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Review article

Ayurvedic approaches used in prevention and treatment of type 2 diabetes mellitus

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ABSTRACT

Ayurveda has a diverse point of view to prevent and treat diabetes which is apparently not associated with the insight of modern science. The ancient literature of Ayurveda described diabetes as *Madhumeha* (sugar related disease) and suggested a number of remedies to cure it. Although in the ancient literature, the mechanism of diabetes is not well-understood but, as far as treatment is concerned, the suggested way of treatment is undoubtedly effective which is confirmed by numerous researches worldwide. Interestingly, Ayurveda mainly focuses on balanced diet, improved lifestyle with routine *Yoga* practice. However, the use of medication in the form of herbal preparation is considered with least priority, given on the basis of *Prakriti* (genotype) of the patient. In the present work, we thoroughly reviewed Ayurvedic concepts for the treatment of type 2 diabetes mellitus using ancient Ayurvedic texts as well as the literature available in the most accepted scientific search engines i.e. PubMed, Scopus and Web of Science. In addition to the use of herbal therapy, this review also describes the use of Panchakarma and Yoga for the management of type-2 diabetes and post-diabetic complication like retinopathy, nephropathy and neuropathy.

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INTRODUCTION

Current scenario of the incidence of chronic diseases revealed that diabetes mellitus (DM) is most rising deadly disease globally. A recent report by the International Diabetes Federation (IDF) shows that there are 415 million adults suffering from DM which is equivalent to about 1 in every 11 persons (IDF Atlas, 2015). This report also reveals that the USA has the highest prevalence among developed countries with 11% whereas China (110 million patients) and India (69 million patients) are at the top. It is unfortunate that even after a tremendous development in modern medical science, the treatment of DM is still an impossible task; however, its management with the help of various treatment procedures, the patient can survive longer.

It is interesting to know that the ancient Ayurvedic texts are rich in the information about diabetes called *Madhumeha* (*Prameha*). As the treatment of DM is difficult, its prognosis had been highly emphasised in ancient texts of Ayurveda. In addition, various complications such as neuropathy, angiopathy, uropathy, retinopathy and proneness to infections had also been considered during the diagnosis and treatment of DM (Kumar et al., 2014). According to Ayurveda, the *Prameha* patients have the problems of reduced digestive fire and depleted Ojas status which resulting to the state of hypometabolism and poor immunity, respectively (Kumar et al., 2014). The main perception of Ayurveda to manage *Prameha* was to improve diet and lifestyle while the use of medicines was considered with least priority, and were given on the basis of *Prakriti* (genotype) of a patient. Ayurveda has a holistic approach to treat the body, mind and spirit through diet, lifestyle and medication. A number of herbs and herbo-mineral formulations are abundantly used to treat DM, which is given on the basis of its stage and type as well as the psychophysiological constitution of the patient (Sharma and Chandola, 2011).

Type 2 diabetes mellitus (T2DM) is a multigenic chronic disease and thus multi-targeted approach is needed for its treatment. As the drug

development with the multi-targeted approach is difficult to achieve with a single compound, polyherbal therapy, which could be safe, multi-targeted and economical, is a possible way to develop more effective drug for T2DM (Aggarwal et al., 2011). Such drugs can be considered as safer that any existing drugs, even than most successful drug Metformin which causes many side effects including diarrhoea, nausea, gas, weakness, indigestion, abdominal discomfort and headache. As a result, nearly 50% of diabetic patients globally use traditional and complementary medicines to treat diabetes. Ayurveda and other traditional systems of medicine describe various herbal drugs for the treatment of DM. These plant-derived drugs have potential to regenerate pancreatic β-cells, promote insulin release and sensitise the receptors in the case of insulin resistance (Singh et al., 2009). Apart from the herbal preparation so-called *Rasayana*, Ayurveda also has a unique concept of purification to remove toxins from the body which is called as Panchakarma therapy. Various researches confirmed the effect of Panchakarma in curing various human ailments including chronic diseases associated with the ageing (Sharma H, et al. 2007). As per our record, a comprehensive review on various popular therapies for type II diabetes mellitus (T2DM) and post-diabetes complications including retinopathy, nephropathy, neuropathy, heart failure and stroke, used in Ayurveda together with their mechanisms of action in the patient is being reported for the first time. A schematic diagram based on Ayurvedic approaches for the treatment of type II diabetes mellitus is given in Fig. 1.

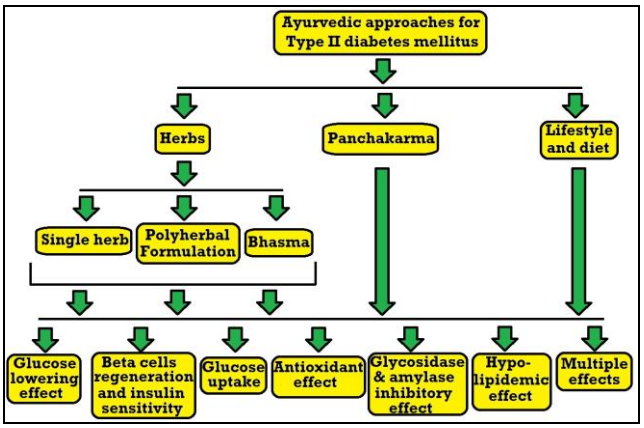

Fig. 1. Schematic diagram for Ayurvedic approaches to treat type II diabetes

HERBAL THERAPY

Ayurveda described numerous medicinal plants to treat diabetes, a complex disorder characterised by hyperglycemia due to malfunction in insulin secretion and action, which are although, very popular but still required systematic information about their active constituents, mode of action and adverse effects. The Pharmacopoeia of India is especially rich in herbal treatments for DM. Among a huge number of treatment procedures, herein, most common and important treatments applied for the management of DM are described. Few selected Ayurvedic herbs used for the treatment of type 2 diabetes mellitus and other associated disorders are given in Table 1.

Table 1. The role of Ayurvedic herbs in the treatment of type 2 diabetes mellitus and other associated disorders.

