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 transcription 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

Received June 22, 2016. Received revised September 23, 2016. Accepted for publication November 21, 2016.

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                | Samhe arabi (gum), Aghabgha (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   | Fruit                        | 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, polymenorrhrea, 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                 | Ghourehe                               | Wound healer, hematopoietic, peptic ulcer, diabetes                        |

As conventional medical management shows many side effects, research on exploring safe treatments is 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.16,20

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-al-advieh (written by Aghili Alavi Khorasani in 1771 CE)21 (1976) Zhawkireh Kharazmshahi (written by Jorjani)22 Tohfat-al-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
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 antidiabetic 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. Fruit showed no significant hypoglycemic action on diabetic rabbit. In contrast, the fruits lessened blood glucose in normal animals. More-
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, PPARβ, 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 arundinacia    | 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-biphosphatase and ↓HDL-cholesterol, as well as improvement of pancreatic tissue and Langerhans islets | —                                    | 27        |
| Bambusa arundinacia    | 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 perinsular cells, ↑G-CSF, ↑GM-CSF, ↑proinflammatory cytokines including: IL-1α, IL-1β, 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        |
| Boswellia 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.                  | 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)
| Plant                  | Part/Route of administration | Method                        | Animal                      | Result                                                                                                                                                                                                                                                                                                                                 | Active Constituents                                                                 | Reference |
|-----------------------|------------------------------|-------------------------------|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------|
| Glycyrrhiza glabra    | Root/glycyrrhizic acid       | High-fat diet induced type 2 diabetes | Sprague-Dawley 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. 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. Improvement of pancreas and kidney tissues, also antioxidant function: SOD, CAT, MDA, and fructosamine. | 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-biphosphatase 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, serum insulin, Hba1c, total cholesterol, triglycerides, glucose-6-phosphatase, fructose-1-6-biphosphatase and HDL-cholesterol. Improvement of pancreatic tissue and Langerhans islets.                                                                                                                                                           | Myricetin                                                                           | 38        |
| Myrtus communis       | Leaf/oral administration of volatile oil | 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 1 diabetes, 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, serum insulin, Hba1c, total cholesterol, triglycerides, glucose-6-phosphatase, fructose-1-6-biphosphatase and HDL-cholesterol. Also improvement of antioxidant function: SOD, CAT, Gpx, 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, serum insulin, 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        |
| 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 1 diabetes                            | 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 proanthocyanins | 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 proanthocyanidin 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            | Proanthocyanidins   | 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; i.v., 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; GSTM, glutathione S-transferase mu; PPAR, peroxisome proliferator-activated receptor; CPT1, carnitine palmitoyl-transferase I; ACO, acyl CoA oxidase; UCP3, uncoupling protein 3; 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                          | Treatment Group | Control Group | Study Design        | Disease                  | No. of Patients | Treatment Duration | Result                                                                                           | Reference |
|--------------------------------|-----------------|---------------|---------------------|--------------------------|-----------------|--------------------|-----------------------------------------------------------------------------------------------|-----------|
| *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. | 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 arundinacea**

In Persian medicine, the dried exude 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 exude on the node of this plant has been consumed for the treatment of diabetes in Persian medicine. 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 exude also demonstrated a significant lessening of glucose-6-phosphatase and fructose-1-6-biphosphatase and also reduction in HbA1c (glycated hemoglobin), total cholesterol, and triglycerides in streptozotocin-induced diabetes. 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.

**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. *Boswellia carterii* oleo-gum resin exhibited antidiabetic action through increase in serum insulin, liver glycogen and also inhibit degenerative changes in the β cells of pancreas in alloxan-induced diabetic model. *Boswellia serrata* oleo-gum demonstrated hypoglycemic activity via suppression of apoptosis of peri-insular 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. 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.

**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. 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. 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 glycosgenesis in diabetic mice. 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.

**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. 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 tissue and reinforcement of antioxidant function in diabetic rats. In an experimental study reported by Takkii et al., 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.

