International Journal of Herbal Medicine
Available online at www.florajournal.com

I J H M International Journal of Herbal Medicine

E-ISSN: 2321-2187
P-ISSN: 2394-0514
IJHM 2016; 4(5): 116-121
Received: 19-07-2016
Accepted: 20-08-2016

Kiran Kumar Kandunuri
Doctoral Researcher, School of Human sciences, Faculty of Life Sciences & Computing, London Metropolitan University, Hollowayroad, London

Kenneth White
Director, Molecular Systems for Health Research Group School of Human Sciences Faculty of Life Sciences & Computing London Metropolitan University, Holloway Road London

Eileen Smith
Senior Lecturer in Pharmaceutical Sciences, School of Human Sciences Faculty of Life Sciences& Computing London Metropolitan University 166-220 Holloway Road London

Correspondence
Kiran Kumar Kandunuri
Doctoral Researcher, School of Human sciences, Faculty of Life Sciences & Computing, London Metropolitan University, Hollowayroad, London

An overview on the efficacy of herbs used in ayurvedic formulations for the treatment of type 2 diabetes

Kiran Kumar Kandunuri, Kenneth White and Eileen Smith

Abstract
Ayurvedic herbs are proven to provide symptomatic relief and prevention of secondary complications of diabetes. Though mainstream treatment is effective in controlling the disease, it is expensive and has adverse side effects. Ayurvedic formulations have the ability to regenerate pancreatic beta cells, while possessing antioxidant and cholesterol lowering properties. The present review is focused on highlighting characteristics of prominent anti-diabetic herbs and their hypoglycaemic activities that have shown proven cellular, pre-clinical or clinical evidences. Poly herbal formulations of multiple herbal extracts are also discussed. The promising nature of herbal therapy is compared against mainstream therapy. Despite the promising nature of the herbal therapy for treatment of diabetes the majority of the herbs have remained unexplored to their full potential. Therefore, it is important to highlight their potentials and ascertain their therapeutic properties and benefits.

Keywords: Ayurveda, Type 2 diabetes, Anti-diabetic activity, Hypoglycaemic herbs, Polyherbal formulations

1. Introduction
People are resorting to herbal therapy as an alternative for mainstream therapy with a perception that it is a natural remedy for diabetes [1]. Despite that, only limited hypoglycaemic herbs have been researched for their efficacy. This article aims to review up to date findings on the efficacy, side effects of herbs. Mainstream drugs tend to establish glucose homeostasis either by promoting insulin secretion or by glucose uptake by muscle cells [2]. These drugs known to have adverse side effects [3]. Administration of external insulin does not always matches the cell demands and oral anti diabetic agents have limitations. Both do not establish complete glucose homeostasis and also in long term usage drug resistance would develop. These disadvantages encourage patients to adapt to alternative therapies such as Ayurveda. In Ayurveda, individual and poly herbal formulations are widely used and will have synergistic effects [4]. Although, Ayurvedic formulations have been used conventionally as herbal remedies for centuries, to date only limited research has been conducted on the therapeutic benefits of Ayurvedic formulations for managing type 2 diabetes. However, it is commonly reported that, herbal remedies cause fewer side-effects relative to pharmacological interventions and could provide a natural alternative or an adjunct therapy to other interventions. The purpose of this review is to look at the open literature related to commonly used herbal remedies for type 2 diabetes and outline the potential benefits and related safety concerns.

2. Method
The search terms used for the compilation of the relevant articles are ayurvedic hypoglycaemic formulations, anti-diabetic ayurvedic drugs, anti-diabetic phytochemicals, Indian anti-diabetic medicinal plants, hypoglycaemic herbal drugs, alternative therapies for diabetes, complimentary therapies for diabetes, traditional drugs for diabetes, and diabetes treatment. And also the names of 9 generally cited anti-diabetic ayurvedic herbs are searched using the following tools: PubMed, Medline, Allied and Complementary Medicine, Ovid MEDLINE, BIOSIS Previews, EMBASE, AMED and The Cochrane library. In addition, the names of 4 prominent anti-diabetic herbal formulations are searched in World Wide Web, and compiled in the literature search.

3. Results
Ayurvedic hypoglycaemic herbs
There are many anti-diabetic herbs used in Ayurveda, the most commonly prescribed individual herbs are summarized below (herbs are described using botanical names).

