol lA, triterpenoid saponins (gymnemosides A-F and gymnemoside W1-2), and dihydroxy gymnemic triacetate. The active constituents that are pharmacologically active in the leaves are gymnemic acids, a class belonging to the oleanane-type triterpenoid saponins also containing gymnemic acids I-VII, gymnema saponins along with their byproducts like deacyl gymnemic acid (DAGA) which is further 3-O-glucuronide of gymnemagenin (3,16,21,22,23,28hexahydroxy-olean-12-ene) [36]. The extracts of G. sylvestre were found to have the ability to restore pancreaticβ cells and also enhance the circulating insulin levels in the blood by increasing its secretion [37]. In an unrestrained trial or open trial conducted 65 individuals associated with both T1DM and T2DM have been administered 800 mg/daily G. sylvestre extract orally. The fasting blood glucose (FBG) and HbA1C levels were significantly reduced by 11% and 0.6%, respectively [38].
- **Momordica charantia** (commonly called bitter melon or bitter gourd, **karela in hindi,** or balsam pear), is a creeper consisting of a tendril and comes under the family of Cucurbitaceae that is used in treating diabetes in China, India, South America, East Africa, and the Caribbean. The main constituents of charantia seeds are mostly eleostearic acid and stearic acid, which make up almost 45% of its entire weight. Apart from this, various glycosides, like charantin and vicine, have also been isolated from their stem and fruit. Polypeptide-p, lipids, triterpenoids, and alkaloids are also found in sufficient amounts in the plant. [32, 39]. T2DM patients have been found to be benefitted from the juice obtained freshly from its fruit, as it lowers the glucose. [40, 41], although the extract of the dried fruit is not so useful [42]. The ethyl acetate extract of M. charantia has shown activity in terms of stimulating peroxisome proliferator-activated receptors (PPAR α and γ) and also by regulating the countenance of the acyl CoA oxidase gene upon the H4IIEC3 hepatoma cells. The restriction of peroxidation and apoptosis causes the enhancements in the functioning of the βcell and also improvises the insulin release. In adipocyte cells, the glucose transporter-4 (GLUT4) triggered transport to the cell membrane and enhanced the action of adenosine monophosphate-activated protein kinase (AMPK), which also can increase the glucose uptake from the blood by momordicosides from M. charantia [43].
- **Morus alba L.**(also known as the mulberry tree, **Shahtut in Hindi**) is found broadly in the Asian continent. With a wide variety of substituents for its leaves, Folium is more used clinically in Chinese ancient medicine as a hypoglycemic, hypotensive, and diuretic agent. Traditionally mori has been used to treat uncontrolled glucose levels in blood or hyperglycemic condition. The key pharmacologically active constituents are flavonoids, alkaloids (1 deoxynojirimycin), and polysaccharides [44, 45]. The extract of F. mori improved glucose uptake and consequently boost the translocation of GLUT-4. The possibilities of ameliorated adipocytokines extract in white adipose tissue is probably due to the constraining of oxidative stress. 1 deoxynorimycin, one of the alkaloidal

- contain has been found to be a powerful suppressor of α-glucosidase [46-49].
- **Trigonella foenum-graecum L** (also known as fenugreek seeds**, Methi in hindi**), belongs to the family Fabaceae. Ancient Egyptians used the fenugreek seed as a traditional remedy and infiltrated it across Asian countries like India and China. These seeds contain a high amount of galactomannan, which is basically a polysaccharide and also known as a source of other chemical components like diosgenin, yamogenin, gitogenin, and tigogenin, which are basically saponins. It is also consisting of other pharmacologically active components like mucilage, volatile oils, alkaloids, and neotigogens [50-52]. An amino acid obtained, purified from fenugreek seeds known as 2S, 3R, 4S, and 4-hydroxy iso leucine, displayed positive feedback towards insulin release that enhanced the glucose uptake by peripheral organs in an In-vitro study [59–61]. A meta-analysis of foenum-graecum also revealed that the herb has the possibility to reduce HbA1C by 1.13% (P = 0.03) [67]. At the same time, it reduces the hepatic enzymatic activity (hexokinase, glucokinase, G6P, and fructose-1,6-bisphosphatase) and increases insulin activity which leads to a reduction in blood sugar levels [53-61].
- **Radix rehmanniae (**Chinese medicine known as **Sheng Di huang**), is a root of the plant Rehmannia glutinosa Libosch, which belongs to the family Scrophulariaceae or It is used as a remedy for several diseases condition related to the blood, immune system, endocrine system, nervous system, and cardiovascular systems. Usually, it is prepared as a mixture of different herbs like R. ginseng, R. scutellariae, and R. astragali. These mixtures triggered the insulin release and β-cell rejuvenation by induction of insulin receptor substrate 2. The presumed mechanism of action are triggering insulin release, improving glucose metabolism, and constraining glycogen activity in hepatic cells [62-64].
- **Stephania tetrandra Moore** (Chinese medicine known as **Hang Fang Ji**), an herbaceous perennial creeper from the family of Menispermaceae, which is a very essential herb used in the Chinese herbal system for the purpose of decreasing inflammation and as a pain reliever (analgesic). The hypothesized anti-hyperglycemic action of tetrandra extract is the provocation of insulin secretion throughβ-cells in the pancreas [65, 66].
- **Rhizoma coptidis** (Chinese name of **Huang Lian**), is a rhizomal part of Coptis chinensis Franch from the family known as Ranunculaceae. It is generally used in innumerable treatment counter to several clinical conditions like intestinal infections, diarrhea, swelling, hypertension, and hypoglycemia. It contains isoquinoline alkaloid and berberine. Berberine is considered for its antihyperglycemic effects. Berberine shows an anti-hyperglycemic effect by stimulating the AMPK pathway or inducing insulin receptor expression leads to enhancement of insulin sensitivity [67, 68].
- **Radix astragali** (in Chinese **Huang Qi**), is a dehydrated root of a long-living herbs Astragalus membranaceus (Fisch.) Bunge and Astragalus mongholicus (Fabaceae) Bunge belongs to the family Leguminosae. The herb is usually found in northern parts of China. The main clinically active constituents in astragali are formononetin, calycosin, and ononin which are chemically classified under the categories of the isoflavones and isoflavonoids. It also contains saponins derivatives like stragaloside IV, astragaloside II, astragaloside I and acetylastragaloside. A saccharide known as astragaluspoly is involved in the improvement of the activity of insulin and diminishing the chances of fatty liver development [69, 70].
- **Eriobotrya japonica Lindl** (Chinese name **Loquat**), belongs to the family Rosaceae. japonica dried leaves are also termed Folium eriobotryae. It is used for several disease management like chronic respiratory conditions like bronchitis, and dry cough. It was also found to be effective in the management of DM. The main chemical constituents identified are classified under a large variance of chemical entities like triterpenes, sesquiterpenes, and flavonoids. It also contains glycosides known as Megastigmane and its derivative. Other polyphenolic derivatives like ursolic acid, oleanolic acid, cinchonain Ib, procyanidin

