Topical Review Article

A Mechanistic Review on Medicinal Plants Used for Diabetes Mellitus in Traditional Persian Medicine

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Abstract

Diabetes mellitus is the most common endocrine disorder and a major cause of morbidity and mortality. Traditional medicines worldwide suggest a wide range of natural remedies for the prevention and treatment of chronic disorders, including diabetes mellitus. This mechanistic review aims to highlight the significance of medicinal plants traditionally used as dietary supplements in Persian medicine in adjunct with restricted conventional drugs for the prevention and treatment of diabetes mellitus. Mounting evidence suggests that these natural agents perform their protective and therapeutic effect on diabetes mellitus via several cellular mechanisms, including regeneration of pancreatic β cell, limitation of glycogen degradation and gluconeogenesis, anti-inflammatory, immunoregulatory, antiapoptosis, antioxidative stress, as well as modulation of intracellular signaling transduction pathways. In conclusion, traditional medicinal plants used in Persian medicine can be considered as dietary supplements with therapeutic potential for diabetes mellitus and maybe potential sources of new orally active agent(s).

Keywords

diabetes mellitus, traditional Persian medicine, herbal medicine, dietary supplement, complementary and alternative medicine

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Diabetes mellitus is a chronic metabolic disease that is characterized by hyperglycemia, inadequate production of insulin, or inadequate sensitivity of cells to the action of insulin. There are 3 major types of diabetes: type 1 or insulin dependent, type 2 or non–insulin dependent, and gestational diabetes.[1,2] The total number of patients with diabetes worldwide is expected to double in 2005-2030. It has been found that diabetes mellitus is a major cause of morbidity and mortality with an increasing prevalence due to sedentary lifestyle and obesity, indicating that research on the prevention and treatment of diabetes deems critical.[2,3] Type 2 diabetes mellitus is the most common form of diabetes accounting for 90% to 95% of patients. The prevalence of diabetes for all age groups was estimated to be 2.8% in 2000 and 4.4% in 2030. According to the World Health Organization, diabetes will be the seventh leading cause of death in 2030.[3,4] Epidemiologic and genetic studies indicate a strong genetic basis for development of type 2 diabetes. The capacity of the β islet cell to produce insulin and to adapt to the increasing demands of the insulin resistance state is genetically predetermined to a great extent.[2] Environmental factors, including diet, obesity, physical activity, and lifestyle as well as increased number of elderly people are among the preliminary causes of diabetes.[5-7] Because of deficient insulin action on target tissues, metabolism of carbohydrates, lipids, and proteins in these patients is abnormal and thus, long-term hyperglycemia causes remodeling of the vessel wall in the retinal and renal circulations and as a result, retinopathy with potential loss of vision and nephropathy, which are highly specific for diabetes.[8-10] Besides, diabetes mellitus is also contributes to heart disease and considered as a major risk factor of cardiovascular diseases.[11,12]

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Table 1. Medicinal Plants with Anti-Diabetes Activity used in Traditional Persian Medicine.[21-24]

Scientific Names	Family	Medicinal Part	Name(s) in Persian Medicine Resources	Uses in Persian Medicine
Acacia arabica	Leguminosae	Gum and fruit	Samghe arabi (gum), Aghaghia (fruit)	Gastric tonic, respiratory disorders, diarrhea, peptic ulcer, inflammatory bowel disease, diabetes
Bambusa arundinacea	Poaceae	Dried exudate on nodes	Tabashir	Gastric and liver tonic, peptic ulcer, dysentery, aphthous, diabetes
Boswellia carterii, *Boswellia serrata*	Burseraceae	Oleo-gum resin	Kondor	Improvement of memory function, gastric tonic, peptic ulcer, inflammatory bowel disease, diabetes
Conium maculatum	Umbelliferae		Shokaran	Hypnotic, diarrhea, diabetes
Coriandrum sativum	Umbelliferae	Fruit	Kozboreh, Geshniz	Carminative, insomnia, inflammation, dermatitis, eczema, scabies, scrofula, infected wounds and injury, diabetes
Glycyrrhiza glabra	Fabaceae	Root	Shirin bayan, Sus	Gastric tonic, gastritis, diabetes, pulmonary disease
Lactuca sativa	Asteraceae	Seed	Kahoo, Khas	Diuretic, hypnotic, diabetes
Myrtus communis	Myrtaceae	Fruit	Murd, Aas	Antidepressant, diarrhea, polymenorrhea, bruise, diabetes
Oxalis species	Oxalidaceae	Fruit	Hammaz, Torshe	Liver tonic, appetizer, peptic ulcer, inflammatory bowel disease, diabetes
Portulaca oleracea	Portulacaceae	Seed	Khorfe, Baghle-al-homgha	Gastric tonic, urinary tract infections, lithontropic, diabetes, peptic ulcer, diabetes
Punica granatum	Punicaceae	Flower	Golnar	Gastric and liver tonic, liver disease, peptic ulcer, inflammatory bowel disease, diabetes
Rosa spp	Rosaceae	Flower and fruit	Gole sorkh, Vard	Antidepressant, gastric tonic, peptic ulcer, wounds and injury, diabetes
Santalum sp	Santalaceae	Wood	Sandal-e-Sefid	Antidepressant, inflammation, headache, diabetes
Vitis vinifera	Vitaceae	Unripe fruit	Ghoureh	Wound healer, hematopoietic, peptic ulcer, diabetes