Azadirachta indica* Linn (*Neem)

Aqueous extracts of *Azadirachta* promotes antioxidant protection in diabetic rat [5]. Leaf extract and seed oil promotes glucose uptake in normal and diabetic rabbits and this effect is similar to Glibenclamide [6]. Leaf extracts demonstrated ulcer healing effects in normal and in diabetic rats. The mechanism inducing the effects was studied on number of parameters such as offensive acid-pepsin secretion and defensive mucin secretion in mucosal cells in rats [7]. Leaf extract promotes anti-hyperglycaemic activity in diabetic rats without altering serum cortisol level [8]. Meliacinolin is a derivative of *Azadirachta*, which behaves as an insulin sensitizer and improves renal function, lipid profile, and antioxidant activity. Meliacinolin may interact with multiple targets involved in diabetes pathogenesis. Meliacinolin inhibits α-Glucosidase and α-amylase enzymes which lowers the levels of post prandial hyperglycaemia and prevent the absorption of carbohydrates [9]. A clinical study showed that administration of *Azadirachta* leaf powder, aqueous extract and alcoholic extract at higher doses for 14 days promotes hypoglycaemic activity [10]. Beta-sitosterol is a steroid obtained from *Azadirachta indica*, may be source for its hypoglycemic activity [11].

Berberis aristata* Linn *(Daruharidhra/Darvi/Darurajani)

Alkaloids such as Berberine, Berbamine, Aromoline, Karachine, Palmatine, Oxycanthine and Oxyberberine [12] are major constituents in *Berberis aristata*. A study shown that active principle like Berberine, encourages glucose-stimulated insulin secretion rather than basal insulin secretion in dose-dependent manner in rat's pancreatic islets [13]. This insulinotropic effect is aided by hepatic nuclear factor 4 alpha and glucokinase, and this mechanism is different from sulphonylurea class of drugs [14]. In a study to stimulate glucose uptake activity, application of 50 µM Berberine along with 0.2 nM insulin in 3T3-L1 adipocytes have shown that the level of insulin increased by 10 nM, which pronounced the efficacy of Berberine. It augmented glucose transporter-4 translocation into the plasma membrane by enhancing insulin signalling pathways and the insulin receptor substrate-1-phosphoinositide 3 Kinase-Akt. Application of Berberine in Min6 cells improved insulin secretion and proliferation with the help of enhanced insulin/insulin-like growth factor-1 signalling cascade. These observations were proving the efficacy of berberine as an insulin sensitizing and insulinotropic agent [13].

It is also found that Berberine exhibits striking glucose uptake activity in human hepatoma cells in a comparative study with other phytochemicals such as Phloretin, Ouabain and Metformin. It is observed that Berberine is promoting more glucose uptake activity than Metformin [15].

Cinnamon zeylaniucm* Linn *(Tvak/Dalchini)

In an experiment Cinnamon promoted a compound known as IRS-1 in rats, which promotes glucose uptake in muscle tissue by promoting insulin secretion. It is also promotes the glucose uptake from the blood stream to muscle tissue by influencing Glucose transporter 4 [16, 17]. The role of Cinnamon in treating diabetes was published in the journal of Diabetes Care in 2003 by Khan and colleagues [18]. This study was conducted with 60 patients around the age of 50. The patients were divided into six groups of 10 patients and Groups 1 through 3 were treated with 1, 3, or 6 grams of Cinnamon on daily for 40 days, while Groups 4 through 6 were given placebo. The researchers analysed the fasting glucose, LDL cholesterol, triglycerides and total cholesterol. The results revealed that no significant changes were observed in the placebo group over the 40-days period. While for the treated groups, the reductions in fasting glucose (reduced by18 percent to 29 percent), triglycerides (reduced by 23 percent to 30 percent), LDL cholesterol (reduced by 7 percent to 27 percent) and total cholesterol (reduced by12 percent to 26 percent) were observed. Also high dosage and long-term consumption of Cinnamon was found to be safe. A similar study was also performed in Germany where 79 patients with type 2 diabetes were examined. In this study, half of the patients received placebo the rest received 3 grams of Cinnamon daily for four months. In this study no difference between the two groups was reported for LDL or HDL cholesterol, triglycerides or HgbA1c, while fasting glucose levels dropped about 7 percent more in the group receiving Cinnamon [19]. In another study, 25 post-menopausal women with type 2 diabetes were treated with 1.5 grams of Cinnamon daily for six weeks and reported that Cinnamon was not associated with a significant change in insulin sensitivity, glucose tolerance or cholesterol profile. In a similar manner another study concluded that Cinnamon did not improve HgbA1c, fasting glucose or blood lipids in patients with either type 1 or type 2diabetes [20]. There are several evidences suggest that Cinnamon extracts contain components that enhance insulin action but effects of cinnamon on non-insulin stimulated glucose uptake need further investigation. A study reported on the effects of cinnamaldehyde on the glucose transport activity of GLUT1 in L929 fibroblast cells under both basal and insulin-stimulated conditions where glucose uptake is activated by glucose deprivation. The result concluded that cinnamaldehyde has a dual action on the glucose transport activity of GLUT1. Under basal conditions it stimulates glucose uptake and reaches a 3.5 fold maximum stimulation at 2.0mM. However, cinnamaldehyde also inhibits the activation of glucose uptake by glucose deprivation in a dose dependent manner. Further to this, experiments with cinnamaldehyde analogs have shown that these activities are fully dependent on the structural motif of the α,β-unsaturated aldehyde in cinnamaldehyde. The inhibitory activity of cinnamaldehyde was continued even after a wash and recovery period. Pre-treating cinnamaldehyde with thiol-containing compounds, such as β-mercaptoethanol or cysteine, blocks the inhibitory activity of cinnamaldehyde. The results suggest that cinnamaldehyde inhibits the activation of GLUT1 by forming a covalent link to target cysteine residues. This dual activity suggests that cinnamaldehyde is not a major contributor to the anti-diabetic properties of cinnamon [21].