- B-2, chlorogenic acid, and epicatechin are also identified. It generally works by stimulating insulin secretion [71-73].
- **Ginkgo biloba** (Chinese name **Maidenhair tree**), improved glucose metabolism by hepatic cells and peripheral muscle. It also plays a role in constraining the formation of atherogenic plaque, which further leads to atherogenesis, which is more often considered to be associated with comorbidity of patients with DM. An In-vitro assay concluded that the anti-hyperglycemic action of ginkgo is due to its suppressing effect upon activities of enzymes like α-glucosidase and amylase. Though in the case of T2DM individuals, oral administration of biloba extract displayed a significant reduction in insulin clearance which further helps the reduction of systemic insulin concentration to preserve the β- cells function and maintain peripheral insulin levels to control the high blood glucose. early use of G.biloba may facilitate endothelial activity in diabetic nephropathy without affecting blood glucose levels [74, 75].
- **Radix ginseng**, ginseng is often named depend up on its demographical occurrence like Asian ginseng, American ginseng, and Chinese ginseng. More than 700+ compounds are found in ginseng. Most of the active chemical constituents known are ginsenosides polysaccharides, peptides, and polyacetylenic alcohols [76]. Anti-hyperglycemic effects have been found more prominent in the case of lipophilic extracts than the aqueous R. ginseng extracts. The extract acted by triggering the insulin excretion from isolated cells of pancreatic islets. Vuksan al., have performed a series of human trials which provide confirmations of significant reduction of postprandial blood glucose (PPG), fasting blood glucose (FBG), and glycosylated hemoglobin (HbA1C) levels, which is an important parameter for the individual with DM and having a risk factor associated with renal impairment [77-79]. At the same time, it helped to reduce β-cell apoptosis by improving adipocytic PPAR-γ protein expression. It also reduces β-cell degeneration by upregulating adipocytic cellular gene known as PPAR-γ protein expression. R. ginseng improves glucose absorption by diminishing glucosidase activity [80,81]. Ginsenoside Rb1, one of the constituents has the ability to increase glucose transport by triggering the adipocyte differentiation by improving the PPAR-γ and C/EBP-α gene expression in adipocytic tissue. Ginsenoside Rb1 also possessed a synergistic affect along with modification in tissue-specific gene expression by increasing GLUT-4 movement to the cell wall which amplified glucose uptake from the systemic circulation by adipocytes [82, 23].
- **Fructus schisandrae,** in China it is well known as "**five-flavor berry**". It is considered a rich source of lignans and gomisins. The lignans are such as schizandrins (schizandrin A) whereas gomisins are of three types gomisin A, J, and N. A subtype of gomisins called angeloylgomisin H is also present as a chemical constituent. It also contains polysaccharides. It has been seen that the basal glucose metabolism by immortalize HepG2 cells obtained from hepatic carcinoma cells of a 15 year old Caucasian male is facilitated by gomisins N and schizandrin A [84]. Other schizandrins were also found which are also having the ability to avert β-cell degeneration and improve insulin sensitivity [85]. The main imagined mechanisms are (i) the triggering the insulin release, (ii) improved insulin sensitivity, (iii) reducing insulin resistance, (iv) improved PPAR-γactivity, and (v) inhibiting the enzyme called aldose reductase schisandrae can also improve glucose homeostasis [86].
- **Pueraria lobata** is also known as It is a dried root of Pueraria lobata (Willd.), Belonging to the family Leguminosae. The vine is frequently found in a native portion of Southeast Asia and is known by different names like yegen, kudzu root, etc. The main chemical constituent in P. lobata is puerarin which has the ability to increase the glucose uptake in a dose-dependent manner in a clinical trial with high glucose-treated preadipocytes [87]. A chemical constituent known as Puerarin facilitates insulin-induced preadipocyte differentiation. The purarin also caused increased mRNA expression upon the PPARγ gene of adipocyte cells, which helps to control several mechanisms like g
- lucose homeostasis by uptaking glucose from the systemic circulation, adipocyte glucose intake, and lipid absorption [88].