S.No.	Name of Herb	Glucose Lowering effect	β-Cell regeneration and insulin sensitivity	Glucose uptake effect	Anti-oxidant effect	Glycosidase and amylase inhibitory effect	Hypo-lipidemic effect
1.	*Abelmoschus esculentus* (L.) Moench	-	-	-	+	-	-
2.	*Aegle marmelos* (L.) Correa Ex. Schultz	+	-	-	-	-	+
3.	*Aerva lanata* (L.) Juss. Ex Schult.	-	+	-	+	+	-
4.	*Asparagus officinalis* L.	-	+	-	+	-	-
5.	*Azadirachta indica* A. Juss.	+	-	-	+	-	-
6.	*Brassica juncea* L. Czern.	+	-	-	-	-	-
7.	*Capparis decidua* (Forsk.) Edgew.	-	-	-	+	-	-
8.	*Carica papaya* L.	+	-	-	-	-	+
9.	*Cassia auriculata* L.	+	-	-	-	-	+
10.	*Catharanthus roseus* (L.) G.Don	+	-	-	-	-	-
11.	*Centratherum anthelminticum* L. Kuntze	-	+	-	-	-	-
12.	*Cinnamomum tamala* Nees & Eberm.	+	-	-	-	-	-
13.	*Coccinia grandis* (L.)	+	-	-	+	-	-

	Voigt						
14.	*Cuminum cyminum* L.	-	-	-	-	-	+
15.	*Curculigo orchioides* Gaertn.	-	-	+	-	-	-
16.	*Curcuma longa* L.	-	-	-	+	+	-
17.	*Dendrocalamus hamiltonii* Nees Ex Arn.	+	-	-	-	-	-
18.	*Desmodium gangeticum* (L.) DC.	-	+	-	-	-	-
19.	*Embelia ribes* Burm.F.	+	-	-	-	-	-
20.	*Ficus bengalensis* L.	+	-	-	-	-	-
21.	*Ficus racemosa* L.	-	-	-	-	-	+
22.	*Gmelina arborea* L.	+	-	-	-	-	-
23.	*Guazuma ulmifolia* Lam.	-	-	+	-	-	-
24.	*Gymnema sylvestre* R.BR.	+	-	-	-	-	-
25.	*Inula racemosa* Hook. F.	+	-	-	-	-	-
26.	*Kokoona zeylanica* Thw.	+	-	-	-	-	-
27.	*Linum usitatissimum* L.	-	-	-	-	+	-
28.	*Momordica charantia* L.	+	+	-	-	-	-
29.	*Moringa oleifera* Lam.	+	-	-	-	-	-
30.	*Morus alba* L.	-	-	-	-	+	-
31.	*Mucuna pruriens* (L.) DC.	+	-	-	-	-	-
32.	*Nymphaea nouchali* Burm.F.	-	+	-	-	-	-
33.	*Nymphaea stellata* Willd.	+	+	-	-	-	+
34.	*Ocimum tenuiflorum* L.	+	-	-	-	+	-
35.	*Picrorhiza kurroa* Royle Ex Benth.	+	-	-	-	-	-
36.	*Premna latifolia* Roxb.	+	-	-	-	-	-
37.	*Pterocarpus marsupium* Roxb.	+	-	-	-	-	-
38.	*Salacia reticulata* Wight	-	-	-	-	+	-
39.	*Saussurea costus* (Falc.) Lipsch.	+	-	-	-	-	-
40.	*Scoparia dulcis* L.	+	-	-	-	-	-
41.	*Spondias pinnata* (L.F.) Kurz	+	-	-	-	-	-
42.	*Strychnos nux-vomica* L.	+	-	-	-	-	-
43.	*Swertia chirayita* Roxb. Ex (Fleming) Karst.	+	-	-	-	-	-
44.	*Swertia corymbosa* (Griseb.) Wt. Ex Clarke	-	-	-	+	-	-
45.	*Symplocos cochinchinensis* S.Moore	-	-	-	-	+	-
46.	*Syzygium caryophyllatum* (L.) Alston	+	-	-	-	-	-
47.	*Syzygium cumini* (L.) Skeels	-	+	-	+	-	-
48.	*Tectona grandis* L.F.	+	+	-	-	-	-
49.	*Terminalia bellirica* (Gaertn.) Roxb.	+	+	-	-	-	-
50.	*Tinospora cordifolia* (Willd.) Hook.F. & Thoms.	+	-	-	+	-	+
51.	*Tinospora crispa* (L.) Hook.F. & Thoms.	-	+	-	-	-	-
52.	*Tragia involucrata* L.	+	-	-	-	-	-
53.	*Trichosanthes cucumerina* L.	+	-	-	-	-	-
54.	*Tridax procumbens* L.	+	-	-	+	-	-
55.	*Trigonella foenum-graecum* L.	+	-	-	-	-	-
56.	*Woodfordia fruticosa* (L.) Kurz	+	+	-	+	-	-
57.	*Wrightia tinctoria* R.BR.	+	-	-	-	-	-
58.	*Zingiber officinale* Rosc.	-	-	-	-	-	+

Symbol : (+) shows positive results and (-) shows negative results.

Treatment with single herb

An Ayurvedic herb as a whole or its selected parts, based on the efficacy, is used in the preparation of single herbal medicine for diabetes mellitus. A crude extract of the herb or its root, stem, flower, leaf, seed, and bark has been considered to be more effective than an isolated ingredient due to the synergistic effect of constituents present in the extract. It is also well-known fact that the use of Ayurvedic formulations is safer than any other synthetic medicines. The theory of Ayurveda treatment is based on Tridoshas (three biological factors) and Prakriti (the unique constitution/ genotype of a patient), which help a practitioner in deciding the herbal protocol. The herbal treatment may have following effects in the diabetic patients.