Gymnema sylvestre Linn (Gurmar/Meshashringi)

A study using crude extracts of *Gymnema* and dihydroxy gymnemic triacetate are exerted hypoglycemic effect in streptozotocin induced diabetic rats [22]. This effect is induced by *Gymnemic acids* that delay the glucose release into the bloodstream. The glucose absorption by the intestines is prevented since *Gymnemic acid* molecules fill the receptor located in the absorptive external layers of the intestine. The crude extract which contains dihydroxy gymnemic triacetate helps to release insulin by the stimulation of regeneration of the remaining beta cells [23]. Studies have also shown that aqueous extract of *Gymnema sylvestre* leaves have the ability to stimulate insulin secretion in mice cells and isolated human islets *in vitro* [24]. It is also revealed that the plasma glucose and insulin levels when measured in the healthy rats with a dose of dihydroxy gymnemic triacetate were not changed and further suggesting that it is a normoglycemic compound. Hydroxy gymnemic triacetate isolated from *Gymnem*

asylvestre lowers the blood glucose levels and biochemical parameters in streptozotocin induced diabetic rats [22]. Extensive clinical trials on human subjects are required for further exploring the prospects of the compound to be used as a drug. Gurmar powder which is prepared from *Gymnema sylvestre* leaves is one of the main ayurvedic product used for the treatment of diabetes. It correlates the metabolic activities of liver, kidney and muscle tissues and stimulates insulin secretion and also exerts blood glucose lowering effect. It also inhibits the intestinal absorption of sugars, there by prevents blood sugar variations and also it is a diuretic and cardiac stimulant. It is also a sugar buster, that when taken it prevents the taste buds from absorbing sugar molecules which discourages glycosuria [25, 1].

Momordica charntia* Linn. *(Karela/ Kareli/ Karavella/ Kathilla/ Sushavi)

Studies have shown that application of *Momordica charantia* extract causes substantial lowering of peripheral blood glucose and elevates the level of plasma insulin in diabetic rats. This effect was due to regeneration of pancreatic beta cells in treated rats. Known anti-diabetic phytochemicals such as Momordicin, Charantin and insulin like protein, galactose binding lectin were isolated from different parts of the plant and the separated compounds proved to possess insulin mimetic activity [26]. Aqueous extracts of unripen, green fruits partially displaying insulin release activity in isolated beta cells of obese diabetic mice and that is indicating insulin stimulation and releasing action is the effect of perturbations of beta cell membranes [27, 28]. *Momordica charantia* promotes renewal of beta cells in the pancreas or promote the recovery of partially damaged beta cells and further stimulate insulin secretion [29]. Due to its intrinsic nature of pancreatic beta cell regeneration, physicians are prescribing active constituents of this herb as an adjuvant for type 2 diabetic patients [30, 31]. Bitter gourd powder (*Momordica charantia*) plays important role in Ayurveda for the treatment of diabetes. It contains glycosides, saponins, alkaloids, reducing sugars, phenolics, oils, free acids, polypeptides, sterols, 17-amino acids including methionine and a crystalline product named p-insulin. It is documented for its hypoglycemic activity along with anti-haemorrhoidal, astringent, stomachic, emmenagogue, hepatic stimulant, anthelmintic and blood purifier activities. It also promotes immunity against general infections, exerts lowering of blood and urine sugar levels [32].