- **Cornus officinalis,** usually found in several parts of Asia like China, Japan, and Korea, belongs to the family Cornaceae. The main chemically active constituents are iridoid glycosides, morroniside, loganin, mevaloside, loganic acid, ursolic acid, oleanolic acid, 5-hydroxymethyl-2-furfural, and 7-O-galloyl-D-sedoheptulose. Fructus corni ethanolic extract stimulated the GLUT-4 transporter in the cell wall by triggering the regeneration of pancreatic islets cells which further leads to improved insulin excretion. Another active constituent known as ursolic acid signaled an inhibitory response toward protein tyrosine phosphatase (PTP) 1B, which improves the sensitivity of insulin towards cells. The stated mechanisms include several pathways like suppression of glucosidase enzyme, reducing the gene modulated hepatic gluconeogenesis, protecting the β-cells against toxicity, and improvement of insulin release [89,90].
- **Barringtonia racemose** (in Hindi **Hijjal)**, is an evergreen mangrove tree that grows in the delta region of Padma river in Bangladesh, the west and east coastal area especially the Bay of Bengal (Sundarban) of India, and Sri Lanka. Several di and tri-terpenoids are found in racemosa extract. The main chemical constituent was found to be a pentacyclic triterpenoid chemically known as bartogenic acid. The hexane and alcoholic extracts including pure bartogenic acid suppressed the intestinal α-glucosidase activity [91].
- **Syzygium cumini (L.) Skeels** (**Jamun** in Hindi), is a tree found in the tropical region of India, China, and Indonesia. Depending upon demographical variances Skeels is also well known by different names like Eugenia jambolana, Jamun, Jambu, Black Plum, or Black Berry. In countries like India and Brazil, cumini is used very frequently as a common remedy in the management of T2DM. It showed significant depletion in glycemic levels especially PPG as well as LDL, and free fatty acids. The extracts of S. cumini exhibit the ability to inhibit α-glucosidase activities. On the other hand, significant reduction of enzymatic activities in the liver by glucokinase and phosphofructokinase, which have a major character in glucose digestion in cases of DM [92, 93].
- **Tinospora cordifolia** (**guduchi, giloy**) falls under the family Menispermaceae. It is a juicy climbing plant. The abundance of this plant was found in tropical areas of Indian subcontinent countries like India, Bangladesh, Myanmar, and Srilanka. The primary bioactive constituents identified are alkaloidal derivatives like palmatine, jatrorrhizine, and magnoflorine. It also contains glycoside and its derivative including di-terpenoid lactones, sesquiterpenoid, steroids, phenolics, aliphatic compounds, and polysaccharides. cordifoliahas have been found to benefit diabetic neuropathy when taken at a dosage of 400 mg/kg body weight. The anti-hyperglycemic effect is often due to the reduction of the formation of thiobarbituric acid-reactive constituents to release oxidative stress. The extract of this plant also enhances the manifestation of thioredoxin and glutaredoxin. The extract of this plant also helps in the regulation of carbohydrate metabolism and decreases gluconeogenesis through the inhibition of G6P and fructose1, and 6-diphosphatase. There are other different ways that are found to increase insulin release and also blockα-glucosidase [94, 95].
- **Ocimum basilicum,** (**Tulsi in hindi**) is commonly known as **basil,** or sweet basil is a herb used in cooking and falls under the family Lamiaceae (mints). The primary constituents of basil contain apigenin, linalool, and ursolic acid, that often-showed various anti-viral actions. Basil improvised lipid metabolism. The ethanolic extract of basil decreased cholesterol production too. It is advised that basilicum can be used in the case of dietary therapy in minor to moderate T2DM [94, 96].
- **Berberis aristate,** in India, is also known as **Zarshik, Daruharidra**. It belongs to the family Berberidaceae. It is also a traditional herb that has been used since ancient times in South Asia mostly in the form of herbal decoction to enhance the liver and heart functionalities. The prime ingredients from the root are found to be berberine, berbamine, and also palmatine. The root of aristateextract shows a good possibility to control glycemic homeostasis by reducing gluconeogenesis by hepatic cells and also by constraining oxidative stress. B. aristate plant helps to enhance the glucokinase activity which helps glucose break down to glucose-6P

- and reduced the Glucose 6-P dehydrogenase action for further metabolism. B. aristate extract and S. marianum extract synergistic action in fatalities who have conditions like sub-optimal glycemic control, impaired basal insulin, high HbA1C, insulin resistance, uncontrolled amount of total and also low-density lipoprotein cholesterol, and triglycerides were prominently decreased after the 90-day treatment with [94, 97, 98].

Few other Indian herbs which are also used for the prevention and management of Diabetes Mellitus are discussed in Table- 2 along with their mechanism of action

Table-2 Other Indian herbs which show antidiabetic activities [99]

Plant name	Common name	Mechanism
Annona squamosa	Sugar apple	Ethanolic leaf extract of the leaves displays Hypoglycemic and anti-hyperglycemic activities and Improves the plasma insulin level.
Areca catechu	Supari	Hypoglycemic effect
Boerhavia diffusa	Punarnava	Intensify the activity of hexokinase, constraining the activity of glucose-6-phosphatase and fructose bis-phosphatase, surge the plasma insulin concentration, and also impart an anti-oxidant activity.
Bombax ceiba	Semul	Glucose lowering effect
Butea monosperma	Palasa	Glucose lowering effect
Camellia sinensis	Tea	Glucose lowering activity imparts an anti-oxidant activity.
Emblica officinalis	Amla, Dhatriphala, "Triphala"	Diminishes peroxidation of lipid, acts as an anti-oxidant, blood glucose-lowering effect.
Ipomoea batatas	Sakkargand	Declines insulin resistance.
Musa sapientum	Banana	Anti-hyperglycemic, antioxidant effect.
Punica granatum	Anar	Antioxidant, anti-hyperglycemic effect.
Swertia chirayita	Chirata	Triggersinsulin secretion from the pancreas.
Terminalia belerica	Behada, a constituent of "Triphala"	Antibacterial, hypoglycemic
Withania somnifera	Ashwagandha or winter cherry	Glucose lowering effect, as an effective diuretic and constraining the high lipid concentration.

Marketed diabetes formulation in India:

There are several herbal formulations for diabetes management (refer to Table 2) that are already available in the Indian market. These herbal formulations are used more often by the individuals associated with DM as directed by physicians. Below is the table the components of each formulation are enlisted.

