Natural antioxidants in the treatment and prevention of diabetic nephropathy; a potential approach that warrants clinical trials

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ABSTRACT
Diabetic nephropathy is the major cause of end-stage renal disease and effective and new therapeutic approaches are needed in diabetic nephropathy and chronic kidney diseases. Oxidative stress and inflammatory process are important factors contributing to kidney damage by increasing production of oxidants. KEAP1/Nrf2/ARE pathway regulates the transcription of many antioxidant genes and modulation of the pathway up regulates antioxidants. NFκB controls the expression of genes involved in the inflammatory response. Natural substances have antioxidant and anti-inflammatory activities and have an impact on NFκB and KEAP1/Nrf2/ARE pathways. The preclinical studies explored the effectiveness of whole herbs, plants or seeds and their active ingredients in established diabetic nephropathy. They ameliorate oxidative stress induced kidney damage, enhance antioxidant system, and decrease inflammatory process and fibrosis; most likely by activating KEAP1/Nrf2/ARE pathway and by deactivating NFκB pathway. Whole natural products contain balanced antioxidants that might work synergistically to induce beneficial therapeutic outcome. In this context, more clinical studies involving whole plants or herbal products or mixtures of different herbs and plants and their active ingredients might change our strategies for the management of diabetic nephropathy. The natural products might be useful as preventive interventions and studies are required in this field.

Introduction
Diabetic nephropathy (DN) is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD). It is a progressive and irreversible kidney disease that is characterized by initial hyperfiltration, albuminuria, expansion of mesangial matrix, interstitial fibrosis, thickening of basement membranes, and renal cell damage. DN affects 20–30% of the diabetic patients [1].

Many pathways involved in DN have been postulated such as hyperglycemia, oxidative stress (OS), and activation of protein kinase C (PKC) [2–4] (Table 1). The upregulation of the receptors for AGE (RAGE) has been implicated as a major mediator in the development and progression of DN. Renal fibrosis, characterized by the accumulation of extracellular matrix protein, results in CKD including DN. It was found that transforming growth factor (TGF-β1) signaling pathway plays a key role in mediating renal fibrosis. Therefore, agents that antagonize TGF-β signaling might be useful for kidney disease therapy.

OS is characterized by increases in reactive oxygen species (ROS) and/or reactive nitrogen species (RNS). RNS and ROS include various agents that contribute to pathological processes in the renal systems. The antioxidant system includes the major ROS scavenging enzymes. Glutathione (GSH) and thioredoxin-2 system are the principal thiol antioxidant systems in mitochondria, which depend on the reducing power of NADPH/NADP+ [5]. GSH is the major endogenous antioxidant produced by the cells [6]. It has been shown that oxidative damage plays an important role in the pathogenesis of DN. At a high level, ROS have an important role in the generation of OS and several inflammatory cytokines that cause damage to protein, lipid, and nuclear DNA [7–9].

In clinical practice, reduction of blood pressure, normalizing blood sugar, and controlling dyslipidemia are the main strategies to ameliorate albuminuria and to treat diabetic patients with DN [2,5]. However, these interventions do not prevent progression to ESRD. Furthermore, various etiologies and many mechanisms of pathogenesis of DN have been postulated, accordingly, multiple interventions have been tested in clinical settings, but they did not show promising outcome. Traditional herbs and spices are important sources of functional foods. They contain antioxidants and many of them showed considerable effects on biological activities and diseases process. Furthermore, many antioxidants, derived from dietary and medicinal plants, have been found to activate redox-sensitive transcription factors, and potentiate the cellular antioxidant or detoxification capability. This paper summarizes beneficial effects of common herbs and spices in DN.

The transcription factors
Nuclear factor-E2-related factor 2 (Nrf2), silent information regulator factor 2-related enzyme 1 (Sirt1), nuclear factor kappaB (NFκB), and antioxidant response element (ARE) are involved in the pathological progression of DN. Nrf2 plays a major role in the regulation of redox homeostasis and the cellular detoxification response. It modulates the gene expression of a number of enzymes to detoxify pro-oxidative stressors [10]. The activation of Nrf2 results in the upregulation of several antioxidant enzymes and cytoprotective genes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx),

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KEYWORDS
Diabetes mellitus; kidney; antioxidants; oxidative stress; herbs; diabetic nephropathy
and heme oxygenase-1 (HO-1). Several Nrf2 activators have been proved effective at activating Nrf2 signaling through different mechanisms in both in vitro and in vivo models of diabetes [11]. It was found that the activation of Nrf2–ARE pathway led to the quenching of ROS overproduction caused by advanced glycation end products (AGEs) [12]. Nrf2 is the key to regulating GSH levels by upregulating enzymes involved in GSH synthesis. Nrf2 increases glutamate cysteine ligase catalyzes (GCL), the rate-limiting step in GSH synthesis [13].

