



Medicinal plants and diabetic kidney disease; an updated review on the recent findings

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Abstract

In diabetes mellitus, hyperglycemia happens as a consequence of complex metabolic disorders where immune, genetic, lifestyle and environmental factors cause an inadequate or lack of insulin secretion. Diabetic associated hyperglycemia and hyperlipidemia increase susceptibility of various macro/micro vascular diseases, including atherosclerosis, stroke, diabetic neuropathy, retinopathy and nephropathy. Among the various diabetic complications, nearly 40% of individuals are influenced diabetic nephropathy that may result from an interaction of hemodynamic, pro-inflammatory, metabolic and cellular organelles disorders. Hyperglycemia related injurious pathways induced diabetic nephropathy, include elevated oxidative stress, renal polyol and hexosamine pathway activation and AGEs formation that cause overproduction of pro-sclerotic mediators such as TGF- β 1. This review has been directed to detail the role of diabetes induced oxidative damage in kidney disease pathogenesis, afterward summarize recently available evidence on the anti-diabetic properties of several plants, with special focus on their biological mechanisms.

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Introduction

In diabetes mellitus, hyperglycemia happens as a consequence of complex metabolic disorders where immune, genetic, lifestyle and environmental factors cause an inadequate or lack of insulin secretion. Type 1 diabetes (T1D) is characterized as an autoimmune disease that are destroyed the pancreatic Langerhans islet β cells by autoreactive CD⁴⁺ and CD⁸⁺ T cells and autoantibodies targeting β -islets antigens, leading to subjects depending essentially on exogenous insulin injection for survival. Numerous factors are associated with autoimmunity of T1D including genetic, environmental agents and life behaviors that may accelerate the presence of T1D, cause the stimulation or development of mechanisms for the autoimmune state progression. Although T1D is an insulin-deficient condition, insulin resistance characteristics are enhanced through injecting the high insulin doses (1).

Type 2 diabetes (T2D) is the major form of the disease, comprising some 85% of individuals. In this form, there is peripheral tissue insulin resistance. Mainly, pancreatic insulin secretion increases to compensate insulin insensitivity. However, in most pa-

Key Point

Diabetic nephropathy may result from an interaction of hemodynamic, pro-inflammatory, metabolic and cellular organelles disorders. The investigation regarding efficient and safer antidiabetic medications with protective impacts on diabetic kidney disease has continued to be a remarkable interest for study topic. Moreover, the alternative medicine is recommended especially in countries where access to synthetic medications is insufficient.

tients, the relative reduction in insulin secretion is the final event resulting in glycaemia. The prevalence enhancement of T2D is due to life style change, mostly in developing countries. It is determined the increased consumption of foods with high calorie and fat, in the context of decreased exercise elevates possibility of T2D (2).

Diabetic associated hyperglycemia increases susceptibility of macro/micro vascular diseases, include atherosclerosis, stroke, diabetic neuropathy, retinopathy and nephropathy. Among the various diabetic complications, nearly 40% of individuals are influenced

diabetic nephropathy that is a main reason of death from diabetes. It is proved inflammatory processes and oxidative stress have key role in aggravation of diabetic kidney disease (3).

This review has been directed to detail the role of diabetes induced oxidative damage in kidney disease pathogenesis, afterward summarize recently available evidence on the anti-diabetic properties of several plants, with special focus on their biological mechanisms.

Materials and Methods

In this review a variety of sources have been used by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and, or their equivalents consisting diabetes mellitus, diabetic nephropathy, hyperglycemia, oxidative stress, immune processes, bioactive components, molecular mechanisms, antidiabetic property and medicinal plants.

Molecular pathways complicated diabetic kidney disease

Diabetic nephropathy may result from an interaction of hemodynamic, pro-inflammatory, metabolic and cellular organelles disorders. Hyperglycemia related injurious pathways induced diabetic nephropathy, include elevated oxidative stress, renal polyol and hexosamine pathway activation and advanced glycation end products (AGEs) formation that cause overproduction of pro-sclerotic mediators such as TGF- β 1. These pathways finally enhance glomerular albumin permeability and accelerated accumulation of extracellular matrix that in turn leads to proteinuria, tubulointerstitial fibrosis, glomerulosclerosis and end-stage renal failure (4).