Table-3: Marketed formulation of herbal mixture in India and their mechanism of action [99].

Drug	Company	Composition	Mechanism of action
Pancreatic tonic 180 cp	Ayurvedic herbal supplement	Vijaysar (P. marsupium), Gurmar (G. sylvestre), Karela (M. charantia), Jamun (S. cumini), Methi(T. foenum graceum), Neem (A. indica), Gular (F. racemose), Bael (A. marmelos),Tjapata (C. tamala)	As a dietary supplement.
Ayurveda alternative herbal formula for Diabetes	Chakrapani Ayurveda	Gurmar, Karela, Pushkarmool (I. racemosa) Jamun Gutli (S. cumini) Neem (A. indica) Methi (T. foenum gracecum), Guduchi (T. cordifolia)	Gurmar trigger insulin release and reduce blood sugar level. It possesses the ability to block the sweet taste buds if applied to the tongue in diabetic patients to avoid glycosuria. Act as a cardiotonic. Act as a diuretic. Help to improve metabolic events that occur in hepatic cells, renal tissues, and skeletal muscles.
Bitter gourd Powder	Garry and Sun natural Remedies	Karela (M. charantia)	It lowers blood & urine sugar levels. Anti-hemorrhoidal helped in protein precipitation (astringent), improved digestion, improve the sexual problem, improve hepatic activity, act as an anthelmintic, and also helped in blood purification.
Dia-care	Admark Herbals Limited	Sanjeevan Mool; a mixture of Kali harad (black Himej), Jamun beej, Kadu/chirota (A. Paniculate), Namejav, Neem chal powder (A. indica)	Lowering blood & urine glycemic levels.
Diabetes-Daily Care	Nature's Health Supply	α-Lipoic Acid, 4% Cinnamon Extract, Chromium picolinate (chromax®), Vanadium, 50% Fenugreek seed extract, 25% alcoholic extract of Gymnema sylvestre, 7% alcoholic Momordica extract, 20% ethanolic extract of Licorice Root.	Exhibited insulinotropic effects that enhanced the peripheral glucose uptake
Epinsulin	Swastik Formulations	Vijaysar (P. marsupium)	Mechanism not disclosed
Diabecure	Nature beaute sante	Common walnut (J. regia), Common berry (B. vulgaris), Common centaury (C. erytharea), Yarrow (Millefolium), Dudhi/Baran (T. officinale)	It helps to provide comfort from the conditions like normal cold associated with weakness, leg pain, and lethargy. Also, help in the case of multi urination (polyuria) and hypersensitivity reaction like pruritis.

Diabetica	Ayurvedic cure Ayurvedic Herbal Health Products	Gurmar (G. sylvestre), Sadabahar/ Periwinkle (V. rosea), Haldi/Turmeric (Curcuma longa), Neem (A. Indica), Kino Tree (P. Marsupium), Karela/ Bitter Gourd (M. charantia), Jamun/ Black Plum (S. cumini), Black Babhul (A. arabica), Guduchi (T. Cordifolia), Ginger/adrakh (Z. officinale).	As an anti-hyperglycemic agent. Act as potent immunomodulators. Imparts a lipid-lowering effect, is an anti-depressant, and possesses hepatoprotective activity. Help to improve the sensitivity of oral hypoglycemic agent while used as an adjuvant.
Syndrex	Plethico Laboretaries	The germinated Fenugreek seed extract	Mechanism not disclosed
Diabecon	Himalaya	Gurmar (G. sylvestre), Vijaysar (P. marsupium), Mulathi/liquorise (G. glabra), Saptarangi (C. esculenta), Jamun (S. cumini), Shatavai (A. racemosus), Punarnava (B. diffusa), Chagul nudi (S. indicus), Guduchi (T. cordifolia), Chirayata (S. chirata), Gokharu (T. terrestris), Amla (P. amarus), Ghamar (G. arborea), Kapas (G. herbaceum),Zarshik/ Daruharidra (B. aristate), Aloe vera (A. barbadensis miller), Triphala, Gugul (C. wightii), Shilajeet, Karela (M. charantia), Pudina (P. nigrum), Tulsi (O. sanctum), Kanghi (A. indicum), Turmric(C. longa), Palak (R. maritimus).	Facilitate exterior glucose metabolism. Intensification of glucagon concentration in the liver and skeletal muscle. Facilitate B cells restoration and prevention from oxidative stress. Upsurge c peptide concentration. Constrain HBA1C level. Stabilizing the microalbuminuria. Correction of lipid profile.
Diasulin	Himalaya	Tarwar (C. auriculate), Telakucha/tondikay (C. indica), Haldi/Turmeric (C. longa), Amla (E. officinalis), Guduchi (G. sylvestre), Karela (M. charantia), Tulsi (S. dulcis), Jamun (S. cumini), Guduchi (T. cordifolia), Meethi (T. foenum graecum)	Epicatechin triggers a surge of cAMP concentration in islet, which is facilitating the improved insulin secretion. A high concentration of cathepsin promotes insulin conversion from proinsulin. Shows an effect like insulin upon osmotic breakability of red blood cells by Constraining Na/K ATPase pump. Amends the neuro Retinopathy. It also helps to facilitate glucose and lipid metabolism.

Discussion and Conclusion

Herbal treatments were engraved in their marks as one of the most accepted methods to manage and treat several physiological conditions including DM. In the current scenario, an urge to know about The mechanism of action along with their associated benefits and adverse events of these herbal alternatives can be encountered frequently. Keeping that into consideration we performed an extensive review to re-establish the herbal drugs as individuals or as adjunctive therapy to effectively manage the Diabetes mellitus triumph. In this review, we, draw a potential image of a gamut of medicinal plants as a standout option for the prevention, well-being, and treatment of diabetes. In addition, adverse events of herbal medication were found to be less than the conventional synthetic approaches. Hence, the growing demand for marketed formulations of herbal mixtures in India shows the future perspective of the polyhebal medication to manage diabetes mellitus.