Pterocarpus marsupium Linn (Vijaysar/Pitashalaka/Bijaka/ Pitasara)

Active principles in *Pterocarpus marsupium* such as Epicatechin, Pterosupin, Marsupin and Pterostilbene are known to promote insulin sensitivity [33] and Marsupin, Pterosupin and Liquiritigenin also demonstrates anti-hyperlipidemic activity [34]. Epicatechin promotes insulin secretion, insulin release and adaptation of proinsulin to insulin *in vitro* experiments. Epicatechin increases glycogen content of rat diaphragm in a dose-dependent manner and encourages oxygen uptake in adipose cells and tissues of different organs by its insulin mimicking nature [35]. Tannates in the *Pterocarpus marsupium* extract promotes anti diabetic activity. Pancreatic beta cell regeneration has been observed after application of flavonoid fraction [36].

In a multi-centre clinical trial, *Pterocarpus marsupium* was studied for glucose lowering effect and to determine adverse side effects compared with a standard pharmacological agent Tolbutamide. It is concluded that Pterocarpus is as effective as Tolbutamide in the management of type 2 diabetes without any adverse side Effects [37].

Syzygium cumini* Linn. *(Jambu/Badijamun)

Mycaminose is an active principle isolated from Syzygium seed extract. In a study, Mycaminose, ethyl acetate and methanol extracts of *S. cumini*seeds were administered to diabetic rats and significant reduction in blood glucose level was noticed. This effect is comparable with standard drug Glibenclamide. Bark extracts stimulate the insulin positive cells from the pancreatic duct epithelial cells [38].

Tinospora cordifolia* Linn. *(Guduchi/Giloe/ Gurcha)

A study has shown that administration of extracts of *Tinospora cordifolia* decreases the blood glucose level and increases glucose tolerance in rodents. The oral administration of root extracts for about 6 weeks in alloxan induced diabetic rats caused a decrease in glucose level in blood, urine and also a decrease of lipids in serum, brain and tissues, while an increase of body weight is also observed. A dosage of 400 mg/kg aqueous extract could cause significant anti-hyperglycemic effect in animal models [39, 40].

Trigonella foenum-graecum* Linn. *(Methi/Medhika)

4-Hydroxyisoleucine is prominent amino acid in *Trigonella* and it exhibits insulin-stimulating characteristics [41]. The prominent isomer of 4-hydroxyisoleucine, which is a typical branched-chain amino acid, that derived from fenugreek seeds, is responsible for the effects on glucose and lipid metabolism in experimental rats and proves to increase glucose stimulated insulin release by isolated islet cells in rats, mice and humans [1, 41, 42]. *In vitro* and *in vivo* studies have shown that 4-hydroxyisoleucine promotes glucose-induced insulin release [43]. The fibre content in seeds promotes insulin sensitivity, by slowing down carbohydrate metabolism that leads to reduced insulin levels and lowers blood glucose. The anti- hyperglycaemic effect of the seed extracts, powder and gum of fenugreek seeds and leaves are related to slow gastric emptying because of its high fibre content and also inhibition of carbohydrate digestive enzymes and stimulation of insulin secretion [44]. Syndrex is an ayurvedic product used for the treatment of diabetes, in which main ingredient is germinated fenugreek extract. It lowers blood sugar in people with diabetes and promotes slow absorption of sugars in the intestines and stimulates insulin [45].

4. Polyherbal formulations

Mixture of antidiabetic herbs is also used in Ayurveda, commonly known as polyherbal formulation. Some of the well-known polyherbal formulations are Ayush-82, Diabecon, Epiinsulin and Diabeta. The characteristics of the individual formulations are summarised below.

Ayush-82

Ayush-82 is a blend of following four herbs: *Syzygium cuminii*, *Momordica charantia*, leaves of *Gymnema sylvestre* and the seeds of *Mangifera indica* [46, 47]. It exerts glucose lowering effects and these are prominent polyherbal formulation in Ayurveda. Further study is needed in order to consolidate their effectiveness.