Under physiological conditions, Nrf2 locates in the cytoplasm and combines with its inhibitor Kelch-like ECH-associated protein-1 (KEAP1). During OS, Nrf2 is free from KEAP1 and binds to the genes encoding antioxidant enzymes in the nucleus to increase their expression [14,15]. It was found that Nrf2 has a protective effect on high glucose-induced oxidative damage in the cultured cells and on the diabetic complications in animal models [16]. Hyperglycemia activates the Nrf2 pathway through the generation of ROS in the kidney tissue of human or animals with DN as well as tissue cultures (Figure 1) [17–21].

NFKB controls the expression of genes involved in chemokines, inflammatory response, growth factors, cytokines, and adhesion molecules. Increased activation of NFkB was observed in DN in animal and human studies [17,22]. In CKD and anti-GBM-glo-merulonephritis, the increased activation of p65/NFkB molecule interacts with KEAP1 in the cytoplasm and prevents the release and translocation of Nrf2 in the nucleus, and in the nucleus, it prevents binding of Nrf2 to the ARE of its target genes [23,24].

IkB (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha) is a cellular protein that inhibits the NFkB by masking the nuclear localization signals of NFkB proteins and keeping them sequestered in the cytoplasm and by inhibiting NFkB to bind to DNA. IKK-β, inhibitor of nuclear factor kappa-B kinase subunit beta, causes activation of NFkB and phosphorylates IkBα which is degraded by the ubiquitination pathway. Then NFkB is free and enters into the nucleus of the cell to activate various genes involved in inflammatory reactions.

Sirt1, a member of deacetylation enzymes, can deacetylate NFKB and Nrf2 [25,26]. Sirt1 can release Nrf2 by changing KEAP1 conformation, and then Nrf2 translocates into the nucleus and binds with ARE [26,27]. Sirt1 can inhibit the transcriptional activity of NFKB and reduce the levels of proinflammatory cytokines [28,29]. It was found that Sirt1 is downregulated in diabetic rats [30]. Another study showed that AGEs/RAGE system downregulated Sirt1 expression and promoted TGF-β1 expression in male rat glomerular mesangial cells [31].

### Diabetes and oxidative stress

OS and inflammation are involved in the pathogenesis of DN. OS is an intercellular biochemical dysregulation of the redox status, whereas inflammation is the biological response to OS. Data from experimental and diabetic patients showed that increase of OS plays a major role in the initiation and progression of diabetic complications [32,33]. Furthermore, epidemiological studies have demonstrated an association between inflammation and OS markers with cardiovascular disease (CVD) and renal outcomes in CKD and ESRD [34]. Compared with control subjects, antioxidative agents, such as SOD, GPx, CAT, and vitamin C, were decreased in patients with DN. There was a significant increase in serum malondialdehyde (MDA), AGEs, protein carbonyl, and 8-hydroxy-2′-deoxyguanosine in diabetes patients [7]. Data showed that various factors and agents such as inflammatory cells, cytokines, and profibrotic growth factors including TGF-β, monocyte chemoattractant protein-1 (MCP-1), connective tissue growth factor (CTGF), tumor necrosis factor (TNF-α), interleukin (IL) IL-1, IL-6, IL-18, and cell adhesion molecules (CAMs) are involved in the pathogenesis of DN via increased vascular inflammation and fibrosis [10].

Hyperglycemia causes high production of ROS [8,9]. It is known that free radicals cause oxidative damage to the kidney and it contributes to hypertension (HTN)-induced kidney and vascular injury and enhances fibrosis, cell proliferation, and matrix accumulation [35,36].

OS induces NFKB and activation of NFKB was observed in DN in animal and human studies [37,38]. NFKB mediates damages in extracellular matrix, glomerulosclerosis, and renal failure, and provides a molecular mechanism responsible for the inflammation and insulin resistance in diabetes mellitus (DM) [39]. PKC activates NFKB and intensifies the
inflammatory response [40]. PKC-βII, isoform of PKC, induces the formation of production of TGF-β, CTGF, AGE, and vascular endothelial growth factor (VEGF) [40,41].