Glucose-lowering effect

There are many active compounds found in a plant which is including dietary fibres, alkaloids, flavonoids, saponins, amino acids, steroids, peptides and terpenoids. Many of these constituents have been proven to produce potent antihyperglycemic and glucose suppressive effects either individually or in the form of crude extract (Saxena et al., 2006). *Pterocarpus marsupium, Eugenia jambolana* and *Gymnema sylvestre* were found to be effective antidiabetic plants which showed potent DPP-4 inhibitory activity as well as a hypoglycemic activity through increased GLP-1 levels in plasma (Kosaraju et al., 2014). *Salacia reticulata* has been proven to be an effective remedy for DM as it decreased blood glucose levels by acting on liver cells and down-regulates the gluconeogenic pathway through regulation of FBP expression (Im et al., 2009). A separate study by Prince and Menon (2000) found that oral administration of root extract of *Tinospora cordifolia* reduced blood glucose and brain lipids, and also increased body weight, total haemoglobin and hepatic hexokinase. In addition, it reduced hepatic glucose-6-phosphatase and serum acid phosphatase, alkaline phosphatase, and lactate dehydrogenase.

β-Cell regeneration and insulin sensitivity

Type 2 diabetes mellitus (T2DM) occurs due to insufficient functional β-cell mass to counteract the increase in insulin demand in the body. Before this failure occurs, the body responds to an early increase in nutrient oversupply by enhancing compensatory β-cell proliferation and consequent β-cell expansion. The interest has been growing recently in identifying factors and signalling pathways that regulate β-cell expansion in acute nutrient oversupply and insulin resistance to leverage this knowledge into future therapies for β-cell regeneration (Lakshmipathi et al., 2016).

Various researches confirmed the role of herbal therapies in the β-cell regeneration and insulin sensitivity. *Momordica charantia* fruits have shown to repairs damaged β-cells, increases insulin levels and enhances the sensitivity of insulin (Chaturvedi et al., 2012). *Terminalia bellerica*, used in Ayurvedic medicine to treat diabetes, has been found to increase the secretion of insulin by the modulation of cAMP and intracellular calcium levels in the β-cells of the pancreas and also normalise the altered biochemical parameters in diabetic rats (Latha et al., 2013). A recent study by Antu et al. (2016) revealed that *Symplocos cochinchinensis* has potential to enhance the insulin sensitivity by downregulating lipogenesis and insulin resistance in high energy diet rat. The extract obtained from the stems of *Salacia reticulata* was also found effective in improving insulin resistance, glucose metabolism and reducing obesity (Medagama, 2015). A preclinical study on the flowers of *Tectona grandis* reported that the flower extract has an insulin-sensitizing action together with an inhibitory effect on α-amylase and α-glucosidase activities (Ramachandran and Rajasekaran, 2014). However, Devi et al. (2003) found that fenugreek leaves exhibited antidiabetic activity in STZ-induced diabetic rats by restoring insulin parameters similar to that of glibenclamide.

Cell culture and preclinical studies suggested that various constituents i.e. diterpenes, triterpenes, phytosterols, alkaloids and their glycosides of *Tinospora crispa* stimulated secretion of insulin from pancreatic β-cells (Thomas et al., 2016) whereas the seeds of *Nymphaea nouchali* increased glucose consumption in 3T3-L1 adipocytes through activation of peroxisome proliferator-activated receptor gamma and insulin sensitization (Parimala et al., 2015). Besides, *Centratherum anthelminticum* (Arya et al., 2012), *Desmodium gangeticum* (Govindarajan et al., 2007) and *Croton klozchianus* (Govindarajan et al., 2008) were also found to stimulate insulin secretion in pancreatic β-cells.

Glucose uptake

The most desirable situation would be the development of new types of antidiabetic drugs that are anti-hyperglycemic without showing adverse effect like obesity. Reducing obesity can slow down the rate of occurrence of T2DM (Yates et al., 2011). Hence, finding new antidiabetic agents that stimulate glucose uptake by adipose or muscle cells can be an effective strategy in this direction. However, thiazolidinedione and insulin are effective agents to control sugar level but simultaneously induced obesity or other side effects in the patients. *Guazuma ulmifolia* is mediated by the stimulation of glucose uptake in normal and diabetic adipocytes without inducing adipogenesis (Alonso-Castro and Salazar-Olivo, 2008). The increase in adipocyte lipid content can

influence adipocyte function by reducing adiponectin secretion which promotes adipocyte differentiation, insulin sensitivity and lipid accumulation (Yeo et al., 2011). *Acacia kempeana*, *Santalum spicatum* and *Curculigo orchioides* were also found to stimulate glucose uptake in adipocytes (Gulati et al., 2015). On the other hand, the intake of *Piper betle* influences glucose metabolism (Santhakumari et al., 2006) whereas *Azadirachta indica* improves the insulin signalling molecules and glucose utilization in the skeletal muscle (Satyanarayana et al., 2015). Furthermore, Sridevi et al. (2015) also found that *Solanum surattense* effectively improved the glucose uptake in the body.

Antioxidant effect

Oxidative stress plays a major role in the pathogenesis of type 1 and types 2 DM. Earlier studies demonstrated that the elevation of reactive oxygen species (ROS) caused by oxidative stress is associated with decreased antioxidant capacity in the islet β-cells in type 1 and type 2 diabetic subjects. The pancreatic β-cells are susceptible to oxidative stress leading to cell apoptosis and consequent insulin secretion reduction (Kalekar et al., 2013). *Phyllanthus emblica, Curcuma longa* and *Tinospora cordifolia* were found to exhibit an antioxidant activity which was scientifically validated in various experimental *in vitro* and *in vivo* models (Kalekar et al., 2013). The studies indicated that *Capparis decidua* may have potential use as an antidiabetic agent and in lowering oxidative stress in alloxan-induced diabetic rats (Yadav et al., 1997). Moreover, *Ficus amplissima* bark (Arunachalam and Parimelazhagan, et al., 2013) and *Abelmoschus esculentus* fruits (Sabitha et al., 2012) were also found to show strong antioxidant activity in diabetic rats. *Azadirachta indica*, a well-known Ayurvedic plant has been found effective in reducing hyperglycemia-induced oxidative stress, and it can be used as an alternative medicine to prevent long-term complications of diabetes (Shailey and Basir, 2012). Venkateswaran and Pari (2003) found that *Coccinia indica* leaves caused a significant increase in plasma vitamin C and reduced glutathione in STZ-diabetic rats. Similarly, *Tinospora cordifolia* roots showed a significant reduction in thiobarbituric acid reactive substances and an increase in reduced glutathione, catalase and superoxide dismutase in alloxan diabetic rats (Prince and Menon, 2001).