Reference

1. Ahmed AM. History of diabetes mellitus. Saudi Med J 2002;23(4):373-8.

2. Diabetes mellitus history- from ancient to modern times. Available at http://science.jrank.org/pages/2044/Diabetes-Mellitus.html. Accessed July 2011.

3. Maitra A, Abbas AK. Endocrine system. In: Kumar V, Fausto N, Abbas AK (eds). Robbins and Cotran Pathologic basis of disease (7th ed) 2005. Philadelphia, Saunders; 1156-226.

4. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus: present and future perspectives. Nature reviews endocrinology. Available at: www.nature.com/uidfinder. (Accessed 22nd December 2011)

5. Genetic basis of type 1 and type2 diabetes, obesity, and their complications. Advances and emerging opportunities in diabetes research: a Strategic Planning report of the DMICC. www2.niddk.nih.gov/NR. (Accessed 22nd December 2011)

6. Joshi SR, Parikh RM. India - diabetes capital of the world: now heading towards hypertension. J Assoc Physicians India. 2007; 55:323–4.

7. Kumar A, Goel MK, Jain RB, Khanna P, Chaudhary V. India towards diabetes control: Key issues. Australas Med J. 2013;6(10):524-31.

8. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes-estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(3):1047-53.

9. Whiting Dr, Guariguata L, Weil C, Shawj. IDF Diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract. 2011; 94:311-21.

10. Seema AK, Jon C. The current state of diabetes mellitus in India. Aus Med J. 2014, 7, 1, 45-48.

11. Anjana RM, Ali MK, Pradeepa R, Deepa M, Datta M, Unnikrishnan R, Rema M, Mohan V. The need for obtaining accurate nationwide estimates of diabetes prevalence in India - rationale for a national study on diabetes. Indian J Med Res. 2011; 133:369-80.

12. Zargar AH, Khan AK, Masoodi SR, Laway BA, Wani AI, Bashir MI, Dar FA. Prevalence of type 2 diabetes mellitus and impaired glucose tolerance in the Kashmir Valley of the Indian subcontinent. Diabetes Res Clin Pract. 2000;47(2):135-46.

13. Ramachandran A, Snehalatha C, Kapur A, Vijay V, Mohan V, Das AK, Rao PV, Yajnik CS, Prasanna Kumar KM, Nair JD; Diabetes Epidemiology Study Group in India (DESI). High prevalence of diabetes and impaired glucose tolerance in India: National Urban Diabetes Survey. Diabetologia. 2001;44(9):1094-101.

14. Arora V, Malik JS, Khanna P, Goyal N, Kumar N, Singh M. Prevalence of diabetes in urban Haryana. Australas Med J. 2010;3(8): 488-94.

15. "Standards of medical care in diabetes—2012," Diabetes Care.2012;35(1):11–63.

16. SE Inzucchi, RM Bergenstal, JB Buseetal. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012;55(6):1577–96.

17. D Galuska, J Zierath, A Thorne, T Sonnenfeld, H Wallberg-Henriksson. Metformin increases insulin-stimulated glucose transport in insulin-resistant human skeletal muscle. Diabetes Metabolism. 1991;17(1):159–63.

18. M Stumvoll, N Nurjhan, G Perriello, G Dailey, JE Gerich. Metabolic effects of metformin in non-insulin dependent diabetes mellitus. N EngJofMed. 1995; 333(9):550–4.

19. S Matthaei, H Greten. Evidence that metformin ameliorates cellular insulin-resistance by potentiating insulin-induced translocation of glucose transporters to the plasma membrane. Diabetes Metabolism. 1991;17(1):150–8.

20. WC Knowler, E Barrett-Connor, SE Fowleretal. Reduction in the incidence of type 2 diabetes with life style intervention or metformin. New England Journal of Medicine. 2002;346(6):393–403.

21. CN Halesand, RD Milner. The role of sodium and potassium in insulin secretion from rabbit pancreas. J Physio. 1968;194(3):725–743.

22. Standards of medical care in diabetes—2012. Diabetes Care. 2012;.35(1):11–63.

23. SE Inzucchi, RM Bergenstal, JB Buseetal. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012;55(6):1577–96.

24. H Yki-Jarvinen. Thiazolidinediones. The N Eng J Med.2004;351(11):1106–18.

25. SE Nissen, K Wolski. Effect of rosiglitazone on the risk of myocardial infraction and death from cardiovascular causes. N Eng J Med. 2007;356(24):2457–71.

26. DJ Drucker and MA Nauck. The incretin system: glucagon like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. The Lancet. 2006;368(9)548:1696–1705.

27. J Gerich, P Raskin, L Jean-Louis, Durkayastha, MA Baron. PRESERVE-beta: two-year efficacy and safety of initial combination therapy with nateglinide or glyburide plus metformin. Diabetes Care. 2005;28(9):2093–9.

28. FA Van de Laar, PL Lucassen, RP Akkermans, EH Van de Lisdonk, WJ DeGrauw. Alpha-glucosidase inhibitors for people with impaired glucose tolerance or impaired fasting blood glucose. Cochrane Database of Systematic Reviews. No. 4, p.CD005061, 2006.

29. A Peters. Incretin-based therapies: review of current clinical trial data. American J of Med. 2010;123(3):28–37.

30. BJ Hoogwerf. KB Doshi, D Diab. Pramlintide, the synthetic analogue of

Amylin: physiology, pathophysiology, and effects on glycemic control, bodyweight, and selected biomarkers of vascular risk. Vascular Health and Risk Management. 2008;4(2):355–62.