ROS are produced due to hyperglycemia, AGEs, PKC, free fatty acids, cytokines, and TGF-β that activate the NADPH/NADPH oxidase system in renal cells [42,43]. ROS are involved in the expression of mediators of inflammation, fibrosis, and cell death, and these are affected by the activation of NFκB, activator protein-1, and specificity protein-1 [44,45]. Another study showed that GSH level and GSH/GSSG ratio were decreased in diabetic rats [46]. The increased production of ROS could compromise nitric oxide (NO) bioavailability and lead to the formation or activation of vasoconstrictive mediators that could affect tissue perfusion and glomerular filtration [47]. In DM, NO availability is usually decreased, and it might contribute to the vasculopathy present in DN [47]. Endothelial dysfunction has been commonly found in subjects with DN. It was found that blocking endothelial NO leads to an increase in microvascular disease in animals with CKD and arteriosclerosis [48].

Therefore, OS, inflammation, Nrf2, Sirt1, and NFκB have a great role in the pathogenesis and prevention of DN. Factors upregulating Nrf2 and Sirt1 and downregulating NFκB and damping inflammation will contribute to new interventions for the management of DN. Natural products have antioxidant properties and many studies showed that they have important effects on the Nrf2, Sirt1, and NFκB.

Natural antioxidants in diabetic nephropathy

Many natural antioxidants, herbs, seeds, and plants’ extracts were tested in animals’ model of DN. Some of these natural products with their beneficial effects on DN and possible mechanism of action are summarized in Table 2.

Ginger (Zingiber officinale Roscoe)

Ginger shows an antioxidant activity, and more than 50 antioxidants were isolated from the rhizomes of ginger [49]. Ginger also possessed antioxidants, anti-inflammatory, anticancer, anticoagulant, antihyperglycemic, diuretics, and analgesic activities [50–53]. It reduces blood glucose levels (BGL) in STZ-induced DM in rats [54]. The combination of honey and ginger reduced SOD and CAT activities and lowered the MDA level and increased GSH level and GSH/GSSG ratio back to normal level in diabetic rats [55]. Ginger increases insulin release and sensitivity, which involve interaction with the 5-HT3 receptor [56].

Another study demonstrated that ethanolic ginger extract reduced BGL and restores the total carbohydrates, pyruvate, glycogen, and total protein in the kidney tissue of STZ-induced diabetic rats [57]. Furthermore, ginger extract injected intraperitoneally decreased significantly serum glucose and urine protein, and it effectively attenuated the progression of structural nephropathy in diabetic rats [58].
Table 2. Effects of common plants and spices on kidney function in diabetic animals and human experiments with suggested mechanism of action.