Glycosidase and amylase enzyme inhibitory effect

α-Amylase is a prominent enzyme found in the pancreatic juice and saliva which breaks down large insoluble starch molecules into absorbable molecules. On the other hand, mammalian α-glucosidase in the mucosal brush border of the small intestine catalyses the end step of digestion of starch and disaccharides that are abundant in the human diet. Inhibitors of α-amylase and α-glucosidase delay the breaking down of carbohydrates in the small intestine and diminish the postprandial blood glucose excursion (Kazeem et al., 2013). Interestingly, *Symplocos cochinchinensis* exhibited the antidiabetic activity mainly via α-glucosidase inhibition, improved insulin sensitivity, with moderate antiglycation and antioxidant activity (Antu et al., 2014). In addition, *Linum usitatisumum*, *Morus alba* and *Ocimum tenuiflorum* act effectively as PPA inhibitors, leading to a reduction in starch hydrolysis and hence eventually to lowered glucose levels (Sudha et al., 2011). The volatile oil obtained from *Curcuma longa* showed antidiabetic activity and inhibited glucosidase activity. On the other hand, the Turmeric volatile oil was found to inhibit glucosidase enzymes more effectively than acarbose, a standard compound (Lekshmi et al., 2012). *Salacia reticulate* and its active principles i.e. salacinol, kotalanol, and de-O-sulfonated kotalanol were also found to inhibit the human intestinal maltase-glucoamylase (Sim et al., 2010).

Hypolipidemic effect

The increased risk of coronary artery disease in subjects with DM can be partially explained by the lipoprotein abnormalities associated with DM. Hypertriglyceridemia and low levels of high-density lipoproteins are the most common lipid abnormalities. Hyperlipidemia is an associated complication of DM, and there are many herbs effective to treat this complicacy. *Ficus racemosa* bark, used for thousands of years in Ayurveda possesses antidiabetic, hypolipidemic and protective effects in rat models (Keshari et al., 2016). The root of *Salacia oblonga* was found to be a PPAR-alpha activator which provides a potential mechanism for improvement of postprandial hyperlipidemia and hepatic steatosis in diabetes and obesity (Huang et al., 2006). Prince et al. (1999) reported that *Tinospora cordifolia* root at 2.5 and 5.0 g/kg body weight showed better hypolipidemic effect than glibenclamide, and restored all the parameters to near normal values in rats. Moreover, *Momordica cymbalaria* fruits (Rao et al., 1999) and *Aegle marmelos* seeds (Kesari et al., 2006) showed antidiabetic and hypolipidemic effects in the alloxan-induced diabetic rats. Dhandapani et al. (2002) found that *Cuminum cyminum* significantly reduced the fatty changes and inflammatory cell infiltrates in diabetic rats. *Zingiber officinale* rhizomes exhibited lipid lowering activity in diabetic rats and protected the tissues from lipid peroxidation (Bhandari et al., 2005) whereas *Phaseolus vulgaris* was found to prevent the fatty acid changes in liver, kidney, and brain of diabetic rats (Pari and Venkateswaran, 2004).

Multiple effects

The insulin resistance and β-cell dysfunction are the pathophysiological hallmarks of Type 2 DM. Increase in oxidative stress and changes in antioxidant capacity, induced by high glucose, play a central role in complications of DM (Kavitha et al., 2016). A hydroalcoholic extract of the *Nymphaea stellata* flower showed the antidiabetic effect and the possible mechanism of this activity includes the stimulation of β-cells, a subsequent release of insulin and activation of the insulin receptors. The antihyperglycemic action may be due to the potentiation of pancreatic secretion of insulin, which is clearly evident from the increased level of insulin in the treated rats. On the contrary, no effect was seen in normal rats, both in the glucose and lipid plasma levels. In addition, the hypocholesterolemic effect of the ethanolic extract of the leaves of *N. stellata* could possibly be related to its amino acid and saponin composition (Raja et al., 2010). The extract of *Aerva lanata* showed antidiabetic effect through α-glucosidase inhibition, antiglycation, and adipogenic potential. In addition, insulin sensitization and antioxidant potential also enhance its therapeutic potential (Riya et al., 2015). Similarly, *Leucas cephalotes* (Lamiaceae), an ayurvedic medicinal plant, regulates both carbohydrate and lipid metabolism and improves body antioxidant defence systems in both type 1 and type 2 diabetes (Bavarva and Narasimhacharya, 2010).