Metabolic disorders

The common mechanisms contributing hyperglycemia-induced diabetic kidney damage are mentioned below.

Advanced glycation end products formation

The non-enzymatic reactions of glucose and oxidized fatty acid derived glycation compounds with proteins generate AGEs that are a consequence of diabetic condition. They induce functional and structural modifications in intra- and extracellular proteins. Extracellular glycated proteins are invulnerable to hydrolyzation of matrix metalloproteinases that cause them to accumulate and bind to AGEs receptors which lead to induce reactive species (RSs) generation through activating the transcription factor nuclear factor (NF)- κ B pathway. Furthermore, glycation of sulfated proteoglycans attenuates their electronegativity, therefore alters the basement membrane filtration properties, resulting in microalbuminuria (5).

Enhancement polyol pathway

In hyperglycemic state, the increased aldose reductase activity converts glucose to sorbitol that finally sorbitol is oxidized to fructose with NADPH as a cofactor. Sorbitol ac-

cumulation in renal vasculature and mesangial cells results in modulation of prostaglandin E2 (PGE2) and depletion of NADPH that induce overproduction of RSs and protein kinase C (PKC) activity (5).

Hexosamine pathway

Induction of fatty acids mobilization and oxidation are dependent to hyperglycemia and have important role in diabetic nephropathy pathogenesis through activating the hexosamine pathway. In this pathway, glycolysis derived fructose 6-phosphate provides substrate for this pathway enzymes which have capability to stimulate transcription of TGF- β 1 and TGF- α genes (6).

Enhancement of protein kinase C activity

Hyperglycemia, RSs and interaction of AGEs with their receptors enhance activity of an enzyme family, is responsible to phosphorylate various proteins, which called PKC. It can mediate injurious pathways such as enhancement of growth factors expression that finally lead to accumulation of extracellular matrix and end-stage renal failure (7).

Activation of pro-inflammatory cytokines and growth factors

AGEs, RSs, AngII, PKC and hexosamine pathways can trigger TGF- β 1 signaling processes that lead to matrix proteins synthesis and expand extracellular matrix.

Tumor necrosis factor-alpha (TNF- α) is a pro-inflammatory cytokine that is mostly generated by monocytes in diabetic oxidative condition. It possesses cytotoxic impacts for tubular and glomerular cells through up-regulating inflammatory cascade, proliferation of mesangial cells, adhesion molecules and elevating renal vasculature permeability and leucocytes infiltration into interstitial space (8).

Mitochondrial stress

RSs generation is increased by hyperglycemia triggered expression of NADPH oxidase (NOX) family in renal epithelial tubular and mesangial cells. It has been determined NOX2 and NOX4 implicate extremely in renal mitochondrial stress. Indeed, RSs mediated oxidative stress expands mesangial cells and changes some enzymes activity such as endothelial nitric oxide synthase (eNOS), converts to superoxide anion generation source. In addition, these molecules disrupt electron transport chain and destroy mitochondrial membrane integrity. All interactions between NOX family and RSs exacerbate diabetic nephropathy development (9).

Renin angiotensin system

Renin enzyme is generated by juxtaglomerular cell in renal tissue. This enzyme is responsible to convert angiotensinogen to angiotensin I (Ang I) and then formed angiotensin II (Ang II) via angiotensin-converting enzyme (ACE). AngII acts as a vasoconstrictor and pro-inflammatory agent. This system have important role in maintenance of tissue hemodynamic state and volume of extracellular matrix. In diabetic condition, renin can stimulate over-

production of inflammatory cytokines such as TNF- α and IL1 β that increase TGF- β 1 expression, lead to tubulointerstitial fibrosis and glomerulosclerosis. Likewise, hyperglycemia induced overproduction of Ang II in mesangial cells triggers pro-sclerotic processes enhancement and hypertension in renal vasculature that disrupts glomerular filtration rate (10).