As conventional medical management shows many side effects, research on exploring safe treatments are needed. Herbal medicines and their extraction can be used for the treatment of several chronic diseases.[13,14] Despite the discovery of insulin and even during the progress in the development of oral antihyperglycemic drugs, one of the main therapeutic approaches of diabetes mellitus and its complications involves dietary manipulation, starvation, and the intake of various medicinal plants or their extracts based on the traditional and folklore medicines.[15,16] Complementary and alternative medicine such as acupuncture, herbal medicines, homeopathy, traditional medicine, and other medicinal approaches, may be helpful in the management of diabetes.[17]

Traditional medicines all over the world encompass a wide variety of natural drugs for the treatment of symptomatologies associated with chronic disorders such as diabetes mellitus. Scientists are discovering within nations' traditional medicine to find future antidiabetic agents.[18,19] History of medicine in Iran originated almost in the fourth century BC. The golden era of traditional Persian medicine was at the period when the well-known college of Jundishapur invited the physicians and scientists of all over the world and welcomed the knowledge originated in the cultures of different nations, including Greece, India, and Egypt. Thus, traditional Persian medicine has been combined with medical sciences from various ancient countries such as Greece, China, and India for more than 4000 years.[18,19] Pharmaceutical science and practice encompass an important part of Persian medicine, and most of the drugs in Persian medicinal systems are natural agents, mainly herbal medicine. The famous traditional Persian medicine scientists, including Rhazes (854-925 CE), Avicenna (980-1037 CE), Jorjani (1042-1137 CE), Tonkaboni (17th century CE), and Aghili Khorasani (17th-18th century CE) had a pivotal contribution to the growth of medical and pharmaceutical practices.[18-20]

This mechanistic review aims to highlight the scientific evidence of traditional medicinal plants used as dietary supplements, which can be used in adjunct with restricted conventional drugs for the prevention and treatment of diabetes mellitus. We describe popular medicinal plants that are generally applied in traditional Persian medicine for the prevention and treatment of diabetes based on recent studies established their efficacy and mechanisms of action.

Methods

In the present review article, a list of medicinal plants traditionally used for the prevention and management of diabetes mellitus was gathered from traditional Persian text books, *Makhzan-ol-advieh* (written by Aghili Alavi Khorasani in 1771 CE)[21] (1976) *Zhakhireh Kharazmshahi* (written by Jorjani)[22] *Tohfat-ol-Moemenin* (written by Mohammad Tonkaboni in 1670 CE)[23] and *Al-Qanoon fi al-Tibb* (The Canon of Medicine, written by Avicenna in 1025 CE).[24] Subsequently, electronic databases including Cochrane library, Scopus, PubMed, Web of Science, and Google Scholar were searched for each of these medicinal herbs, and all retrieved articles were evaluated to ascertain any in vitro, in vivo, or clinical evidence for their efficacy and pharmacological mechanisms. The retrieved studies demonstrated either apparent efficiency of these remedies or their indirect effectiveness on the mechanisms involved in the management of diabetes mellitus. Data were collected from 1970 to 2016 (June). Only published articles

Table 2. In Vitro Studies of Medicinal Plants used for the Treatment of Diabetes in Traditional Persian Medicine.

Plant	Part/Extraction	Result	Active Constituent	Reference
Bambusa arundinasia	Dried exudate/ methanol extract	α-Amylase enzyme and α-glucosidase inhibitory activity	—	27
Boswellia serrata	Oleo-gum resin	↓Rat lens and kidney and human recombinant polyol enzyme aldose reductase activity and its advanced glycation end-products, which resulted in ↓chronic diabetic complications	Boswellic acid	31
Coriandrum sativum L.	Fruit/aqueous extract	↑Glucose uptake, ↑glucose oxidation and ↑glycogenesis in mice abdominal muscle and ↑insulin secretion in rat pancreatic β-cell	—	33
Lactuca sativa	Seed/methanol extract	α-Amylase enzyme and α-glucosidase inhibitory activity	—	27
Myrtus communis	Aerial part/isolated compound from 80% methanol extract	α-Glucosidase enzyme inhibitory activity	Myrtucommulone D, myrtucommulone E, myrtucommulone C, and myrtucommulone B	41
Oxalis corniculata	Leaf/various extract	α-Amylase enzyme inhibitory activity, aqueous extract showed the highest action	—	43
Portulaca oleracea	Seed/methanol extract	α-Amylase enzyme and α-glucosidase inhibitory activity	—	27
Punica granatum	Flower/methanolic extract	↑mRNA and protein expression of PPAR-γ, ↑PPAR-γ-dependent mRNA expression and ↑lipoprotein lipase in human THP-1-differentiated macrophage cells	Gallic acid	49
Punica granatum	Flower/methanolic extract	α-Glucosidase enzyme inhibitory activity	—	50
Rosa damascena Mill	Flower/methanolic extract	Inhibitory activity on α-glucosidase, which was noncompetitive	—	54
Vitis vinifera	Seed/procyanidin extract	↑Glucose uptake dose-dependently in insulin-sensitive cell lines (L6E9 myotubes and 3T3-L1 adipocytes), and ↑stimulation of insulin pathway mediators, which indicate insulinomimetic activity of procyanidins	Procyanidins	56

were included in this review. Language restriction was considered, and English language articles were included. The search terms were "diabetes mellitus" or "diabetes" or "hypoglycemia" or "hypoglycemic effect" and the name of each mentioned plant in the whole text. Results from primary search were screened by 2 independent investigators. References of finally included articles were reviewed for relevant studies. Included articles were reviewed to extract scientific names of plants, part and extract of the plants, active components (if mentioned), type of diabetes, animal model for in vivo and type of cell line for in vitro studies. Results were summarized in Tables 1-4. Table 1 presents the selected medicinal plants used for the treatment of diabetes mellitus in traditional Persian medicine. Tables 2-4 show in vitro, in vivo, and clinical evidence for the efficacy of the medicinal plants in diabetes. In human studies, factors such as study design, number of patients, interventions, duration of treatment, and efficacy and tolerability of the herbal treatment were also collected.