The roots of *Cyclea peltata* were found to improve serum glucose, lipid profile, insulin secretion, inflammatory marker TNF-α and muscle glycogen in type 2 diabetic rats. The root extract of the plant at 40 and 60 mg/kg doses increased the glycogen levels in skeletal muscle by 58% and 60%, respectively. The improved glycogen in peripheral tissue such as skeletal muscle indicates the ability of the plant to combat insulin resistance of type 2 diabetes (Kirana and Srinivasan, 2010). Gulati et al. (2012) found that *Euphorbia drummondii* and *Pterocarpus marsupium* extracts have a good potential for the management of hyperglycemia and the related condition of oxidative stress. A mechanism based study revealed that *Asparagus officinalis* extract exerts antidiabetic effects by improving insulin secretion and β-cell function, as well as the antioxidant status (Hafizur et al., 2012). Based on both *in silico* and *in vivo* analyses, it has been revealed that *Cassia auriculata* mediates glucose/lipid metabolism via the PI3K signalling pathway, and influence AKT thereby causing insulin secretion and insulin sensitivity in peripheral tissues (Mohd Fauzi et al., 2016). *Pterocarpus marsupium*, popularly known as Vijayasar was found useful in the treatment of newly diagnosed or untreated mild type 2 diabetes patients. (ICMR, 1998). However, the extract of *Woodfordia fruticosa* flowers ameliorates hyperglycemia, oxidative stress and improves β-cell function in STZ-nicotinamide induced diabetic rats (Arya et al., 2015). Fenugreek (*Trigonella foenum-graecum*) has a long history of medical uses in Ayurvedic and Chinese medicine and has been used for numerous indications, including labor induction, aiding digestion, and as a general tonic to improve metabolism and health. The preliminary animal and human trials suggest possible anti-hyperglycemic properties of the seeds powder of fenugreek when taken orally (Basch et al., 2003). A pilot clinical study by Desai et al. (2015) revealed that coatbuttons (*Tridax procumbens*) exhibited potent blood glucose-lowering properties together with anti-inflammatory effects.

The aerial parts of *Swertia corymbosa* were found to exhibit antidiabetic and antioxidant activities which provide the scientific proof for the folklore medicine (Mahendran et al., 2014) whereas *Carica papaya* was found effective in controlling blood glucose levels and in improving lipid profile in diabetic rats (Maniyar and Bhixavatimath, 2012). On the other hand, *Momordica charantia* not only improves glucose metabolism but also ameliorates obesity and associated diabetic dyslipidemia (Snee et al., 2011). It was found to maintain the normal glucose levels in diabetic rats, reduced triglyceride and low-density lipoprotein levels, and increased high-density lipoprotein levels. It also improved the antioxidant status, indicated by low levels of thiobarbituric acid-reactive substances and normal levels of reduced glutathione (Chaturvedi and George, 2010).

On the other hand, curcumin has capability to affect most of the leading aspects of diabetes, including insulin resistance, hyperglycemia, hyperlipidemia, and islet apoptosis and necrosis. In addition, curcumin can prevent the deleterious complications of diabetes (Zhang et al., 2013). *Picrorhiza kurroa* is mentioned in Ayurveda for the treatment of many disorders, but it has not been subjected to systematic scientific investigations to assess its antidiabetic effect. The oral administration of aqueous and methanol extracts of *P. kurrooa* rhizomes (250 and 500 mg/kg/day) for 15 days significantly reduced blood glucose, glycosylated haemoglobin and increased total hemoglobin, plasma insulin in alloxan-induced diabetes in rats (Chauhan et al., 2008). Diabetic therapeutic and antioxidative effects of an ethereal fraction of the ethanolic extract of the seed of *Syzygium cumini* was studied in STZ-induced diabetic rats and found that it significantly improve the fasting blood glucose level and the activity of hepatic glucose-6-phosphatase. The possible hypothesis for the therapeutic effect of the plant against diabetes may be due to its pancreatic β-cell regenerative effect and/or due to its antioxidant properties (Mandal et al., 2008). *Embelia ribes*, commonly known as Vidanga is extensively used in traditional system of medicine for treatment of

various disorders. Oral administration of the *E. ribes* ethanolic extract (100 and 200 mg/kg) significantly reduced the levels of blood glucose, glycated haemoglobin, heart rate and systolic blood pressure in diabetic rats (Bhandari et al., 2008).

Treatment with polyherbal formulation

In Ayurveda, single as well as multiple herbal formulations are used for the treatment. *Sarangdhar Samhita*, the *Ayurvedic* text, highlighted the concept of polyherbalism to achieve greater therapeutic efficacy. The active phytochemicals of the individual plant are insufficient to achieve the desirable therapeutic effects, but when combining the multiple herbs in a particular ratio, it will give a better therapeutic effect and reduce the toxicity (Parasuraman et al., 2014). The polyherbal formulation containing hydroalcoholic extracts of four plants namely *Salacia oblonga*, *Salacia roxbhurgii*, *Garcinia indica* and *Lagerstroemia parviflora* showed antidiabetic and antihyperlipidemic activities in high fat diet/STZ induced diabetic rats (Subhasree et al., 2015). The administration of indigenous drug preparations (nisakathakathi Kashayam and rasnairandadi Kashayam and its mixture) ameliorated the diabetic hypertensive condition by reversing these effects (Kumari and Devi, 1993). A polyherbal tablet called Glucova Active (contains *Pterocarpus marsupium*, *Enicostemma littorale*, *Eugenia jambolana*, *Tinospora cordifolia*, Pramehahara Kwatha and Chandraprabha Vati) is a proprietary Ayurvedic formulation with ingredients reported for anti-hyperglycemic, antihyperlipidemic and antioxidant properties which can be attributed to synergistic effect of multiple herbal ingredients of formulation (Soni et al., 2014). Similarly, Diasulin, a polyherbal drug, controls the blood glucose level by increasing glycolysis and decreasing gluconeogenesis with a lower demand for pancreatic insulin than in untreated rats. This is possible because it regulates the activities of hepatic glucose metabolic enzymes (Pari and Saravanan, 2004). Mangiferin, berberine, kaempferol and curcumin were found to active consitituents of the polyherbal Ayurvedic preparation DB14201 which showed antidiabetic activity without toxic effects (Pillai et al., 2016).

Various herbs such as *Glycyrrhiza glabra, Ficus infectoria, Shorea robusta, Curcuma longa, Berberis aristata, Rubia cordifolia, Azadirachta indica*, *Pongamia glabra, Ficus religiosa, Ficus bengalensis,* and *Centella asiatica* together with some *bhasma* and oils were also found effective for diabetes and wound healing in different combinations (Nehete et al., 2016). *Salacia oblonga, Tinospora cordifolia, Emblica offinalis, and Gymnema sylvestre* are the well-known Ayurvedic medicinal plants reported lowering plasma glucose level. These herbs not only attenuate the hyperglycemia but also act as hypolipidemic agent in patients with diabetes (Kurian et al., 2014).