| Name of the plants/herbs (active ingredients) | Effects on diabetic nephropathy in rats or mice | Mechanism of action | References |
|-----------------------------------------------|------------------------------------------------|---------------------|------------|
| Ginger (Gingerdione) (Zerumbone) (Gingerol) | Decreases BGL, increases insulin release | Antioxidant | [49–64] |
|                                               | Decreases BUN, urinary albumin | Anti-inflammatory |            |
|                                               | Reduces antioxidants SOD and CAT and lowers MDA level | Increases NOQ1 activity |            |
|                                               | Attenuates the progression of structural nephropathy | Decreases iNOS, MCP-1, TGF-β1, and NFκB activation |            |
|                                               | Increases GSH level and GSH/GSSG ratio | Upregulates the expression of ARE-target genes |            |
|                                               | Reducing degradation of iκBα |            |            |
| Turmeric (Curcumin) (Curcuminoids)            | Induces expression of SOD, CAT, GR, GPx, HO-1, and GST | Antioxidant | [65–82] |
|                                               | Lowers mesangial area, proteinuria, BUN, and Scr | Anti-inflammatory |            |
|                                               | Protects the kidneys of rats or mice with DM | Induction of Nrf2 |            |
|                                               | Inhibits inflammatory gene expression and ameliorates DN | Suppresses phosphorylation of cavelin-1 |            |
|                                               | Prevents epithelial–mesenchymal transition of podocytes and proteinuria | Inhibits phosphorylation of STAT3 and degradation of iκBα |            |
|                                               | Decreases albuminuria and attenuates glomerular sclerosis |            |            |
|                                               | Lowers mesangial area, proteinuria, BUN, and Scr |            |            |
| Coenzyme Q10                                  | Attenuates diabetes-induced decreases in antioxidant defense mechanisms | Antioxidants | [83–90] |
|                                               | Inhibits leukocyte infiltration, glomerulosclerosis, and MDA | Induces Nrf2 nuclear translocation |            |
|                                               | Increases serum levels of GSH, CAT, and SOD | Suppresses TGF-β1 |            |
|                                               | Prevents altered mitochondrial function and morphology, glomerular hyperfiltration, and proteinuria |            |            |
| Green tea (Catechins) (Epigallocatechin-3-gallate) | Protects kidney against gentamycin, cyclosporine, and i.v. contrast | Antioxidant | [91–105] |
|                                               | Has renoprotective properties comparable with ACEi | Anti-inflammatory |            |
|                                               | Reduced BGL, HbA1c, Scr, and BUN | Increases NFκ2 and NQO1 mRNA |            |
|                                               | Attenuates proteinuria, hyperfiltration, glomerulosclerosis, and tubulointerstitial fibrosis | Diminishes AKT/ERK/NFκB pathways |            |
|                                               | Ameliorates cisplatin-induced acute kidney injury and lupus nephritis | Activates Sirt1 |            |
| Guava (Psidium guajava) (Total triterpenoids) | Decreases BGL and increases the insulin sensitivity index | Antioxidant | [106–110] |
|                                               | Protects renal lesions in diabetic rats | Anti-inflammatory |            |
|                                               | Decreases BUN and Scr and improves the renal structural damages | Inhibition of NFκB activation |            |
|                                               | Reduces BGL and increases the insulin sensitivity index | Suppresses LPS-induced iκBα degradation |            |
|                                               | Protects renal lesions in diabetic rats | Inhibits iNOS, COX-2 |            |
|                                               | Decreases BUN and Scr and improves the renal structural damages |            |            |
|                                               | Reduces renal antioxidant enzyme activity and defences against SOD and CAT and lowers MDA level | Anti-inflammatory | [178–188] |
|                                               | Decreases proteinuria, suppresses AGEs/RAGE axis | Antioxidant, anti-inflammatory |            |
|                                               | Improves renal function parameters | Reduces the levels of CRP and the expression of TNF-α, monocyte chemoattractant protein 1, and intercellular adhesion molecule 1 |            |
|                                               | Decreases proteinuria, attenuates the progression of nephropathy in diabetic rats | Inhibiting NFκB activation and subsequent iNOS and COX-2 expression |            |
|                                               | 5-reduced albuminuria | Increases ARE-responsive HO-1 and GSR |            |
|                                               | Decreases fasting BGL, serum insulin, HbA1c, and systolic blood pressure | Down regulating expression of CTGF |            |
|                                               | Reduces albuminuria and attenuates glomerular sclerosis | Suppresses AGERAGE |            |
| Ginkgo biloba                                | Reduces OS, and improves the renal tissue structure and renal functions | Antioxidants and anti-inflammatory | [189–197] |
|                                               | Protects against glomerulosclerosis of mesangial cells | Inhibits sAGEs production |            |
|                                               | Decreases BGL, Scr, BUN, urine protein, and OS | Reduces CTGF and TGF-β1 mRNA |            |
|                                               | Inhibits AGE production | Increases Nrf2 and upregulation of HO-1 |            |
|                                               | Improves renal tissue structure and renal functions |            |            |
|                                               | Decreases the urinary albumin excretion, BGL, Scr, and BUN in diabetic patients |            |            |
|                                               | Prevents heavy metals-induced nephrotoxicity and OS damage | Antioxidants and anti-inflammatory | [198–212] |