**Lactuca sativa**

The seed, which is traditionally known as “Khas” or “Kahoo,” has been used for the treatment of diabetes in Persian medicine. 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-biphosphatase and also improvement of pancreatic tissue and Langerhans islets in streptozotocin-induced diabetic rats.

**Myrtus communis**

The fruits, traditionally called “Murd” or “Ass,” have cold and dry nature and possess antidepressant, anti-diarrheal, and anti-diabetic activity in Persian medicine. The leave exhibited hypoglycemic activity via enhancement of antioxidant function in hepatic tissue of diabetic animal. It also inhibited initial hyperglycemia in streptozotocin-induced diabetic mice. 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. In addition, α-glucosidase enzyme inhibitory activity is another anti-diabetic pharmacological mechanism of this plant, which myrtucommulone D, E, C, and B are responsible for this action.
**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. 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.

**Portulaca oleracea**

The seed possesses antidiabetic activity in Persian medicine. In a clinical trial, seed powder was administered to 16 type 2 diabetic patients which leaded to enhancement of glucagon like peptide-1 level. 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. α-Amylase enzyme and α-glucosidase inhibitory activity are among other mechanism of its antidiabetic action. 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. Moreover, its leaf exhibited antidiabetic function by activation of antioxidant enzyme and suppression of lipid peroxidation in the kidney and liver of diabetic animals.

**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 flowers are known as “Gol-e-Sorkh,” and are 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. The flowers exhibited antidiabetic action through α-glucosidase inhibitory activity 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. In addition, it reduced triglyceride, cholesterol, and low-density lipoprotein and elevated high-density lipoprotein in diabetic animals. Gallic acid is an active constituent responsible for antidiabetic activity. 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. Malini et al 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.

**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. Antihyperglycemic and α-glucosidase inhibitory functions of methanolic extract from *Rosa damascena* flowers have been proven. 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. The fruits of *Rosa canina* exhibited reduction of serum glucose via reinforcement of antioxidant function in type 1 diabetic rats.

**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. The procyanidins from seeds perform antidiabetic activity via insulinomimetic function, including upgrading glucose uptake and stimulation of insulin pathway mediators. In addition, the oligomeric proanthocyanidins from seeds possess protective activity from nerve fiber against diabetic peripheral neuropathy in type 2 diabetic mice. It has been suggested that reduction in advanced glycation end products, improvement of kidney function via diminishing interstitial fibrosis, and suppressing over-expression of oxidative stress proteins are among other pharmacological mechanisms against chronic diabetes associated complications in type 1 diabetic animals. 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. 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. Also, Pourghassem-Gargari
et al\textsuperscript{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.\textsuperscript{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.\textsuperscript{62,63} Scientists are exploring within nations traditional medicine in order to find alternative antidiabetic drugs.\textsuperscript{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.\textsuperscript{55,66}

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 \( \alpha \)-amylase and \( \alpha \)-glucosidase, sucrase and maltase enzymes are among the antidiabetic mechanisms of traditional natural remedies. Regeneration of pancreatic \( \beta \) cell, inhibiting the atrophy of pancreatic islet 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 (PPAR\( \gamma \), and \( \delta \)), and attenuating enzymes involved in fatty acid synthesis process in the liver (like fatty acid synthase (FAS), lipoprotein lipase (LPL)).\textsuperscript{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 reduct 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)-\( \gamma \), tumor necrosis factor (TNF)-\( \alpha \), granulocyte colony-stimulating factor (G-CSF) and granulocyte/macrophage colony-stimulating factor; IL, interferon (GM-CSF)), and leukocytes infiltration.\textsuperscript{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. Table 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, alamine transaminase, aspartate transaminase, \( \gamma \)-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.

**Declaration of Conflicting Interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

**Ethical Approval**

The current study was performed with ethical approval from the Ethics Committee of Tehran University of Medical Sciences. Tehran University of Medical Sciences approved this study; however, no approval number is released for this article.
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