Diabecon

It is a combination of herbs consist of *Gymnema sylvestre*, *Pterocarpus marsupium*, *Glycyrrhiza glabra*, *Casearia esculenta*, *Syzygium cumini*, *Asparagus racemosus*, *Boerhavia diffusa*, *Sphaeranthus Indicus*, *Tinospora cordifolia*, *Swertia*

chirata, *Tribulus terrestris*, *Phyllanthus amarus*, *Gmelina arborea*, *Gossypium herbaceum*, *Berberis aristata*, *Aloe vera*, *Triphala*, *Commiphora wightii*, *shilajeet*, *Momordica charantia*, *Piper nigrum*, *Ocimum sanctum*, *Abutilon indicum*, *Curcuma longa*, *Rumex maritimus*. It reduces long term diabetic complications and acts like insulin analog and discourages glycated haemoglobin levels. It also encourages repair, regeneration and protects beta cells from oxidative stress. In addition, it increases c peptide level, peripheral utilization of glucose, enhances hepatic and muscle glucagon levels and normalizes the microalbuminuria and regulates the lipid profile [48].

Epi insulin

It is a combination of active principles such as Epicatechin and Benzopyran. Epicatechin stimulates eleveated Insulin secretion by promoting cAMP content of islets of langerhans. It raises cathepsian activity which converts proinsulin to insulin. Due to its insulin mimicking nature, it promotes osmotic hemolysis and inhibits Na/K ATPase activity in red blood cells. It promotes glucose and lipid metabolisms, therefore encouraging comprehensive health. Although the use is limited to treatment of type 2 diabetes, it can also be used as an adjuvant for the treatment of type 1 diabetes to reduce the amount of external insulin administration. Due to its gentle hypoglycemic nature, generally prescribers recommend epiinsulin as preventive medication for potential diabetic patients and as an adjuvant for established patients [1].

Diabeta

The formulation is a blend of *Gymnema sylvestre*, *Vincarosea*, *Curcuma longa*, *Azadirachta*, *Pterocarpus arsupium*, *Momordica charantia*, *Syzygium cumini*, *Acacia arabica*, *Tinospora cordifolia* and *Zingiber officinale*. Diabeta promotes comprehensive health to the patients and gives symptomatic relief. It corrects and prevents degenerative complications of diabetes with its effective mechanism of action on omnious octet. It can be used as an adjuvant for main stream drugs in order to prevent resistance to oral hypoglycemic drugs [1].

5. Discussion

The mainstream oral anti-diabetic drugs have adverse side effects such as rapid drop in blood glucose level, lactic acidosis, liver damage, neurologic deficits, hypoglycaemia ,weight gain, back pain, upper respiratory infections, nausea, cramps, diarrhoea, lactose intolerance , vitamin B-12 deficiency, digestive disorders, intestinal gas formation, fluid retention, anaemia and menstrual problems [3]. These disadvantages with mainstream anti diabetic drugs encourage diabetic patients to adapt to alternative therapies such as Ayurveda because of its affordability and it is proven to cause less side effects. Since Ayurvedic herbal formulations constituted mainly plant extracts or intact herbs, they are rich in antioxidants and essential nutrients which promote comprehensive health without adverse side effects even after prolonged administration. Herbal drugs are comparatively cheaper than synthetic drugs. One of the known issues with the Ayurvedic herbal formulation is heavy metal toxicity [49] which often leads to heavy metal poisoning risk to the patient [50-52]. To date there is no proper scientific evidence for safety, efficacy and understanding of herbal medicines. Therefore patients undergoing herbal treatment might be unknowingly exposing themselves to the risks of toxicity or overdose. Due to the absence of a clear understanding of the mechanisms of the apparent therapeutic effect, the progression of many promising herbs have been hindered to date. Large proportion of the side effects when herbal medications are consumed are attributable to the poor quality of herbal drugs resulting from contamination of raw ingredients and incorporation of heavy metals in order to enhance their potency. Ironically, plant-derived phytochemicals are secondary metabolites and these are not always benign molecules and many of them express toxicity up on application [53]. Therefore, it is vital to implement proper cultivation, harvestation and production processes and adapting modern analytical techniques and international regulation to enhance the quality of herbal drugs [54].