Findings

Table 1 shows the scientific and vernacular names of the plants used in Persian medicine for the treatment of diabetes with their plant family and pharmacological activities in Persian medicine. The following sections describe the plants that have been used for the prevention and treatment of diabetes in Persian medicine with modern evidence of their antidiabetes efficacy.

Acacia arabica

The gum of *Acacia arabica,* traditionally known as "Samghe arabi," is an important and efficient remedy in Persian medicine. The fruits which traditionally known as "Aghaghia" has been used for its astringent, diuretic, antimicrobial, wound healing as well as liver tonic effects in Persian medicine. Based on traditional text books, its fruit and gum have been used for the treatment of diabetes in Persian medicine.[23] Fruit showed no significant hypoglycemic action on diabetic rabbit. In contrast, the fruits lessened blood glucose in normal animals.[25] Moreover, polyphenols from *Acacia meansii* bark demonstrated hypoglycemic activity and reduced body weight via improvement of insulin sensitivity and energy expenditure–related mediators and also reduction of fatty acid synthesis in an animal model of type 2 diabetes, which indicate its positive action on diabetic metabolic action. Robinetinidol and fisetinidol are 2 chemical compounds responsible for this function.[26]

Table 3. In Vivo Studies of Medicinal Plants Used for the Treatment of Diabetes in Traditional Persian Medicine.

Plant	Part/Route of administration	Method	Animal	Result	Active Constituents	Reference
Acacia arabica	Fruit/oral administration of fruit powder suspension	Aloxan (150 mg/kg s.c.) induced type 1 diabetes	Albino rabbit	Acute hypoglycemic activity in normal rabbit but there was no hypoglycemic action on diabetic animals	—	25
Acacia meansii	Bark/polyphenols	High-fat diet induced type 2 diabetes	KKAy mice	↓Body weight, ↓FBS, ↑GLUT4 in skeletal muscle tissue and ↓serum insulin which indicate ↑insulin sensitivity. Improvement of energy expenditure-related mediators: ↑expression PPARα, PPARδ, CPT1, ACO and UCP3; as well as ↑expression of adiponectin and ↓TNF-α in white adipose tissue. Moreover, it suppresses fatty acid synthesis and fat intake in the liver	Robinetinidol and fisetinidol	26
Bambusa arundinasia	Dried exudate/oral administration of polyherbal formula	STZ (50 mg/kg i.p.) induced type 1 diabetes	Wistar rat	↓FBS, ↑serum insulin, ↓HbA1c, ↓total cholesterol, ↓triglycerides, ↓glucose-6-phosphatase, ↓fructose-1-6-biphophatase and ↑HDL-cholesterol, as well as improvement of pancreatic tissue and Langerhans islets	—	27
Bambusa arundinasia	Leaf/oral administration of ethanol extract and fractions	STZ (60 mg/kg i.p.) induced type 1 diabetes	Wistar rat	↓FBS via improvement of antioxidant function: ↓LPO, ↑SOD, ↑CAT and ↓GSH in pancreatic tissue. Also regeneration of Langerhans islet and pancreas tissue near to normal, as well as improvement of hepatocyte cells and kidney glomeruli and tubules	β-Sitosterol glucoside and stigmasterol	28
Boswellia serrata	Oleo-gum resin/i.p.	Multiple low-dose STZ (40 mg/kg STZ for 5 days) induced type 1 diabetes	BK+/+ wild type mouse	↓Penetration of lymphocytes into pancreatic islets, ↓apoptosis of periinsular cells, ↓G-CSF, ↓GM-CSF, ↓proinflammatory cytokines including: IL-1A, IL-1B, IL-2, IL-6, IFN-γ, TNF-α in the blood, inhibition of atrophy of pancreatic islet tissue and also ↓FBS in diabetic group in comparison with control mice	11-Keto-β-boswellic acid and *O*-acetyl-11-keto-β-boswellic acid	30
Bosswellia carterii	Oleo-gum resin/orally	Aloxan (120 mg/kg s.c.) induced type 1 diabetes	Albino rat	↑Body weight, ↓FBS, ↑serum insulin, ↑liver glycogen and also ↓degenerative changes in the β cells of pancreas in comparison with control group	—	29
Coriandrum sativum L	Fruit/i.p. administration of ethanol extract	STZ (70 mg/kg i.p.) induced type 1 diabetes	Wistar rat	↓FBS, ↑number and activity of pancreatic β cells, ↑insulin release from β cells	—	32
Coriandrum sativum L	Fruit/as supplement in diet and drinking water	STZ (200 mg/kg i.p.) induced type 1 diabetes	Heterozygous lean mouse	↓FBS, which was comparable to normal group	—	33

(continued)