Antidiabetic herbal medications

The incidence of diabetes mellitus associated complications and its healthcare have been progressively rising worldwide. The investigation regarding efficient and safer antidiabetic medications with protective impacts on diabetic kidney disease has continued to be a remarkable interest for study topic. Moreover, the alternative medicine is recommended especially in countries where access to synthetic medications is insufficient. Administration of medicinal plants has a long history for diabetes treatment. Interestingly, the results of experimental studies on diabetic patients and animal models have revealed, medicinal plants are enriched from numerous constituents with anti-diabetic value. These compounds have ability to regulate blood glucose level near normal range through contributing to physiological molecular pathways (11). An overview of several common anti-diabetic plants, with special focus on their activity mechanisms are mentioned below.

Asparagus officinalis L.

Asparagus officinalis L. is a flowering perennial vegetable of *Asparagaceae* family that has been known as an antioxidant, reducer blood lipid, anti-diabetic, antifungal, anti-hypertension and anti-carcinogenic medication in traditional medicine. It is richness of bioactive constituents, namely, flavonoids (isorhamnetin, quercetin, rutin, kaempferol), steroidal saponins, oligosaccharides, vitamins (carotenoids, acid ascorbic), polyphenolic (ferulic acid) which are responsible to exert medicinal properties. It is suggested *A. officinalis* extract is able to elevate serum insulin level, mediated through stimulation of insulin synthesis as well as insulin releasing by pancreatic β cell. Histopathological examinations have revealed streptozotocin (STZ) administration in animal models induces alterations in distribution pattern and number of Langerhans islet β cells, however, *A. officinalis* extract can attenuate β cell dysfunctions in the diabetic rats through making β cell hypertrophy and hyperplasia. Moreover, this medicinal vegetable possesses 2-hydroxynicotianamine and a little amount nicotianamine components that are identified as angiotensin converting enzyme (ACE) inhibitor. In fact, 2-hydroxynicotianamine is efficient agent to disrupt renin angiotensin system (RAS), as a pathological process involved diabetic nephropathy progression. It has been indicated angiotensin II elevated activity during diabetic renal disease causes tubulointerstitial cells hypertrophy and renovascular hypertension that induce pro-inflammatory/apoptotic pathways such as monocyte chemoattractant protein-1 generation, finally aggravates renal fibrosis. Therefore, ACE inhibitor and antioxidants components of

asparagus may be effective to maintain renal normal function in diabetic patients (12-14).

Lamiaceae family

Lamiaceae family is aromatic bilateral flowering plant, has been belonged nearly 236 genus and 7200 species. These plants are considered therapeutic applications due to be rich in various bioactive components such as vitamins, rosmarinic acid, flavonoids derivatives, tannins, phenolic terpenoids which have antitumor, radical scavengers, antibacterial, anti-inflammatory and anti-diabetic activities. It will be mentioned some common genus of this family that have been known their antidiabetic property.

Origanum majorana

Origanum majorana or marjoram is cold sensitive perennial plant, native in Middle East countries. Recent evidence have reported its antiglycation action, maybe mediated by preventing alteration of dicarbonyl groups to AGEs, generation of methylglyoxal derivatives and as well as expression of pathogenic mediators involved in progression of diabetic nephropathy, including TGF and pro-inflammatory cytokines. In diabetic condition, abnormal lipid metabolism and lipid accumulation, also, increases lipid peroxidation. It has been conducted; antioxidant components of marjoram alleviate renal failure associated with oxidative damage (15,16).