Regardless of above limitations, by implication of proper scientific methods, tools and further investigation of well-known anti-diabetic herbs in traditional medicine may provide a new understanding for valuable resources for innovative, evidence-based and effective treatment solutions for the treatment of diabetes.

Conclusion

To date, the active principles of many hypoglycaemic herbs have not been well characterized. Further investigations must be carried out in order to evaluate the mechanism of action of ayurvedic herbs which exhibits insulin mimetic activity. Though there is a perception that generally herbs are safe to consume, many herbal formulations are not safe due to the issues such as heavy metal toxicity, and therefore toxicity study should be elucidated. It is important to isolate, purify, elucidate structure and conduct cellular, preclinical and clinical studies of Ayurvedic Hypoglycemic herbs, in order to innovate better alternatives for treatment of type 2 diabetes.

Conflict of interest statement: We declare that we have no conflict of interest.

6. References

1. Modak M, Dixit P, Devasagayam TPA. Indian herbs and herbal drugs used for the treatment of diabetes. J Clin Biochem Nutr. 2007; 40(3):163-173.
2. Kokil GR, Rewatkar PV, Verma A, Thareja S, Naik SR. Pharmacology and chemistry of diabetes mellitus and antidiabetic drugs: a critical review. Curr Med Chem. 2010; 17(35):4405-4423.
3. Bell DSH. Current status of diabetes treatment. South Med J. 2002; 95(1):24-29.
4. Mishra L, Singh BB, Dagenais S. Ayurveda: A historical perspective and principles of the traditional healthcare system in India. Alternative Therapies in Health and Medicine. 2001; 7(2):36-42.
5. Shailey S, Basir SF. Strengthening of antioxidant defense by *Azadira chtaindica* inalloxan-diabetic rat tissues. J Ayurveda Integr Med. 2012; 3(3):130-135.
6. Khosla P, Bhanwra S, Singh J, Seth S, Srivatsava RK. A study of hypoglycaemic effects of *Azadiracta indica* (Neem) in normal and alloxan induced diabetic rabbits. Indian J Physiol Pharmacol. 2000; 44(1):69-74.
7. Babu DM, Joshi MC, Bhawani G, Kumar MM, Chaturvedi A, Goel RK. Effect of aqueous extract of neem (*Azadirachta indica*) leaves on offensive and diffensive gastric mucosal factors in rats. Indian J Physiol Pharmacol. 2006; 50(3):241-249.
8. Gholap S, Kar A. Hypoglycaemic effects of some plant extracts are possibly mediated through inhibition in corticosteroid concentration. Pharmazie, 2004; 59(11):876-878.
9. Perez GRM, Damian GM. Meliacinolin: a potent α-