Table 3. (continued)

Plant	Part/Route of administration	Method	Animal	Result	Active Constituents	Reference
Glycyrrhiza glabra	Root/glycyrrhizic acid	High-fat diet induced type 2 diabetes	Sprague-Drawley rat	↓Mean blood glucose, ↑insulin sensitivity, as well as ↓insulin level. ↑Expression of lipoprotein lipase in visceral and subcutaneous adipose tissues, kidney, heart, and abdominal muscle, ↓fatty acid, ↓total cholesterol, ↓LDL cholesterol and also ↓lipid deposition in tissues	Glycyrrhizic acid	35
Glycyrrhiza glabra	Root/glycyrrhizin	STZ induced diabetes	Wistar rat	↓FBS, ↑serum insulin level, ↑pancreatic islet cells, ↓HbA1c, ↓cholesterol, ↓triglyceride, improvement of pancreas and kidney tissues, also ↑antioxidant function: SOD, CAT, MDA, and fructosamine	Glycyrrhizin	36
Lactuca sativa	Dried exudate/oral administration of polyherbal formula	STZ (50 mg/kg i.p.) induced type 1 diabetes	Wistar rat	↓FBS, ↑serum insulin, ↓HbA1c, ↓total cholesterol, ↓triglycerides, ↓glucose-6-phosphatase, ↓fructose-1-6-biphophatase and ↑HDL-cholesterol. Improvement of pancreatic tissue and Langerhans islets	—	27
Myrtus communis L	Leaf/oral administration of volatile oil	Alloxan (200 mg/kg i.v.) induced diabetes	New Zealand albino rabbit	↓FBS, ↓triglyceride, ↑CAT, ↑SOD, ↓nitrite-nitrate and ↓MDA in hepatic tissue; but no significant effect on liver activity biomarker	—	38
Myrtus communis	—/i.p.	STZ (50 mg/kg i.p.) induced diabetes	Wistar rat	↓FBS, ↓MDA, improve kidney function such as ↑kidney weigh, ↓urine volume, ↓renal MDA, ↓urinary protein excretion, ↑Creatinine clearance, ↑renal GPx and ↓BUN	Myricetin	40
Myrtus communis L	Leaf/oral administration of 50% ethanol extract	STZ (150 mg/kg i.p.) induced type 1diabetes, administration of the extract before (1) and after (2) diabetes induction	Mouse	Inhibition of initial hyperglycaemia (1), ↓FBS significantly (2)	—	39
Oxalis corniculata	Whole herb/oral administration of aqueous extract	Alloxan (120 mg/kg, i.p.) induced diabetes	Swiss albino mice	↓FBS, ↓triglyceride, ↓LDL, ↓cholesterol, ↑HDL-cholesterol. Also improvement of antioxidant function: ↑SOD, ↑CAT, ↑GPx, ↓LPO, ↑Vit E, ↑Vit C and ↓GSH.	—	42
Portulaca oleracea	Aerial part/oral administration of aqueous extract	Genetic induced type 2 diabetes	db/db mice	↓FBS, ↑insulin secretion, improvement of diabetic endothelial dysfunction through ↓triglyceride, ↓LDL-cholesterol, ↑HDL-cholesterol, ↓systolic blood pressure and ↑endothelium relaxant responses (↓vascular tension); as well as suppressing diabetic vascular inflammation: ↓ICAM-1, ↓VCAM-1, ↓MMP-2 and ↓E-selectin in aortic tissue	—	47
Portulaca oleracea	Leaf/oral administration of ethanolic extract	STZ (50 mg/kg i.p.) induced type 1 diabetes	Sprague-Dawley rat	↓FBS via ↑antioxidant enzyme: ↑SOD and ↑CAT, ↑GSH-R and ↓LPO in liver and kidney tissue	—	48

(continued)

Table 3. (continued)

Plant	Part/Route of administration	Method	Animal	Result	Active Constituents	Reference
Punica granatum	Flower/oral administration of aqueous extract	STZ (60 mg/kg i.p.) induced type 1 diabetes	Albino Wistar rat	↓FBS, ↓triglycerides, ↓cholesterol, ↓LDL-cholesterol, ↓VLDL, ↓LPO, ↑HDL-cholesterol, improvement of antioxidant enzymes: ↑GPx, ↑GSH-R, ↑GST, ↑SOD, ↑CAT and ↓GSH	—	51
Punica granatum	Flower/oral administration of methanolic extract	Zucker diabetic fatty rats (type 2 diabetes)	Zucker rat	No significant effect on FBS, improve glucose tolerance effect, as well as ↑insulin sensitivity via ↑PPAR-γ mRNA expression and ↑GLUT4 mRNA expression (the insulin-dependent isoform of GLUTs)	Gallic acid	49
Punica granatum	Flower/oral administration of methanolic extract	Sucrose loading mice (in vivo α-glucosidase enzyme inhibitory test), glucose loading and normal mice	Mouse	↓Blood glucose in sucrose loading mice, but no effect on blood glucose in glucose loading and normal mice	—	50
Rosa damascena Mill	Flower/oral administration of methanolic extract	Maltose loaded normal and STZ (50 mg/kg i.p.) induced type 1 diabetes (in vivo α-glucosidase enzyme inhibitory test)	Wistar rat	Inhibition of hyperglycemia subsequent to high-dose maltose uptake in both normal and diabetic rats, which indicate α-glucosidase activity	—	54
Rosa canina	Fruit/oral administration of ethanol extract and various fractions	STZ (55 mg/kg i.p.) induced type 1diabetes	Albino rats	↓FBS with antioxidant function	—	55
Vitis vinifera	Seed/oral administration of water-acetone extract	High-fat diet induced type 2 diabetes	C57BL/6J mouse	↑Protective activity from nerve fiber against diabetic peripheral neuropathy	Oligomeric proanthocyanidins	57
Vitis vinifera	Seed/oral administration of ethanol extract and its fractions	Genetic induced type 2 diabetes	db/db mice	Whole extract and the ethylacetate/ethanol fraction showed ↓FBS, ↓HbA1c, but no effect on mice body weight	—	59
Vitis vinifera	Seed/oral administration of proanthocyanidin extract	STZ (55 mg/kg i.v.) induced type 2 diabetes	Wistar rat	↓FBS, ↓advanced glycation end products, ↓HbA1c, improve kidney function: ↓BUN, ↓creatinine, ↓kidneys/body weight ratio, ↓glomerular hypertrophy, ↓interstitial fibrosis, and also suppression of various protein overexpression ie, ↓GSTM, ↓glutamate carboxypeptidase and ↓β-actin protein expression	Proanthocyanidin	58
Vitis vinifera	Seed/oral administration of procyanidin extract	STZ (70 mg/kg i.p.) induced type 1 diabetes	Wistar rat	↓Blood glucose level, which was strengthened in accompany with low dose of insulin	Procyanidins	56