Diashis, a polyherbal proprietary formulation, consists of eight plants, *i.e., Syzygium cumuni, Gymnema sylvestre, Holarrhena antidysenterica, Tinospora cordifolia, Pongamia pinnata, Asphultum, Psoralea corylifolia*, and *Momordica charantia* help in inducing insulin secretion (Bera et al., 2010). In the same way, Chandraprabha vati which contains *Acorus calamus, Cyperus rotundus, Phyllanthus niruri, Tinospora cordiofolia, Curcuma longa, Berberis aristata, Piper longum, Coriandrum sativum, Terminalia chebula, Terminalia belerica, Embelica officinalis, Embelia ribes, Zingiber officinale, Piper nigrum, Hordeum vulgare, Ipomoea turpethum, Cinnamomum zeylanicum* and *Asphaltum punjabianum* as the active ingredients can be considered as a best example of polyherbal antidiabetic formulation. Most of the important ingredients of this formulation demonstrated hypolipidemic, curative and lipid lowering effects (Wanjari et al., 2016). Besides, Sapatarangyadi ghanavati is a combination of *Salacia chinensis, Momordia charantia, Trigonella foenum-graecum, Tinospora cordifolia, Emblica officinalis, Terminalia belerica* and *Terminalia chebula* which showed antidiabetic activity (Singh et al., 2014). The Ilogen-Excel, an Ayurvedic herbal formulation is composed of eight herbs i.e. *Curcuma longa, Strychnos potatorum, Salacia oblonga, Tinospora cordifolia, Vetivelia zizanioides, Coscinium fenestratum, Andrographis paniculata* and *Mimosa pudica*. This formulation was found to exhibit the antihyperglycemic effect in rats (Umamaheswari and Prince, 2007). The present study aims at developing an Ayurvedic-based polyherbal formulation (ADPHF6) and the assessing its antidiabetic and antioxidant property.

A clinical trial of Cogent db (an herbal preparation) revealed that it decreases the levels of fasting and postprandial blood glucose, cholesterol, triglycerides, and glycated hemoglobin without altering the liver function tests, hematologic parameters, and kidney function tests (Shekhar et al., 2002). Similarly, a clinical trial of Nishamalaki (a combination of *Curcuma longa*, and *Emblica officinalis*) showed a significant reduction in blood glucose level (Yadav et al., 2001). A polyherbal combination of *Curcuma longa*, *Emblica officinalis* and *Salacia oblonga* called Rajanyamalakadi showed significant antidiabetic, hypolipidemic and antioxidant effects. In addition, it showed significant ameliorating effects on the elevated serum AST and ALT activities (Faizal et al., 2009).

Treatment with Bhasma

Bhasmas are unique Ayurvedic-metallic preparations with herbal extracts, widely recommended to treat variety of chronic ailments

include DM. Trivanga bhasma, a calcinated preparation, possesses anti-diabetic and diuretic activity without showing any hazardous effects (Rasheed et al., 2014). The oral administration of Tarakeswara rasa (prepared with purified mercury, sulphur, mica and honey) exhibited a significant decrease in the blood glucose in rats in addition to the reduction of cholesterol, triglyceride and phospholipid content (Vasanthakumari and Shyamala Devi, 1997). A cytotoxicity test of *Jasada bhasma* (zinc based bhasma) revealed no loss of cell viability and no effects on cell morphology; hemolysis was found to less than 5% (within acceptable limits) after its oral administration to rats (Umrani and Paknikar, 2015). The swarnabhasma (gold ash) has showed no toxicity as judged by examining SGPT, SGOT, serum creatinine and serum urea level as well as by histological studies. A study by Mitra et al. (2002) found that the swarnabhasma significantly increased superoxide dismutase and catalase activity, which are responsible to reduce free radical concentrations in the body. On the other hand, Makaradhwaja, a gold mercury and sulphur containing preparation, was also found to reduce the blood glucose level and exhibit an anti-diabetic effect in rats (Khedekar et al., 2016).

Bhasmas are known to be effective at very low doses and devoid of toxic effects. Once the active ingredients of *bhasmas* are identified, these metal oxides can be synthesised and evaluated as a new chemical entity in modern drug discovery. Taking inspiration from the fact that *bhasmas* contain submicronic or nanoparticles that enhance bioavailability, metal based nanomedicines can be developed for diabetes. This would be helped in utilising the age-old wisdom of Ayurveda for the development of newer drugs in modern medicine.

PANCHAKARMA THERAPY

Panchakarma is believed to help in cleansing the impurities of the body those can lead to disease. This treatment is one of the prominent Ayurvedic tools used to restore balance to the body through the use of herbalized oils, body treatments, steam therapy, herbal paste therapy, nasal therapy, vomiting therapies, enema therapy, and purgation therapies. Panchakarma is designed to allow the body to rid itself of wastes that have accumulated and lodged in the body, creating blockages in the intelligent flow of the various systems, including the circulatory, nervous, and digestive systems. Once this cleansing process is complete, the body can resume its natural functioning without interference (Conboy et al., 2009). It can be believed that both *Vamana* and *Virechana* cause marked a reduction in fasting and postprandial blood sugar levels. It seems that *Vamana* by reducing *Kapha* and *Meda* helps to minimise insulin resistance, whereas *Virechana* by lowering down the hepatic glucose production helps to control blood sugar. As *Prameha* is an *Aanushangivyadhi*, neither *Vamana* nor *Virechana* alone acts as the complete treatment for it (Jindal and Joshi, 2013). However, *Basti*, due to its purification property, eliminates the excess of deranged metabolic waste and in turn clears the *Avarana* of *Vata* and normalises the functions of *Vyana* and *Apana Vata*. Thus, the normalized *Vata* helps to stop the depletion of vital *Dhatus* (body elements) through urine. Ramteke et al. (2012) found that Gokshura-Punarnava *Basti* showed 79% improvement in the complaints of diabetes, urine microalbumin, sugar level and blood pressure when compared to that of enalapril which showed 33% improvement in patients. Hence, it can be considered as a suitable alternative for the management of microalbuminuria in diabetes. In addition, *Vamana* and *Virechana* along with palliative treatment showed that the *Vamana* provided better relief of signs and symptoms as well as on fasting and postprandial blood sugar in comparison of *Virechana* (Pandey, et al., 2011). A combined treatment of *Virechana* and Nyagrodhadi ghanavati exhibited better results in the patients with DM in comparison with Nyagrodhadi ghanavati when administered alone (Kumari et al., 2010).