glucosidase and α-amylase inhibitor isolated from *Azadirachta indica* leaves and *in vivo* antidiabetic property in streptozotocin-nicotinamide-induced type 2 diabetes in mice. Biol Pharm Bull. 2012; 35(9):1516-1524.
10. Waheed A, Miana GA, Ahmad SI. Clinical investigation of hypoglycemic effect of seeds of *Azadirachta-inidca*in type-2 (NIDDM) diabetes mellitus. Pak J Pharm Sci. 2006; 19(4):322-325.
11. Mukherjee PK, Maiti K, Mukherjee K, Houghton PJ. Leads from Indian medicinal plants with hypoglycemic potentials. J Ethnopharmacology. 2006; 106:1-28.
12. Mitra MP, Das S, Das S, Das MK. Phyto- Pharmacology of *Berberis aristata* DC. A Review: Journal of Drug Delivery & Therapeutics. 2011; 1(2):46-50.
13. Ko BS, Choi SB, Park SK, Jang JS, Kim YE, Park S. Insulin sensitizing and insulinotropic action of berberine from Cortidisrhizoma. Biol Pharm Bull. 2005; 28(8):1431-1437.
14. Wanq ZQ, Lu FE, Lenq SH, Fang XS, Chen G, Wang ZS *et al*. Facilitating effects of berberine on rat pancreatic islets through modulating hepatic nuclear factor 4 alpha expression and glucokinase activity. World J Gastroenterol. 2008; 14(39):6004-6011.
15. Kandunuri K, White K. Potential replacement of Metformin with Berberine in the treatment of Type 2 diabetes. Diabetes Spring conference, 2012.
16. Anand P, Murali KY, Tandon V, Murthy PS, Chandra R. Insulinotropic effect of cinnamaldehyde on transcriptional regulation of pyruvate kinase, phosphoenolpyruvate carboxykinase, and GLUT4 translocation in experimental diabetic rats. Chem Biol Interact. 2010; 186(1):72-81.
17. Qin B, Polansky MM, Sato Y, Adeli K, Anderson RA. Cinnamon extract inhibits the postprandial overproduction of apolipoprotein B48-containing lipoproteins in fructose-fed animals. J Nutr Biochem. 2009; 20(11):901-908.
18. Khan A, Safdar M, Ali Khan MM, Khattak KN, Anderson RA. Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes Care. 2003; 26(12):3215-3218.
19. Mang B, Wolters M, Schmitt B, Kelb K, Lichtinghagen R, Stichtenoth DO *et al*. Effects of a Cinnamon extract on plasma glucose, HbA, and serum lipids in diabetes mellitus type 2.Eur J Clin Invest. 2006; 36(5):340-344.
20. Vanschoonbeek K, Thomassen BJ, Senden JM, Wodzig WK, van Loon LJ. Cinnamon Supplementation Does Not Improve Glycemic Control in Postmenopausal Type 2 Diabetes Patients. J Nutr. 2006; 136(4):977-980.
21. Plaisier C, Cok A, Louters LL. Effects of cinnamaldehyde on the glucose transport activity of GLUT1Biochimie, 2011; 93(2)339-344.
22. Daisy P, Eliza J, Mohamed Farook KA. A novel dihydroxy gymnemic triacetate isolated from Gymnemasylvestre possessing normoglycemic and hypolipidemic activity on STZ-induced diabetic rats. J Ethnopharmacol. 2009; 126(2):339-44.
23. Kanetkar P, Singhal R, Kamat M. Gymnema sylvestre: A Memoir Journal of Clinical Biochemistry and Nutrition. 2007; 41(2)77-81.
24. Al-Romaiyan A, King AJ, Persaud SJ, Jones PM. A Novel Extract of *Gymnema sylvestre* Improves Glucose Tolerance *In Vivo* and Stimulates Insulin Secretion and Synthesis *In Vitro*. Phytother Res. 2013; 27(7):1006-1011.
25. Paliwal R, Kathori S, Upadhyay B. Effect of Gurmar (*Gymnema sylvestre*) Powder Intervention on the Blood Glucose Levels among Diabetics. Ethno-Med. 2009; 3(2):133-135.
26. Raman A, Lau C. Anti-diabetic properties and phytochemistry of *Momordica charantia* L. (Cucurbitaceae). Phytomedicine, 1996; 2(4):349-362.
27. Ahemed I, Adeghate E, Sharma AK, Pallot DJ, Singh J. Effects of *Momordica charantia* fruit juice on islet morphology in the pancreas of the streptozotocin-diabetic rat. Diabetes Res Clin Pract, 1998; 40(3):145-151.
28. Abdollahi M, Zuki AB, Goh YM, Rezaeizadeh A, Noordin MM. Effects of *Momordica charantia* on pancreatic histopathological changes associated with streptozotocin-induced diabetes in neonatal rats. Histol Histopathol, 2011; 26(1):13-21.
29. Hafizur RM, Kabir N, Chishti S. Modulation of pancreatic β-cells in neonatallystreptozotocin-induced type 2 diabetic rats by the ethanolic extract of *Momordica charantia* fruit pulp. Nat Prod Res, 2011; 25(4):353-367.
30. Singh N, Gupta M. Regeneration of beta cells in islets of Langerhans of pancreas of alloxan diabetic rats by acetone extract of *Momordic acharantia* (Linn.) (Bitter gourd) fruits. Indian J Exp Biol. 2007; 45(12):1055-1062.
31. Nagy MA, Bastawy MA, Abdel-Hamid NM. Effects of *Momordica charantia*on Streptozotocin-Induced Diabetes in Rats: Role of Insulin, Oxidative Stress and Nitric Oxide. Journal of Health Science. 2012; 2(2):8-13.
32. Grover JK, Yadav SP. Pharmacological actions and potential uses of *Momordica charantia*: a review. J Ethnopharmacol. 2004; 93(1):123-132.
33. Grover JK, Vat V, Yadav SS. *Pterocarpus marsupium* extract (Vijayasar) prevented the alteration in metabolic patterns induced in the normal rat by feeding an adequate diet containing fructose as sole carbohydrate. Diabetes Obes Metab, 2005; 7(4):414-420.
34. Jahromi MA, Ray AB. Antihyperlipidemic effect of flavonoids from *Pterocarpus marsupium*. J Nat Prod. 1993; 56(7):989-994.
35. Ahmad F, Khalid P, Khan MM, etal. Insulin like activity in (-) epicatechin. Acta Diabetol Lat. 1989; 26(4):291-300.
36. Chakravarty BK, Gupta S, Gambhir SS, Gode KD. Pancreatic beta cell regeneration. A novel antidiabetic mechanism of *Pterocarpus marsupium* Roxb. Ind J Pharmacol, 1980; 12:123-127.
37. ICMR study group on the efficacy of vijayasar in Type2 diabetes mellitus. Efficacy of Vijayasarb (*Pterocarpus marcupium*) in the treatment of newly diagnosed patients with type2 diabetes mellitus: A flexible dose double blind multicentre randomized controlled trial. Diabetologia Croatica, 2005, 34-41.
38. Kumar A, Ilavarasan R, Jayachandran T, Krishnan MRV. Anti-diabetic activity of *Syzygium cumini* and its isolated compound against streptozotocin-induced diabetic rats. Journal of Medicinal Plants Research. 2008; 2(9):246-249.
39. Stanely MPP, Menon VP, Gunasekaran G. Hypolipidaemic action of *Tinospora cordifolia* roots in alloxan diabetic rats. J Ethnopharmacol. 1999; 64(1):53-57.
40. Sinha K, Mishra NP, Singh J, Khanuja SPS. *Tinospora cordifolia* (Guduchi), a reservoir plant for therapeutic applications: A Review. Indian journal of traditional knowledge. 2004; 3:257-270.
41. Broca C, Gross R, Petit P, Sauvaire Y, Manteghetti M,