Abbreviations: FBS, fasting blood glucose; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte/macrophage colony-stimulating factor; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; i.p., intraperitoneal; s.c., subcutaneous; iv., intravenous; CAT, catalase, SOD, superoxide dismutase; MDA, malondialdehyde; GPx, glutathione peroxidase; BUN, blood urea nitrogen; ICAM, intercellular cell adhesion molecule; VCAM, endothelial vascular cell adhesion molecule; MMP, matrix metalloproteinase; GSH, reduced glutathione; GSH-R, glutathione reductase; LPO, lipid peroxidation; HbA1c, glycosylated hemoglobin; GSTM, glutathione S-transferase mu; PPAR, peroxisome proliferator-activated receptor; CPT1, carnitine palmitoyl-transferase1; ACO, acyl CoA oxidase; UCP3, uncoupling protein3; GLUT, glucose transporters; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low density lipoprotein; GST, glutathione S-transferase.

Table 4. Human Studies of Medicinal Plants used for the Treatment of Diabetes in Traditional Persian Medicine.

Plant	Preparations		Study Design	Disease	No. of Patients	Treatment Duration	Result	Reference
	Treatment Group	Control Group						
Coriandrum sativum L	Fruit/powder	—	Quasi-experimental study	Type 2 diabetic patients	50	6 weeks	↓FBS, ↓total cholesterol, ↓triglyceride, and ↓LDL- cholesterol ($P < .001$), no change in HDL-cholesterol level. ↓Atherosclerotic index (total plasma cholesterol−HDL-cholesterol/HDL-cholesterol) and ↑cardioprotective indices (HDL-cholesterol/total cholesterol)	34
Portulaca oleracea	Seed/powder		Randomized double-blind placebo-controlled clinical trial	Type 2 diabetic women	16	8 weeks	↑Glucagon like peptide-1 concentrations, but no significant effect on Glucagon-like peptide-1 receptor	45
Portulaca oleracea	Seed/sachet	Metformin	Randomized double-blind controlled clinical trial	Type 2 diabetic patients	30	8 weeks	↓Serum triglycerides, ↓total cholesterol, ↓LDL-cholesterol, ↓total and direct bilirubin, ↓fasting and postprandial blood glucose, ↓insulin (improvement of insulin resistance), ↓body weight and BMI, ↑HDL-cholesterol, and ↓liver biomarkers, including ALT, AST, and GGT	46
Punica granatum	Fruit/concentrated juice	—	Quasi-experimental study	Type 2 diabetic patients	26	8 weeks	↓Total cholesterol, ↓LDL-cholesterol, ↓LDL-cholesterol/HDL-cholesterol, ↓total cholesterol/HDL-cholesterol and no significant effect on serum triacylglycerol and HDL-cholesterol level	52
Vitis vinifera	Fruit/polyphenol extract	—	Randomized double-blind placebo controlled clinical trial	First-degree relatives of type 2 diabetic patients	38	9 weeks	↑Hepatic insulin sensitivity index, ↓glucose infusion rate, ↓oxidative stress: systemic and muscle MDA and protein carbonylation and ↑mitochondrial respiration	59
Vitis vinifera	Fruit/resveratrol	—	Randomized double-blind placebo controlled clinical trial	Type 2 diabetic patients	19	4 weeks	↓FBS, ↑insulin sensitivity index, ↓oxidative stress including ↑platelet Akt phosphorylation, ↑urinary ortho-tyrosine excretion, but no effect on β-cell function and serum insulin level were observed	48
Vitis vinifera	Seed/ethanolic extract	—	Randomized double-blind placebo controlled clinical trial	Type 2 diabetic patients		2 months	There was no significant effect on FBS, antioxidant parameters, including total antioxidant capacity, SOD, GPx, and MDA levels in comparison with placebo group	61

Abbreviations: ND, not determined; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALT, alanine transaminase; AST, aspartate transaminase; GGT, γ-glutamyl transaminase; BMI, body mass index; MDA, malondialdehyde; Akt, protein kinase B; SOD, superoxide dismutase; GPx, glutathione peroxidase; FBS, fasting blood glucose.