Salvia officinalis

Salvia officinalis are the most enormous *Lamiaceae* family subdivisions that nearly possess 58 species, one-third of which have been identified in Iran. The various species of this plant contain several important substances that have several therapeutic targets in diabetic kidney disease. They can contribute with multiple mechanisms to lower blood glucose level, including reduction of intestinal absorption rate of simple sugar through preventing α -amylase activity, up-regulation of insulin releasing via enhancing epinephrine level. In addition, its glycoside kaempferol, a flavonol glycoside, components increase muscular glucose uptake in normal Wistar rates. These plants are able to inhibit diabetic complications progression through limiting advanced glycated end products creation and excess glucose conversion to sorbitol by stopping aldose reductase activity. It has been indicated, glycoside isorhamnetin constituent is phenolic compound, has inhibitory potency of aldose reductase that disrupts polyol pathway. In fact, flavonoids and phenolic contents of salvia may detain protein carbonyl formation under the glycoxidative processes through scavenging hydroxyl radical and chelating transient metals. Lee et al found that *Salvia miltiorrhiza* is effective to attenuate renal dysfunction aggravation in diabetic animal models. The results were indicated this plant could prevent glomerulosclerosis and tubulointerstitial fibrosis through suppressing TGF- β 1, pro-inflammatory cytokines and AGE receptors expression. Moreover, Kim et al reported, tanshinone IIA component of *Salvia miltiorrhiza* rhizome acts as a stimulating factor induced

eNOS activity which reduces renal hypertension and aggravation of diabetic kidney disease. Also, this substance is able to present anti-inflammatory impact by inhibiting NF- κ B pathway and reactive species production (17-19).

Momordica charantia

Momordica charantia, bitter melon or bitter gourd and balsam pear, is a climber plant of *Cucurbitaceae* family and indigenous of Amazon, Africa and Asia tropical area that has been known as a unique plant with pharmaceutical properties. Mostly, it is recommended for diabetes mellitus, peptic ulcer and hepatitis treatment, wound healing in different countries. Its fruit is richness of beneficial components, mostly have nutritional value. Anthraquinones, phenols, isoflavones, terpenes, flavonoids and glucosinolates are some such phytochemical components that exert antioxidant impacts. Also, the main hypoglycemic chemicals of its fruit include vicine, P-insulin and charantins. P-insulin or polypeptide-p is plant originated insulin that can be novel in therapeutic application for type 1 diabetic patients. This plant influences on various physiological and biochemical processes to exert its antidiabetic activity such as enhancement of glucose uptake of muscular cells, reduction of intestinal glucose absorption, prevention of adipogenesis, suppression of gluconeogenesis and regeneration, protection and as well as increase number of Langerhans islets β cells throughout inhibiting NF- κ B and mitogen-activated protein kinases (MAPKs) pathways. It was detected triterpenes constituents of its fruit, are capable to activate insulin signaling pathway through down regulating protein tyrosine phosphatase 1B (PTP1B). This enzyme is a negative regulator factor that can deactivate insulin receptors by hydrolyzing phosphotyrosines of insulin receptor binding domain in insulin independent diabetes. Likewise, it has been revealed adiponectin, as an anti-inflammatory adipokine, is suppressed and TGF α and phospho- NF- κ B (p65) are overexpressed in diabetic and obesity condition. In fact, imbalances between pro and anti-inflammatory can lead to insulin resistance in adipocyte, hepatocytes and muscular cells due to inhibiting signaling transduction of insulin and promote insulin resistance induced metabolic disorders in cardiovascular system, kidney and liver. Fruit extract of *Momordica* can involve in improvement of insulin signaling transduction and suppression of inflammatory processes through alleviating phospho-c-Jun N-terminal kinase (JNK) and p65. Wang et al examined differential hypoglycemic effect of charantin richness extract of *Taiwanese Momordica charantia* between type 1 and 2 diabetic rats. They reported charantin richness extract of *Taiwanese Momordica charantia* is efficient compound for upregulating GLUT4 expression in type 2 diabetic rats. In addition, this compound has potential impact to regenerate Langerhans islets β cells in type 1 diabetic rats that is more gradual than enhancement of insulin sensitivity in T2D (20-23).