31. M Samsom, LA Szarka, M Camilleri, A Vella, AR Zinsmeister, RA Rizza. Pramlintide, an amylin analog, selectively delays gastric emptying: potential role of vagal inhibition. Am J Physio. 2000;278(6):946–51

32. PK Prabhakar, M Doble. Mechanism of action of natural products used in the treatment of diabetes mellitus. Chinese J of Integrative Med. 2011;17(8):563–574.

33. WL Li, HC Zheng, J Bukuru, ND Kimpe. Natural medicines used in the traditional Chinese medical system for therapy of diabetes mellitus. J of Ethnopharmacology. 2004;92(1):1–21.

34. M Bhat, SS Zinjarde, SY Bhargava, AR Kumar, BN Joshi. Anti-diabetic Indian plants: a good source of potent amylase inhibitors. Evidence-Based Complementary and Alternative Medicine. 2011;2011(ArticleID810207).

35. JK Grover, S Yadav, V Vats. Medicinal plants of India with anti-diabetic potential of Ethnopharmacology. 2002;81(1):81–100.

36. XM Zhu, P Xie, YT Di, SL Peng, LS Ding, MK Wang. Two new triterpenoid saponins from Gymnema sylvestre. Journal of Integrative Plant Biology. 2008;50(5);589–92.

37. P Daisy, J Eliza, KAM Mohamed Farook. A novel dihydroxy gymnemic triacetate isolated from Gymnema sylvestre possessing normal glycemic and hypolipidemic activation STZ induced diabetic rats. Journal of Ethnopharmacology. 2009;126(2):339–44.

38. R Nahas, M Moher. Complementary and alternative medicine for the treatment of type 2 diabetes. Canadian Family Physician. 2009;55(6):591–6.

39. L Leung, R Birtwhistle, J Kotecha, S Hannah, S Cuthbertson. Anti-diabetic and hypoglycaemic effects of Momordica charantia (bitter melon): a mini review. British Journal of Nutrition. 2009;102(12):1703–1708.

40. J Welihinda, EH Karunanayake, MHR Sheriff, KSA Jayasinghe. Effect of Momordica charantia On the glucose tolerance in maturity onset diabetes. Journal of Ethnopharmacology. 1986;17(3):277–82.

41. N Ahmad, MR Hassan, H Halder, KS Bennoor. Effect of Momordica charantia (Karolla) extracts on fasting and postprandial serum glucose levels in NIDDM patients. Bangladesh Medical Research Council Bulletin. 1999;25(1):11–3.

42. A Tongia, SK Tongia, M Dave. Phytochemical determination and extraction of momordica charantia fruit and its hypoglycemic potentiation of oral hypoglycemic drugs in diabetes mellitus (NIDDM). Indian Journal of Physiology and Pharmacology. 2004;48(2):241–4.

43. RM Hafizur, N Kabir, S Chishti. Modulation of pancreatic β-cells in neonatally streptozotocin-induced type 2 diabetic rats by the ethanolic extract of Momordicacharantia fruit pulp. Natural Product Res. 2011;25(4):353–67.

44. LX Yang, TH Liu, ZT Huang, JE Li, LL Wu. Research progress on the mechanism of single-chinese medicinal herbs in treating diabetes mellitus. Chinese J of Integrative Med. 2011;17(3):235–40.

45. H Kim, MH Jang, MC Shin et al. Folium mori increases cell proliferation and neuropeptide Y expression in dentate gyrus of streptozotocin-induced diabetic rats. Biological and Pharmaceutical Bulletin. 2003;26(4):434–7.

46. J Naowaboot, CH Chung, P Pannangpetchetal. Mulberry leaf extract increases adiponectin murine 3T3-L1adipocytes. Nutrition Research. 2012;32(1):39–44.

47. J Naowaboot, P Pannangpetch, V Kukongviriyapan. et al. Mulberry leaf extract stimulates glucose uptake and GLUT4 translocation in rat adipocytes. The American Journal of Chinese Med. 2012;40(1):163–75.

48. T Oku, M Yamada, M Nakamura, N Sadamori, S Nakamura. Inhibitory effects of extractives from leaves of Morus alba on human and rat small intestinal disaccharidase activity. British Journal of Nutrition. 2006;95(5):933–8.

49. T Kimura, K Nakagawa, H Kubota. Food-grade mulberry powder enriched with 1-deoxynojirimycinsup presses the elevation of post prandial blood glucose in humans. Journal of Agri and Food Chem. 2007;55(14):5869–74.

50. HA Bawadi, SN Maghaydah, RF Tayyem, RF Tayyem. The postprandial hypoglycemic activity of fenugreek seed and seeds' extract in type 2 diabetics: apilotstudy. Pharmacognosy Magazine. 2009;4(18):134–8.

51. X Pang, L Kang, H Yuetal. Rapid isolation of new furostanol saponins from fenugreek seeds based on ultra-performance liquid chromatography coupled with a hybrid quadrupole time of-flight tandem mass spectrometry. Journal of Separation Science. 2012;35(12):1538–50.

52. A Mandegary, M Pournamdari, F Sharififar. Alkaloid and flavonoid rich fractions of fenugreek seeds (Trigonella foenum-graecum L.) with antinociceptive and anti-inflammatory effects. Food and Chemical Toxicology. 2012;50(7):2503–7.

53. C Broca, R Gross, P Petit. 4-hydroxyisoleucine: experimental evidence of its insulinotropic and anti-diabetic properties. Amarican Journal of Physio. 1999;277(4):617– 23.

54. MV Vijayakumar, S Singh, RR Chhipa, MK Bhat. The hypoglycaemic activity of fenugreek seed extract is mediated through the stimulation of an insulin signaling pathway. British Journal of Pharmcol. 2005;146(1):41–8.

55. C Broca, V Breil, C Cruciani-Guglielmacci. Insulinotropic agent ID-1101 (4-hydroxyisoleucine) activates insulin signaling in rat. Amarican Journal of Physio. 2004;287(3):463–71.