LIFESTYLE AND DIETARY

The number of people with diabetes is increasing due to population growth, aging, urbanisation, and increasing prevalence of obesity and physical inactivity. The rising trend of type 2 DM in developing countries like India, presumably, mainly because of changes in health status of the demographic structure; lifestyle, food habit and mental stress (Sharma and Prajapati, 2015). However, the dietary interventions and lifestyle modifications improve glycemic control, insulin sensitivity and cardiovascular fitness (Sharma et al., 2015). According to Gupta et al. (2014), the reduction of the signs, symptoms, weight and BMI also indicates that dietary interventions and lifestyle modifications are important tools for the management of type 2 DM. Besides, fatty items, marshy animals, aquatic animals are also the important causes of diabetes. Ayurveda cautions sedentary lifestyles as a factor for diabetes; it also cautions excessive starvation, excessive exercises which may also lead to another complicacy. The contemporary scientific world deliberates that if body mass index is more than 25, one should lose weight to prevent DM (Prasad et al., 2006). Dietary interventions and lifestyle modifications are two important tools by which adequate glycemic control can be obtained, especially in newly diagnosed T2DM patients and in patients who are on antidiabetic medication, but not properly controlled. Besides, involving yoga in daily routin is all the time beneficial for the health; it could act as a complementary therapy for the treatment of

diabetes (Semwal et al., 2016a). Many reports revealed that yoga has the ability to rejuvenate the main glands involved with diabetes, i.e. the pancreas that is involved with insulin release. Moreover, the stress glands are believed to be involved where a high-stress level can overload the blood with high sugar as a response to stress (Semwal et al., 2016b).

POST DIABETIC COMPLICATIONS AND THEIR TREATMENT

Poorly managed DM can lead to a host of long-term complications such as heart attacks, strokes, blindness, nerve damage, amputation of limb, weakness and itching. The complexity of this metabolic disorder increased by hyperglycaemia and impaired lipid, carbohydrate and protein metabolism as a result of defects in insulin secretion, insulin action or both. As a consequence of these metabolic alterations, the patient develops retinopathy, neuropathy, nephropathy, myocardial infarction, heart failure and stroke (Moodley et al., 2015). The individual complications are described below with their mechanism and possible treatment with the help of Ayurveda.

Retinopathy

Retinopathy is persistent or acute damage to the retina of the eye. Ongoing inflammation and vascular remodelling may occur over periods of time where the patient is not fully aware of the extent of the disease. Frequently, retinopathy is an ocular manifestation of systemic disease as seen in diabetes or hypertension. Diabetic retinopathy is the leading cause of blindness in working-aged people. Various researches on the herbal medicines confirmed their efficacy against retinopathy. An extract of *Aegle marmelos* was shown to have a potential effect to inhibit rat lens AR and consequential decrease in osmotic stress. Besides, the extract also inhibits the loss of antioxidants contributing to the integrity of α-crystallin's chaperone activity and thereby delaying cataract (Sankeshi et al., 2013). Moreover, the water and alcoholic extracts of *Momordica charantia*, *Eugenia jambolana*, *Tinospora cordifolia* and *Mucuna pruriens* exhibited their potential against cataract in alloxan-induced diabetic mice at various doses of 200 and 400 mg/kg p.o. (Rathi et al., 2002).

Neuropathy

Peripheral neuropathy is a disease affecting nerves, which may impair sensation, movement, gland or organ function, or other aspects of health, depending on the type of nerve affected. DM is one of the common causes of peripheral neuropathy. It affects the CNS and produce disturbances such as behavioural changes, autonomic dysfunctions, altered neuroendocrine functions, and neurotransmitter alterations and thus leading to organ damage. There is a growing importance for the treatment of diabetic neuropathic pain for which there are no appropriate treatment strategies (Chundi et al., 2016). The plant-derived flavonoids are extensively studied to identify therapeutically active constituents for neuropathic pain. Flavonoids like hesperidin have been demonstrated to be beneficial in experimental neuropathic pain (Visnagri A et al., 2014). Besides, biochanin-A, an O-methylated isoflavone found in *Glycine max*, *Medicago sativa*, *Arachis hypogaea* and *Cicer arietinum* was also found active against neuropathy (Tan et al., 2013). Solanki and Bhavsar (2015) found the protective role of *Ficus racemosa* L. in STZ-induced diabetic neuropathy with neuro-degeneration.

Nephropathy

Diabetic nephropathy is the leading cause of kidney disease in patients starting renal replacement therapy and affects around half of the diabetic patients. It increases the risk of death, mainly from cardiovascular causes, and is defined by increased urinary albumin excretion in the absence of other renal diseases. An Ayurvedic herb *Pueraria tuberosa* attenuates diabetic nephropathy by upregulating the MMP-9 expression in the kidney of diabetic rats (Tripathi et al., 2017). Similarly, the treatment of carbendazim-treated rats with the root of *Withania somnifera* for 48 days showed complete cure of damaged organs (Akbarsha et al., 2000).