Bambusa arundinasia

In Persian medicine, the dried exudate plant is called "Tabashir," and has a cold and dry nature and was used for the treatment of gastrointestinal disorder like peptic ulcer, dysentery, and aphthous. The exudate on the node of this plant has been consumed for the treatment of diabetes in Persian medicine.[24] It exhibits α-amylase and α-glucosidase enzyme inhibitory function, as well as hypoglycemic activity via improvement of serum insulin and regeneration of pancreatic tissue and Langerhans islets. The exudate also demonstrated a significant lessening of glucose-6-phosphatase and fructose-1-6-biphophatase and also reduction in HbA1c (glycated hemoglobin), total cholesterol, and triglycerides in streptozotocin-induced diabetes.[27] The leaves possess antidiabetic activity via improvement of antioxidant function and regeneration of Langerhans islet, pancreas tissue, hepatocyte cells and kidney glomeruli and tubule. β-Sitosterol glucoside and stigmasterol are identified compounds related to this pharmacological action.[28]

Boswellia carterii

Different species of the genus *Boswellia* (from the family Burseraceae) including *Boswellia serrata* and *Boswellia carteri* produce oleo-gum resin exudates. *Boswellia* spp. is called as "Kondor" in Persian medicine, which has a hot and dry nature. It has been used for the treatment of gastrointestinal complications related to the excess accumulation of phlegm humor, improvement of memory, and several types of inflammation in Persian medicinal books. In addition, the oleo-gum resin possesses antidiabetes function in Persian medicine.[21] *Boswellia carterii* oleo-gum resin exhibited antdiabetic action through increase in serum insulin, liver glycogen and also inhibit degenerative changes in the β cells of pancreas in alloxan-induced diabetic model.[29] *Boswellia serrata* oleo-gum demonstrated hypoglycemic activity via suppression of apoptosis of periinsular cells, proinflammatory cytokine, penetration of lymphocytes into pancreatic islets, and also atrophy of pancreatic islet tissue, which has been attributed to 11-keto-β-boswellic acid and *O*-acetyl-11-keto-β-boswellic acid.[30] The oleo-gum resin and the active component boswellic acid showed inhibitory activity on chronic diabetic complications via polyol enzyme aldose reductase activity and its advanced glycation endproducts.[31]

Coriandrum sativum

This plant is a member of Umbelliferae (Apiaceae) family which has a wide range of application as food additive and medicinal remedy. The fresh or dried aerial parts as well as its aromatic fruits are used in culinary as well as for different therapeutic indications such as carminative effects. In Persian medicine, the plant is called "Geshniz" or "Kozborah" and has a cold and dry nature and was used for the treatment of gastrointestinal or other disorders related to accumulation of bile or blood humors.[21] The fruit is used for the treatment of diabetes in Persian medicine. It showed hypoglycemic activity via enhancement of insulin release from β cells and number and activity of pancreatic β cells in type 1 diabetic animals.[32] Moreover, administration of the fruits as supplement in diet and drinking water showed anti-diabetic function with elevating insulin secretion, and enhancement of the level of glucose uptake, glucose oxidation and glycogenesis in diabetic mice.[33] In a clinical trial on 50 type 2 diabetic patients, the fruit exhibited hypoglycemic activity with reduction of total cholesterol, triglyceride, and low-density lipoprotein cholesterol, as well as improving atherosclerotic index and cardioprotective indices.[34]

Glycyrrhiza glabra

The root has been used as antidiabetic agent in Persian medicine. Glycyrrhizic acid isolated from roots possesses antidiabetic action by improvement of insulin sensitivity, enhancement of lipoprotein lipase expression in visceral and subcutaneous adipose tissues, kidney, and heart. It also reduced serum levels of fatty acid, total cholesterol, low-density lipoprotein cholesterol and lipid deposition in type 2 diabetic rat tissue.[35] Furthermore, glycyrrhizin an active component from the roots exhibited hypoglycemic action with enhancement of serum insulin level and pancreatic islet cells, improvement of pancreas and kidney tissues and reinforcement of antioxidant function in diabetic rats.[36] In an experimental study reported by Takkii et al,[37] long-term (9 weeks) treatment with glycyrrhizin (2.7, 4.1 g/kg diet) showed a significant improve in tolerance to oral glucose loading as well as blood insulin level in genetically diabetic KK-A^y mice, an animal model of noninsulin-dependent diabetes.[37]

Lactuca sativa

The seed, which is traditionally known as "Khas" or "Kahoo," has been used for the treatment of diabetes in Persian medicine.[21,24] It possesses α-amylase and α-glucosidase enzyme inhibitory activity. Moreover, seeds in a polyherbal formula demonstrated anti-diabetic action through elevating serum insulin, lessening glucose-6-phosphatase, and fructose-1-6-biphophatase and also improvement of pancreatic tissue and Langerhans islets in streptozotocin-induced diabetic rats.[27]