56. BA Devi, N Kamalakkannan, PSM Prince. Supplementation of fenugreek leaves to diabetic rats. Effect on carbohydrate metabolic enzymes in diabetic liver and kidney. Phytotherapy Research. 2003;17(10):1231–3.

57. MV Vijayakumar, MK Bhat. Hypoglycemic effect of a novel dialyzed fenugreek seeds extract is sustainable and is mediated, in part, by the activation of hepatic enzymes. Phytotherapy Research. 2008;22(4);500–5.

58. Z Madar, R Abel, S Samish, J Arad. Glucose-lowering effect of fenugreek in non-insulin dependent diabetics. European Journal of Clinical Nutrition. 1988;42(1):51–54.

59. RD Sharma, TC Raghuram, NS Rao. Effect of fenugreek seeds on blood glucose and serum lipids in Type I diabetes. European Journal of Clinical Nutrition. 1990;44(4):301–6.

60. JR Mathern, SK Raatz, W Thomas, JL Slavin. Effect of fenugreek fiber on satiety, blood glucose and insulin response and energy intake in obese subjects. Phytotherapy Research. 2009;23(11):1543–8.

61. N Suksomboon, N Poolsup, S Boonkaew, CC Suthisisang. Meta-analysis of the effect of herbal supplement on glycemic control in type 2 diabetes. Journal of Ethnopharmacology. 2011;137(3):1328–33.

62. SM Park, SM Hong, SR Sung, JE Lee, DY Kwon. Extracts of rehmanniae radix, ginseng radix and Scutellariae radix improve glucose-stimulated insulin secretion and beta cell proliferation through IRS 2 induction. Genes and Nutrition. 2008;2(4):347–51.

63. KM Lau, KK Lai, CL Liu. Synergistic interaction between Astragali Radix and Rehmanniae Radix in a Chinese herbal formula to promote diabetic wound healing. Journal of Ethnopharmacology. 2012;141(1):250–6.

64. T Kiho, T Watanabe, K Nagai, S Ukai. Hypoglycemic activity of polysaccharide fraction from rhizome of Rehmannia glutinosa Libosch. f. hueichingensis Hsiao and the effect on carbohydrate metabolism in normal mouse liver. Yakugaku Zasshi. 1992;112(6):393–400.

65. W Ma, M Nomura, T Takahashi-Nishioka, S Kobayashi. Combined effects of fangchinoline from Stephania tetrandra Radix and formononetin and calycosin from Astragalus membranaceus radix on hyperglycemia and hypoinsulinemia instreptozotocin-diabeticmice. Biological and Pharmaceutical Bulletin. 2007;30(11):2079–83.

66. T Tsutsumi, S Kobayashi, YY Liu, H Kontani. Anti-hyperglycemic effect of fangchinoline isolated from Stephania tetrandra Radixinstreptozotocin-diabeticmice. Biological and Pharmaceutical Bulletin. 2003;26(3):313–7.

67. SL Lin, LH Zhao, YM Wang, SS Dong, DK An. Determination of berberine in Angong Niuhuang Wan by HPLC. Acta Pharmaceutica Sinica. 1989;24(1);48–52.

68. ZJ Huang, Y Zeng, P Lan, PH Sun, and WM Chen. Advances in structural modifications and biological activities of berberine: an active compound in traditional Chinese medicine. Mini-Reviews in Med Chem. 2011;11(13):1122–9.

69. JZ Song, HHW Yiu, CF Qiao, QB Han, HX Xu. Chemical comparison and classification of Radix Astragali by determination of isoflavonoids and astragalosides. Journal of Pharm and Biomed Analysis. 2008;47(2):399– 406.

70. ZM Lu, YR Yu, H Tang, XX Zhang. The protective effects of Radix Astragali and Rhizoma Ligustici Chuanxiong on endothelial dysfunction in type 2 diabetic patients with micro albuminuria. Journal of Sichuan Uni. 2005;36(4):529–32.

71. H Ito, E Kobayashi, SH Li. Antitumor activity of compounds isolated from leaves of Eriobotrya japonica. Journal of Agri and Food Chem. 2002;50(8):2400–03.

72. EH Lee, DG Song, JY Lee, CH Pan, BH Um, SH Jung. Inhibitory effect of the compounds isolated from Rhus verniciflua on aldose reductase and advanced glycation end products. Biological and Pharmaceutical Bulletin. 2008;31(8):1626–30.

73. EN Li, JG Luo, LY Kong. Qualitative and quantitative determination of seven triterpene acids in Eriobotryajaponica Lindl. by high-performance liquid chromatography with photodiodearray detection and mass spectrometry. Phytochemical Analysis. 2009;20(4):338–43.

74. M da Silva Pinto, YI Kwon, E Apostolidis, FM Lajolo, MI Genovese, K Shetty. Potential of Ginkgo biloba L. leaves in the management of hyperglycemia and hypertension using In vitro models. Bio resource Technology. 2009;100(24):6599–609.

75. XS Li, WY Zheng, SX Lou, XW Lu, SH Ye. Effect of ginkgo leaf extract on vascular endothelial function in patients with early stage diabetic nephropathy. Chinese Journal of Integrative Medicine. 2009;15(1):26–9.

76. LW Qi, CZ Wang, CS Yuan. Isolation and analysis of ginseng: advances and challenges. Natural Product Reports. 2011;28(3):467–95.

77. V Vuksan, MK Sung, JL Sievenpiper et al. Korean red ginseng (Panax ginseng) improves glucose and insulin regulationinwell-controlled, type 2 diabetes: results of a randomized, double-blind, placebo-controlled study of efficacy and safety. Nutrition, Metabolism and Cardiovascular Diseases.2008;18(1):46–56.