|                                               | Reduces proteinuria and glomerular and tubulointerstitial lesions | Inhibits thromboxan A2 and B, prostaglandin E, and prostaglandin I, activating protein-1, MCP-1, and mitogen-activated protein kinase/extracellular signal-regulated kinase signaling |            |
|                                               | Reduces levels of OS and increases the antioxidant defense systems | Anti-inflammatory |            |
|                                               | Protects rodents against ischemic acute renal failure, IgA- or cyclosporine A-induced nephrotoxicity, and STZ-induced type 1 and type 2 DN | Inhibits AGE |            |
|                                               | Attenuates tubulointerstitial fibrosis and inflammation |            |            |
|                                               | Has renal protective effect in DN patients | Has anti-inflammatory and antioxidant activity | [223–233] |
|                                               | Reduces BUN, Scr, BGL, and albuminuria in diabetic patients | Uregulates c-met (a receptor tyrosine kinase) expression in human kidney |            |
|                                               | Reverses the glomerular hyperfiltration state | Reduces TGF-β1 expression |            |
|                                               | Ameliorates the pathological changes of early DN | Reduces mRNA level of NFκB |            |
|                                               | Increases the inhibition of NFκB protein mRNA expression | Increases in inhibitory NFκB protein mRNA expression |            |
|                                               | Modulates TGF-β/Smad signaling |            |            |
|                                               | Reduces proteinuria and glomerular sclerosis |            |            |
|                                               | Lowers mesangial area, proteinuria, BUN, and Scr |            |            |
|                                               | Lowers mesangial area, proteinuria, BUN, and Scr |            |            |
|                                               | Reduces albuminuria and attenuates glomerular sclerosis |            |            |
|                                               | Lowers mesangial area, proteinuria, BUN, and Scr |            |            |
|                                               | Attenuates diabetes-induced decreases in antioxidant defense mechanisms |            |            |
|                                               | Inhibits leukocyte infiltration, glomerulosclerosis, and MDA |            |            |
|                                               | Increases serum levels of GSH, CAT, and SOD |            |            |
|                                               | Prevents altered mitochondrial function and morphology, glomerular hyperfiltration, and proteinuria |            |            |
|                                               | Reduces renal antioxidant enzyme activity and defences against SOD and CAT and lowers MDA level |            |            |
|                                               | Decreases proteinuria, suppresses AGEs/RAGE axis |            |            |
|                                               | Improves renal function parameters |            |            |
|                                               | Decreases proteinuria, attenuates the progression of nephropathy in diabetic rats |            |            |
|                                               | 5-reduced albuminuria |            |            |
|                                               | Decreases fasting BGL, serum insulin, HbA1c, and systolic blood pressure |            |            |
|                                               | Reduces OS, and improves the renal tissue structure and renal functions |            |            |
|                                               | Protects against glomerulosclerosis of mesangial cells |            |            |
|                                               | Decreases BGL, Scr, BUN, urine protein, and OS |            |            |
|                                               | Inhibits AGE production |            |            |
|                                               | Improves renal tissue structure and renal functions |            |            |
|                                               | Decreases the urinary albumin excretion, BGL, Scr, and BUN in diabetic patients |            |            |
|                                               | Prevents heavy metals-induced nephrotoxicity and OS damage |            |            |
|                                               | Reduces proteinuria and glomerular and tubulointerstitial lesions |            |            |
|                                               | Reduces levels of OS and increases the antioxidant defense systems |            |            |
|                                               | Protects rodents against ischemic acute renal failure, IgA- or cyclosporine A-induced nephrotoxicity, and STZ-induced type 1 and type 2 DN |            |            |
|                                               | Attenuates tubulointerstitial fibrosis and inflammation |            |            |
|                                               | Has renal protective effect in DN patients |            |            |
|                                               | Reduces BUN, Scr, BGL, and albuminuria in diabetic patients |            |            |
|                                               | Reverses the glomerular hyperfiltration state |            |            |
|                                               | Ameliorates the pathological changes of early DN |            |            |
|                                               | Has anti-inflammatory and antioxidant activity |            |            |
|                                               | Uregulates c-met (a receptor tyrosine kinase) expression in human kidney |            |            |
|                                               | Reduces TGF-β1 expression |            |            |
|                                               | Reduces mRNA level of NFκB |            |            |
|                                               | Increases in inhibitory NFκB protein mRNA expression |            |            |
|                                               | Modulates TGF-β/Smad signaling |            |            |
|
(Continued)
Table 2. Continued.