Myrtus communis

The fruits, traditionally called "Murd" or "Ass," have cold and dry nature and possess antidepressant, antidiarrheal, and antidiabetic activity in Persian medicine.[21,22] The leave exhibited hypoglycemic activity via enhancement of antioxidant function in hepatic tissue of diabetic animal.[38] It also inhibited initial hyperglycemia in streptozotocin-induced diabetic mice.[39] Moreover, myricetin, an isolated component from this plant, exhibited anti-diabetic action via antioxidant function, as well as improvement of kidney function in diabetic rats.[40] In addition, α-glucosidase enzyme inhibitory activity is another antidiabetic pharmacological mechanism of this plant, which myrtucommulone D, E, C, and B are responsible for this action.[41]

Oxalis spp

The fruits are traditionally known to possess antidiabetic activity in Persian medicine. *Oxalis corniculata* exhibited antidiabetic action via improvement of antioxidant enzymes and function and also α-amylase enzyme inhibitory activity, as well as reduction of serum levels of triglyceride, low-density lipoprotein and cholesterol.[42,43] Dietary supplementation of *Oxalis corniculata* showed a remarkable reduce in fasting serum glucose and postprandial glucose levels of streptozotocin-induced diabetic rats. The antidiabetic activity of this dietary supplement is mediated by improvement of liver tissue antioxidant enzyme (superoxide dismutase), and total antioxidant capacity as well as suppression of oxidative stress markers.[44]

Portulaca oleracea

The seed possesses antidiabetic activity in Persian medicine. In a clinical trial, seed powder was administrated to 16 type 2 diabetic patients which leaded to enhancement of glucagon like peptide-1 level.[45] In addition, administration of the seeds in type 2 diabetic patients resulted in reduction of fasting and post-prandial blood glucose, serum triglycerides, total cholesterol, low-density lipoprotein cholesterol, total and direct bilirubin, increase in high-density lipoprotein cholesterol, improvement of insulin resistance and liver function.[46] α-Amylase enzyme and α-glucosidase inhibitory activity are among other mechanism of its antidiabetic action.[27] Also, the aerial parts of the plant demonstrated hypoglycemic action via improvement of insulin secretion and regeneration of diabetic endothelial dysfunction through reducing triglyceride, low-density lipoprotein cholesterol vascular tension, and systolic blood pressure, and elevating high-density lipoprotein cholesterol, as well as suppressing diabetes associated vascular inflammation in an animal model of type 2 diabetes.[47] Moreover, its leaf exhibited antidiabetic function by activation of antioxidant enzyme and suppression of lipid peroxidation in the kidney and liver of diabetic animals.[48]

Punica granatum

Punica granatum is native to Persia that is grown and used around the world, such as the United States. In traditional Persian medicine the flower is called "Golnar" and is used for different diseases such as peptic ulcer, ulcerative colitis, diarrhea, dysmenorrhea, and burn wounds. According to text books of Persian medicine, the flowers have been widely used for the treatment of diabetes and its complications.[21,24] The flowers executed antidiabetic action through α-glucosidase enzyme inhibition and improvement of insulin sensitivity with enhancement of PPAR-γ (peroxisome proliferator-activated receptor–γ) and GLUT4 (insulin-responsive glucose transporter 4, the insulin-dependent isoform of GLUTs). It also elevated the activity of lipoprotein lipase as well as antioxidant function and enzymes.[49-51] In addition, it reduced triglyceride, cholesterol, and low-density lipoprotein and elevated high-density lipoprotein in diabetic animals.[51] Gallic acid is an active constituent responsible for antidiabetic activity.[38] In a clinical trial on type 2 diabetic patients fruit juice showed decrease in total cholesterol, low-density lipoprotein cholesterol, low-density lipoprotein cholesterol/high-density lipoprotein cholesterol, and total cholesterol/high-density lipoprotein cholesterol.[52] Malini et al[53] demonstrated that ellagic acid, the active phenolic component of *Punica granatum*, reduced plasma glucose levels and blood glycosylated hemoglobin significantly, which is mediated with increase in plasma insulin concentration, in streptozotocin-induced type 1 diabetic rats.[53]

Rosa damascena and Rosa canina

In Persian medicine, the flowers are known as "Gol-e-Sorkh," which have hot and dry nature. The flower and fruits of both species possess antidiabetic activity in Persian medicine sources.[21,23] Antihyperglycemic and α-glucosidase inhibitory functions of methanolic extract from *Rosa damascena* flowers have been proven.[54] In an animal model of type 1 diabetes mellitus (intraperitoneal injection of streptozotocin with 50 mg/kg concentration in Wistar rat), methanol extract of *Rosa damascena* flowers could significantly inhibit hyperglycemia subsequent to high-dose maltose uptake.[55] The fruits of *Rosa canina* exhibited reduction of serum glucose via reinforcement of antioxidant function in type 1 diabetic rats.[55]

Vitis vinifera

Different part of this plant including leaf, roots, unripe fruits, fruits, and barks has been used in traditional Persian medicine. The unripe fruit, which is known as "Ghoureh," was used as wound healer and hematopoietic agent in Persian medicine. In addition, the unripe fruits possess antidiabetic action based on traditional Persian medicine literature.[21,23] The procyanidins from seeds perform antidiabetic activity via insulinomimetic function, including upgrading glucose uptake and stimulation of insulin pathway mediators.[56] In addition, the oligomeric proanthocyanidins from seeds possess protective activity from nerve fiber against diabetic peripheral neuropathy in type 2 diabetic mice.[57] It has been suggested that reduction in advanced glycation end products, improvement of kidney function via diminishing interstitial fibrosis, and suppressing overexpression of oxidative stress proteins are among other pharmacological mechanisms against chronic diabetes associated complications in type 1 diabetic animals.[58] In a clinical trial on type 2 diabetic patient, polyphenol extract of fruits demonstrated elevation of insulin sensitivity index and decrease of glucose infusion rate, which indicate diminishing the cellular insulin tolerance and also suppression of diabetic oxidative stress.[59] Another clinical trial on resveratrol isolated from fruits was resulted in reduction of serum glucose level, improvement of insulin sensitivity index and suppression of diabetic oxidative stress in type 2 diabetic patient. Although, resveratrol did not show any significant effect on β-cell function and serum insulin level.[60] Also, Pourghassem-Gargari

et al[61] reported that administration of the seeds caused no significant effect on serum glucose and antioxidant parameters in diabetic patient in comparison with placebo group.[61]