78. V Vuksan, JL Sievenpiper, J Wong et al. American ginseng (Panax quinquefolius L.) attenuates postprandial glycemia in a time-dependent but not dose-dependent manner in healthy individuals, Amarican Journal of Clinical Nutrition. 2001;73(4):753–8.

79. EA Sotaniemi, E Haapakoski, A Rautio. Ginseng therapy in non-insulin-dependent diabetic patients. Effects of psychophysical performance, glucose homeostasis, serum lipids, serum aminoterminalpropeptide concentration, and bodyweight. Diabetes Care. 1995;18(10):1373–5.

80. M Yoon, H Lee, S Jeong et al. Peroxisome proliferator activated receptor is involved in the regulation of lipid metabolism by ginseng. British Journal of Pharmacology. 2003;138(7):1295–302.

81. IH Jung, JH Lee, YJ Hyun, DH Kim. Metabolism of ginsenoside Rb1 by human intestinal microflora and cloning of its metabolizing beta-D-glucosidase from Bifidobacterium longumH-1. Biological and Pharmaceutical Bulletin. 2012;35(4):573–81.

82. W Shang, Y Yang, B Jiang et al. Ginsenoside Rb1 promotes adipogenesisin3T3-L1cells by enhancing PPARγ 2 and C/EBPα geneexpression. LifeSciences. 2007;80(7):618–25.

83. HL Kong, JP Wang, ZQ Li SM Zhao, J Dong, WW Zhang. Anti-hypoxic effect of ginseno side Rblonneonatalrat cardiomyocytes is mediated through the specific activation of glucosetransporter-4exvivo. Acta Pharmacologica Sinica. vol., 2009;30(4):396–403.

84. V Lukacova, WS Woltosz, MB Bolger. Prediction of modified release pharmacokinetics and pharmacodynamics from In vitro, immediate release, and intravenous data. AAPS J. 2009;11(2):323–34.

85. BH Gu, NV Minh, SH Lee et al. Deoxyschisandrin inhibits H2O2-induced apoptoticcelldeathinintestinal epithelial cells through nuclear factor-κB. International Journal of Molecular Medicine. 2010;26(3):401–6.

86. DY Kwon, DS Kim, HJ Yang, S Park. The lignan-rich fractions of Fructus Schisandrae improve insulin sensitivity via the PPAR-γ pathways in In vitro and In vivo studies. Journal of Ethnopharmacology. 2011;135(2):455–62.

87. ME Xu, SZ Xiao, YH Sun, XX Zheng, Y Ou, C Guan. The study of anti-metabolic syndrome effect of puerar in In vitro. Life Sciences. 2005;77(25):3183–96.

88. BM Forman, P Tontonoz, J Chen, RP Brun, BM Spiegelman, RM Evans. 15-deoxy-Δ12,14-prostaglandin J2 is a ligand for the adipocyte determination factor PPARγ. Cell. 1995;83(5):803–12.

89. DS Qian, YF Zhu, Q Zhu. Effect of alcohol extract of cornus officinalissieb. EtzucconGLUT4 expression in skeletal muscle in type 2 (non-insulin-dependent) diabetic mellitus rats. Zhongguo Zhongyao Zazhi. 2001;26(12):861–2.

90. W Zhang, D Hong, Y Zhou et al. Ursolic acid and its derivative inhibit protein tyrosine phosphatase 1B, enhancing insulin receptor phosphorylation and stimulating glucose uptake. Biochimica et Biophysica Acta. 2006;1760(10):1505–12.

91. KR Patil, CR Patil, RV Jadav, VK Mhajan, PS Gaikwad. Anti-arthritic activity of bartogenic acid isolated from fruits of Barringtonia racemosa Roxb. (Lecythidaceae). Evidence-based Complementary and Alternative Medicine. 2011;2011(ArticleID785245).

92. PSM Prince, N Kamalakkannan, VP Menon. Antidiabetic and antihyperlipidemic effect of alcoholic Syzigium cumini seeds in alloxan induced diabetic albino rats. Journal of Ethnopharmacology. 2004;91(2-3):209–13.

93. J Shinde, T Taldone, M Barletta et al. Alpha-Glucosidase inhibitory activity of Syzygium cumini (Linn.) Skeels seed kernel in vitro and in Goto-Kakizaki (GK) rats," Carbohydrate Research. 2008;343(7):1278–81.

94. Z Wang, J Wang, P Chan. Treating Type 2 Diabetes Mellitus with Traditional Chinese and Indian Medicinal Herbs. Evidence-Based Complementary and Alternative Medicine. 2013;2013(ArticleID343594):43-59.

95. PD Nadig, RR Revankar, SM Dethe, SB Narayanswamy, MA Aliyar. Effect of Tinosporacordifolia on experimental diabetic neuropathy. Indian Journal of Pharmacology. 2012;44(5):580–3.

96. P Agrawal, V Rai, RB Singh. Randomized placebo controlled, single blind trial of holy basil leaves in patients with noninsulin-dependent diabetes mellitus. International Journal of Clinical Pharmacology and Therapeutics. 1996;34(9):406–9.

97. J Singh, P.Kakkar. Anti-hyperglycemic and antioxidant effect of Berberis aristata root extract and its role in regulating carbohydrate metabolism in diabetic rats. Journal of Ethnopharmacology. 2009;123(1):22–6.

98. FD Pierro, N Villanova, F Agostini, R Marzocchi, V Soverini, G. Marchesini. Pilot study on the additive effects of berberine and oral type 2 diabetes agents for patients with suboptimal glycemic control. Diabetes Metabolic Syndrome and Obesity. 2012;5:213–7.

99. M Modak, P Dixit, J Londhe, S Ghaskadbi, TPA Devasagayam. Indian Herbs and Herbal Drugs Used for the Treatment of Diabetes. J Clin Biochem Nutr. 2007;40: 163–73.