| Name of the plants/herbs (active ingredients) | Effects on diabetic nephropathy in rats or mice | Mechanism of action | References |
|-----------------------------------------------|------------------------------------------------|---------------------|------------|
| *Panax ginseng* | Has protection against alloxaan-induced renal damage | Upregulates cellular protein levels of Nrf2, GSH levels, and HO-1 and gamma-glutamyl-cysteine synthetase | [111–113] |
| | Reduces urinary albumin and creatinine | Upregulates cellular GHS levels | | |
| | | Regulates Nrf2 | | |
| | | Increases ARE-activity | | |
| | | Upregulates thioredoxin reductase-1 | | |
| *Rosa laevigata Michx* | Ameliorates renal dysfunction cell injury | Antioxidant | [111–113] |
| | Decreases SCR and BUN levels | Anti-inflammatory | |
| | | Inhibits expression of NF-kB p65 and MCP-1 | |
| | | Increases the expression of the IkBa protein | |
| | | Upregulates the levels of Nrf2, Sirt1 and HO-1 | |
| | | Downregulates the levels of KEAP1 and NFkB p65 | |
| *Garlic* | Reduces hyperglycemia | Antioxidant | [114–130] |
| (Alllicin) | Attenuates mesangial expansion and glomerulosclerosis | Anti-inflammatory | |
| (S-allyl cysteine) | Decreases urinary excretions of albumin | | |
| (Diallyl trisulfide) | Decreases BGL, BUN, and SCR | Activates the Nrf2–ARE signaling pathway | |
| | Normalizes blood pressure and renal clearance function | Decreases the expression of VEGF | |
| | | | Decreases levels of collagen I, TGF–β1 and p-ERK1/2 |
| *Black seed* | Reduces the elevated levels of BGL in diabetic rats | Antioxidant | [131–146] |
| (Thymoquinone) | Stimulates insulin release | Anti-inflammatory | |
| | Lowers SCR and BUN | | |
| | Improves renal function | Reduces TNF-α | |
| | Reduces renal inflammation and oxidative injury in ischemia reperfusion injury | Inhibits the phosphorylation of mitogen-activated protein kinases production of NO by iNOS enzyme | |
| | | Suppresses NFkB activation | |
| | | Ameliorates albuminuria | |
| | | Restores the decrease in IL-10 levels and Nrf2 mRNA levels | |
| *Panax ginseng* | Reduces the cisplatin-induced nephrotoxicity | Antioxidant | [147–154] |
| (Ginsenosides) | Ameliorates hyperglycemia and renal damage in diabetic rats | ARE inducer | |
| (Panaxytriol) | Decreases hyperglycemia and proteinuria | Induces NQO1 | |
| | Normalizes creatinine clearance | | |
| *Fenugreek* | Ameliorates SCR in diabetic animals | Antioxidant | [155–162] |
| (Fenugreek oil) | Reduces the high levels of BGL, BUN, SCR, and IL-6 | Anti-inflammatory | |
| (GI) | Reduces BGL, improves renal functions | Restrains TGF–β1/CTGF signaling pathway | |
| (Glycosides) | Suppresses ECM accumulation | Increases Nrf2 | |
| | Attenuates the cisplatin-induced biochemical and histopathological alterations, inflammation, and apoptosis kidney | | |
| | | | |
| *Rosmarinus officinalis* | Decreases focal glomerular necrosis, dilatation of Bowman’s capsule, degeneration of tubular epithelium, necrosis in tubular epithelium, and tubular dilatation | Antioxidant and anti-inflammatory | [163–177] |
| (Rosmarinic acid) | Prevents ischemia/reperfusion injury in the kidneys | | |
| (Carnosic acid) | Ameliorates glomerulosclerosis | | |
| | Protects podocyte by increasing antioxidative capacity and ameliorating the renal OS | | |
| | Reduces albuminuria, and GBM thickness in the kidneys | | |
| | Decreases BUN, SCR, and urinary albumin excretion rate | | |
| | Increases creatinine clearance rate | | |
| | Lowers albuminuria in type 2 diabetic patients with microalbuminuria | | |
| | Reduces HbA1c levels in diabetic patients | | |
| *Vitamin C* | Protects podocyte | Antioxidants and anti-inflammatory | [234–243] |
| | by increasing antioxidative capacity and ameliorating the renal OS | Increases HO-1 protein expression in a concentration- and time-dependent manner | |
| | Reduces albuminuria, and GBM thickness in the kidneys | Causes Nrf2 activation | |
| | Decreases urinary albumin excretion rate | Downregulates expressions of collagen type IV | |
| | Increases SCR and SCR | | |
| | Increases BUN and creatinine clearance rate | | |
| | Lowers albuminuria in type 2 diabetic patients with microalbuminuria | | |
| | Reduces HbA1c levels in diabetic patients | | |
| *Vitamin E* | Ameliorates SCR in diabetic animals | Suppresses the activation of NFkB signaling pathway | [244–251] |
| (Tocotrienol) | Normalizes elevated baseline creatinine clearance in type 1 diabetic patients | Antioxidant | |
| | Reduces HbA1c levels in type 2 diabetes | Decreases thromboxane A2 production | |
| | Decreases microalbuminuria | Increases GSH level and CAT activity | |
| | Has a nephroprotective effect | Improves the index of NO−/NO3− generation | |
| | Reduces proximal tubular injury and renal LPO | | |
| *Zinc* | Has a favorable effect on glycemic control in diabetic patients | Antioxidant properties and anti-inflammatory | [252–259] |
| | Reduces diabetes-induced renal damage | Prevents hyperglycemia-induced CTGF expression | |
| | Decreases BSL, triglyceride, urinary albumin excretion, and inflammation in type 2 diabetic nephropathy patients | Causes stimulation of metallotriphosine synthesis | |
| | Downregulates Nrf2 function via activating Akt-mediated inhibition of Fyn function | | |
| *Oats* | Slow down renal fibrosis | Downregulates the TGF–β1 and receptors for AGE expression at mRNA levels | [260–264] |
| (β–0-glucan) | Reduce BGL, HbA1c, and OS markers | Causes disruption of the detrimental receptors for AGE-NFkB axis | |
| (Avenanthramides) | Lower BSL and HbA1c in diabetic patients | Normalizes NFkB activation and TNF-α expression | |
| | | Increases HO-1 expression which was mediated by Nrf2 translocation | |
Ginger and its derivatives might decrease inflammatory processes in DN as well as increase antioxidants by affecting KEAP1. Another study showed that gingerol has a protective effect with KEAP1. Zerumbone upregulates the expression of ARE-target genes and decreases levels of HbA1c. Increases SOD, GPx activity, and total antioxidant capacity. Decreases CRP levels, and decreases MDA concentration in diabetic patients. Decreases the urinary albumin–creatinine ratio, urinary levels of TNF-α, and urinary and serum levels of MDA in diabetic patients.