A combined treatment of diabetic nephropathy with Shilajitvadi Vatika, Punarnavadi Mandura, Triphala Guggulu and Pippalimooladi Paneeya added with Amrita and Bringaraja showed significant improvement in microalbuminuria levels, and status of Agni without showing adverse effects (Akarshini and Aruna, 2014). An aqueous root extract (100 mg/kg, p.o. for 6 weeks) of *Salacia oblonga* was found to diminish renal glomerulosclerosis and interstitial fibrosis in Zucker diabetic fatty rats. In addition, it also reduced renal salt-soluble, acid-soluble and salt-insoluble collagen contents. The plant extract and its major component mangiferin suppressed the stimulatory effect of angiotensin II on proliferation and increased mRNA expression and/or activities of collagen I, collagen IV, fibronectin, AT1, TGF-β1 and PAI-1 (He et al., 2011).

Myocardial infarction, heart failure and stroke

Ayurvedic medicines have been proved to have protective effects against myocardial infarction, heart failure and stroke. The bark of *Terminalia arjuna* Roxb. is widely used in Ayurveda for various cardiovascular ailments. Several clinical

studies showed its efficacy in ischemic heart disease, hypertension, and heart failure (Maulik and Talwar, 2012) whereas its crude water extract was found to prevent MCT-induced pulmonary hypertension (Meghwani et al., 2016). Shilajit, a mineral-rich complex organic compound is also used in Ayurveda for treating hypertension and improving the cardiac function with many herbomineral preparations (Gaikwad et al., 2012). Besides, *Withania somnifera* is useful for improving cardiovascular endurance and lowering systolic blood pressure (Sandhu et al., 2010). Hawthorn (*Crataegus oxyacantha*), Pushkarmool (*Inula racemosa*), and Astragalus (*Astragalus membranaceus*) have been found to have therapeutic benefit for the treatment of cardiovascular disease (Miller, 1998).

Wound healing

Delayed wound healing is considered to be one of the most important complications observed in DM. Increase in oxidative stress in type 1 DM results in increased production of ROS which contributes to delay wound healing due to an imbalance between oxidant and antioxidant enzymes. The leaves of *Piper betel* exhibited wound healing activity via the proliferation of fibroblasts and reducing 11β-hydroxysteroid dehydrogenase-1 expression in the diabetic rat (Ghazali et al., 2016). The extracts from the roots of *Hemidesmus indicus* exhibited an ameliorative effect on liver, kidney and pancreatic injury in STZ-induced diabetic rats (Gayathri and Kannabiran, 2010). A paste obtained from *Securinega leucopyrus* was found clinically effective in the diabetic wound (Ajmeer et al., 2015).

DISCUSSION

Ayurveda is the most frequently used complementary and alternative medicinal system mainly for chronic diseases (Bhalerao et al., 2013). It is highly important to know about the authenticity of the herbs before their use as a medicine as many herbs are known by similar vernacular names but showed different activity. There are numerous important Ayurvedic medicinal plants which are used to treat DM but these are yet to be explored to understand their bioactive constituents and mechanism of action. An example of such plants is *Costus igneus* Nak, which is commonly known as fiery costus, step ladder, spiral flag and insulin plant, a native of South and Central America, now introduced in India as an herbal cure for DM. The leaves of this plant have been clinically tested in diabetes patients, and exhibited significant glucose lowering effect; however, these results have to be further evaluated and revalidated by clinical trials with more patients (Hegde et al., 2014). Similarly, *Gymnema sylvestre* (gurmar) has a potent antidiabetic effect, and widely used for DM in Ayurveda (Shiyovich et al., 2010).

Several reports confirmed that around 45% diabetic patients use complementary and alternative medical therapy. Till the date, more than 800 plants are known to possess antidiabetic effect and are used for the management of DM worldwide.

The current pharmacological therapy of type 2 DM reduces the risk of diabetic complications but is not able to achieve a long-lasting normalisation of the metabolic disorder. Thus diabetic patients in increasing numbers are taking dietary supplements and herbs from which they expect additional health benefits. These unconventional antidiabetic agents mainly consist of trace metals like chromium, vanadium and zinc, and a heterogeneous group of traditionally used antidiabetic herbs include *Momordica charantia*, *Gymnema sylvestre*, and *Trigonella foenum-graecum*. It is important to know that although such formulations are effective in glucose lowering but their safety and standardization is still a big challenge.

Nowadays, a variety of antidiabetic brands such as Diabetex, Divya Madhu Nashini, Jambrushila, Diabeticin, and Madhumeh Nashini are available in the market which contains heavy metals. These herbal formulations contain minor and trace elements in bioavailable forms that favourably influence glucose tolerance and possibly increase the body's ability to ameliorate the development of diabetes (Choudhury et al., 2007). Recently, CSIR developed a scientifically validated antidiabetic drug, BGR-34 with the help of ancient Ayurvedic texts. It is interesting to know that its successful rate against type 2 DM is 67%. Besides, CCRAS developed an antidiabetic drug, IME-9 which is known to regenerate β-cells, stimulate insulin production, decrease insulin resistance, delay intestinal absorption and reduce sugar cravings. The positive results of IME-9 were found due to the synergistic effect of four herbs viz. bitter melon (*Momordica charantia*), jamun (*Syzygium cumini*), yellow mombin (*Spondias mombin*), and Cowplant (*Gymnema sylvestre*) together with Shilajit (a sticky tar-like substance which contains around 85 minerals in ionic form together with various triterpenes and humic acids as major components).

CONCLUSION

This review concludes that Ayurveda, an Indian medicinal system has tremendous ability to cure diabetes with the help of herbal therapy. The positive antidiabetic effects of Ayurvedic herbs have been confirmed by numerous scientific studies but most of these studies are based on their glucose lowering effect whereas the toxicity studies, as well as their standardization, have been considered as least. Besides, the proper

documentation of many of such herbs is still needed for their acceptability in International markets. Interestingly, these herbs may have more than one target of action due to the presence of different active constituents; thus, a definite mode of action must be investigated. These herbs can be used alone or in combination with other in the form of a polyherbal formulation for better the outcome. This will further provide a basis for conducting larger and more rigorous clinical trials. After systematically exploring an Ayurvedic drug, it will be easy to provide full information about the mechanism of action, dose forms, compatibility, interaction, and side effects, which will help people to make their mind for accepting the Ayurvedic treatment for diabetes.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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