Discussion

Plants remain as an important source of therapeutic material for maintaining human health with a broad diversity, and they have improved the quality of human life through disease prevention and treatment for centuries.[62,63] Scientists are exploring within nations traditional medicine in order to find alternative antidiabetic drugs.[64] Various medicinal plants have been used for the prevention and treatment of chronic diseases, including diabetes, in Persian medicine, which may be considered as dietary supplement or adjunctive therapy to conventional drugs.[65,66] Results obtained from current review demonstrated that medicinal plants used in Persian medicine for prevention and treatment of diabetes performed their therapeutic effects via various well-established pharmacological mechanisms of actions. Preclinical studies demonstrated that reduction of glucose absorption through inhibitory effect on activity of α-amylase and α-glucosidase, sucrase and maltase enzymes are among the antidiabetic mechanisms of traditional natural remedies. Regeneration of pancreatic β cell, inhibiting the atrophy of pancreatic islet tissue and apoptosis of peri-insular cells, as well as enhancement of cellular signaling pathways like insulin promoter factor 1 are the main cellular mechanism of traditional natural agents for increasing the secretion of insulin. Traditional herbal remedies in Persian medicine suppress fat accumulation, fatty liver, and dyslipidemia through enhancing energy expenditure enzymes (eg, carnitine palmitoyl-transferase1 (CPT1), acyl CoA oxidase (ACO)) and signaling pathways (PPARα, and δ), and attenuating enzymes involved in fatty acid synthesis process in the liver (like fatty acid synthase (FAS), lipoprotein lipase (LPL)).[67] Anti-inflammatory potential of the traditional remedies plays a pivotal role in acting against diabetic associated metabolic disorders of liver and kidney as well as induction of autoimmune process in pancreatic islet, which is mediated by inhibiting nuclear inflammatory signaling pathway, improving redox sensitive transcription factors (eg, nuclear factor-erythroid 2-related factor (Nrf)-2), and suppressing pro-inflammatory cytokines (Interleukin (IL)-1A, IL-1B, IL-2, IL-6, interferon (IFN)-γ, tumor necrosis factor (TNF)-α, granulocyte colony-stimulating factor (G-CSF) and granulocyte/macrophage colony-stimulating factor; IL, interleukin (GM-CSF)), and leukocytes infiltration.[6,31,58,59,67] Likewise, reducing hepatic glucose output, enhancing glycolysis process, glucose oxidation, and glycogenesis, as well as limitation of glycogen degradation and gluconeogenesis are among their antidiabetic cellular mechanisms. Tables 2 and 3 show the pharmacological mechanisms of antidiabetic natural agents in detail.

Several experimental and clinical studies have been performed to evaluate the effectiveness of medicinal plants traditionally used for management and treatment of diabetes and its complication in Persian medicine. Regarding the finding of the experimental studies, the effectiveness of traditional medicinal plant used in Persian medicine for diabetes were determined based on differences between test groups and control groups in terms of fasting blood glucose, glucose tolerance test, insulin level, inflammatory cytokines, liver biomarkers, cholesterol and lipid parameters, antioxidant enzymes and factors, as well as insulin sensitivity index. Assessment of finding of experimental studies revealed that various in vitro and in vivo research studies support the efficacy of traditional medicinal plants used in Persian medicine on diabetes mellitus. Results obtained from clinical trials showed that using traditional medicinal plants significantly improve the biochemical markers of patients with diabetes mellitus, including fasting blood glucose, glucagon like peptide-1, body mass index, cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, alanine transaminase, aspartate transaminase, γ-glutamyl transferase, as well as liver oxidative stress markers (superoxide dismutase, glutathione peroxidase, malondialdehyde), indicating the effectiveness of traditional medicinal plant in management of patients with chronic diabetes mellitus. Among the clinical trials, no severe adverse effects were observed and the natural preparations were generally safe in human (Table 4). Considering low number of human studies and their different limitations such as low methodological quality, small volume of patients, and single-center study, the levels of evidence for current review are low. Further clinical trials with high methodological quality and adequate sample size are necessary to attain more conclusive findings on the effectiveness and safety of extracts of medicinal plants traditionally used in Persian medicine in the management of diabetes and its complications.

In conclusion, the present review provides a detailed discussion summarizing the current understanding on the effectiveness of plant extracts traditionally used in Persian medicine as dietary supplement or adjunctive therapy for the prevention and treatment of diabetes and its complications.

Author Contributions

F Farzaei, MRM, and F Farjadmand, contributed to study design, data collection, and drafting the manuscript. MHF reviewed data collection, edited the manuscript, and supervised the entire study.

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Ethical Approval

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