Tournier M *et al*. 4-Hydroxyisoleucine: experimental evidence of its insulinotropic and antidiabetic properties. Am J Physiol. 1999; 277(4 Pt 1):E617-23.
42. Grover JK, Yadav S, Vats V. Medicinal plants of India with antidiabetic potential. J Ethnopharmacol. 2002; 81(1):81-100.
43. Saxena A, Vikram NK. Role of selected Indian plants in management of type 2 diabetes: a review. J Altern Complement Med. 2004; 10(2):369-378.
44. Chauhan A, Sharma PK, Srivastava P, Dudhe R. Plants having potential antidiabetic activity: a review. Der Pharm Lett, 2010; 2(3):369-387.
45. Kaczmar T. Herbal support for diabetes management. Clin Nutr Insights, 1998; 6(8):1-4.
46. Chowdhary DP, Dua M. Hypoglycemic effect of a coded formulation: Ayush-82, J Res Ayurveda and Siddha. 1998; 19(3-4):107.
47. Pandey VN, Rajagopalan SS, Chowdhary DP: An effective Ayurvedichypoglycemic formulation. J Res Ayurveda Siddha, 1995; XVI:1-14.
48. Kundu PR, Chattaerjee PS. Meta-analysis of Diabecon tablets: Efficacy and safety outcomes from 15 clinical trials in diabetes melli
49. itus. Indian journal of clinical practice. 2010; 20:9.
50. Umarani RD, Paknikar KM. Ayurvedic medicine zinc bhasma: physicochemical evaluation, anti-diabetic activity and safety assessment. J Biomed Nanotechnol. 2011; 7(1):148-149.
51. Chopra A, Doiphode VV. Ayurvedic medicine: Core concept, therapeutic principles, and current relevance. Medical Clinics of North America. 2000; 86:75-89.
52. Gogtay NJ, Bhatt HA, Dalv SS, Kshirsagar NA. The use and safety of nonallopathic Indian medicines. Drug Safety. 2002; 25:1005-1019.
53. Dargan PI, Gawarammana IB, Archer JRH, Wood DM. Heavy metal poisioning from Ayurvedic traditional medicines: An emerging problem. Int. J. Environment and Health, 2008, 3-4.
54. Gurib-Fakim A. Medicinal plants: traditions of yesterday and drugs of tomorrow. Mol Aspects Med, 2006; 27:1-93.
55. Marcus D, Grollman A. Botanical medicines: The need for new regulations. N Engl J Med. 2002; 347(25):2073-2075.