Citrullus colocynthis

Another anti-diabetic phytotherapies is bitter apple or

Citrullus colocynthis that is known in traditional Iranian medicine as *Hindavane Aboujahl* (Aboujahl's melon) and *Kharboze roubah* (fox melon). It is an annual tropical viny plant of *Cucurbitaceae* family which find in Mediterranean Basin especially Turkey, Iran and Arabian countries. In the traditional medicine, *Citrullus colocynthis* has been administered for diabetes, arteritis, backache, constipation, oedema, fever, inflammation, bacterial infections, and cancer. Its main anti-diabetic parts are comprised of fruit pulp and seed. The components of this plant include alkaloids, coumarins, tannins (mostly gallic acid), anthraquinones, flavonoids (especially catechin, quercetin) and terpenoids. This plant is extremely bitterness due to cucurbitacins constituents which have anti-inflammatory and cytotoxic effects. Its antidiabetic property is exerted by various mechanisms such as improvement of insulin release, antioxidant activity that prevents and declines hyperglycemia induced radical generation, insulin receptors activation, enhancement of cellular glucose uptake by its insulin-like components (especially saponins). Earlier investigations have revealed *Citrullus colocynthis* extracts have effective preservation of β cells mass in STZ induced diabetic rats. In addition, this plant is able to recover histological architecture of liver that leads to reduce serum level of triglyceride, cholesterol and LDL (24-26).

Trigonella foenum-graecum

Trigonella foenum-graecum, fenugreek is an annual vegetable belongs to *Fabaceae* family. It is planted throughout the world for cooking and therapeutic utilizations. This plant is source of components, have been demonstrated to have biological impacts on physiologic reactions, such as glucose tolerance, insulin activity, liver function, blood phospholipids, inflammatory responses, and microvasculature health. Diosgenin is a steroid sapogenin component that is presented in fenugreek. It is biologically efficient in various pathologies, including oxidative stress, inflammation, diabetes mellitus, cardiovascular disease, and hyperlipidemia. The investigations on both type 1 and 2 diabetes mellitus animal models have been indicated this substance participates into molecular mechanisms underlying glucose control, including preservation of Langerhans islets β cells, suppression of hepatic gluconeogenic and lipogenic enzymes expression (FA synthase, stearyl-CoA desaturase1 and acetyl-CoA carboxylase), modulation of hepatic glucokinase, anti-inflammatory activity in adipose tissue by up-regulation of adiponectin production, adipogenesis enhancement, and prevention of hepatic triglyceride accumulation through down-regulating liver X-receptor α gene. Likewise, it has ability to alleviate pancreatic endoplasmic reticulum stress through declining C/EBP homologous protein (CHOP) and elevated PPAR γ expression. In addition, fenugreek seeds contain biological free amino acids that are efficient to present antidiabetic activity through increasing insulin sensitivity in hepatic, adipose and muscular tissues. 4-OH-Ile is a novel branched-chain amino acid derivative identified in fenugreek seed. It increases hepatic insulin response through activating phosphatidyli-

nositide 3-kinase pathway. Administration of 4-OH-Ile for 16 hours could stimulate translocation of GLUT4 in cultured rat muscle cells. Interestingly, it prevents oxidative stress induced inflammation through limiting NF- κ B and p38 MAPK signaling pathways in rats fed a high fat diet. Fenugreek is enriched from dietary fiber such as galactomannan that inhibits lipid and carbohydrate absorption from intestine and exerts protective impacts on renal and hepatic function in diabetic patients. Furthermore, in the recent studies on STZ induced diabetic nephropathy rats, examined antioxidative and renoprotective effects of fenugreek. The findings indicated fenugreek extract prevents accumulation of extracellular matrix through suppressing expression of TGF- β 1 and CTGF and protects renal tissue against oxidative damage (27-30).

Urtica dioica

Urtica dioica, often is named stinging nettle, a perennial flowering vegetable that is cultured in northern Africa, Europe, western North America and Asia and is the best-known member of *Urticaceae* family. In accordance with previous studies, stinging nettle exerts antidiabetic effects through repairing pancreatic islets, inhibiting α -amylase enzyme, up-regulating expression of GLUT4 in peripheral tissue and liver and counteracting diabetes mellitus associated oxidative damage in kidney and liver (31).

Conclusion

Identification diabetic kidney disease concerned molecular mechanisms can be target to find safer and efficient therapeutic approach. Plants are rich of components with wide spectrum of biological effects that can influence metabolic pathways.

Authors' contribution

All authors contributed to design of the research. FDS and SSBM prepared the primary draft. FDS searched the data and conducted primary editing. Editing the final manuscript done by MRK.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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