Compounds isolated from ginger (1-dehydro-6-gingerdione, 6-shogaol, and hexahydrocurcumin) increased NAD(P)H quinone oxidoreductase 1 (NQO1) activity and decreased induced nitric oxide synthase (iNOS) activity in LPS-stimulated macrophages. Zerumbone, one of the pungent constituents of Zingiber zerumbet (L) and Smith (Zingiberaceae family), decreased the expression of intercellular adhesion molecule-1, MCP-1, TGF-β1, and fibronectin in the DN. It improved histological architecture in the diabetic kidney. Furthermore, zerumbone suppresses NFκB activation induced by several proinflammatory stimuli by reducing the phosphorylation and degradation of IkBα by interfering with IKK activity. Zerumbone upregulates the expression of ARE-target genes and downregulates NFκB-targets by direct interaction with KEAP1.

Gingerol (100 mg/kg bw), the major pungent component in ginger, significantly decreased blood glucose in db/db type 2 diabetic mice and lowered lipids and fatty acid. Another study showed that gingerol has a protective effect on pancreatic β-cells and it restored the plasma insulin level. Ginger and its derivatives might decrease inflammatory processes in DN as well as increase antioxidants by affecting NFκB activation, expression of ARE-target genes and by interaction with KEAP1.

Turmeric

Curcumin is a famous spice used in cooking and traditional medicine. It is a polyphenol (diferuloylmethane) and it is the main active component of turmeric isolated from the plant Curcuma longa L. It was found that curcumin has many antidiabetic activities which was postulated to be due to the antioxidant property.

Curcuminoids have an antioxidant activity in several in vitro and in vivo models, such as preventing lipid peroxidation in a variety of cells. Curcumin scavenges superoxide anion (O2·), hydroxyl radical (OH), hydrogen peroxide (H2O2), singlet oxygen, NO, peroxynitrite, and peroxyl radical (ROO·). It can induce the expression of SOD, CAT, GPx, HO-1, GST, NQO1, and γ-glutamyl-cysteine ligase. The renoprotective effect of curcumin has been evaluated in several experimental models including DN, CKD, ischemia and reperfusion, and nephrotoxicity induced by various compounds. The renoprotective effect of curcumin was due to the induction of Nrf2, inhibition of mitochondrial dysfunction, attenuation of the inflammatory response, preservation of antioxidant enzymes, and prevention of OS. Another study has suggested that curcumin treatment ameliorates DN via inhibition of inflammatory gene expression by reversing caveolin-1 Tyr14 phosphorylation that influenced Toll-like receptor 4 activation.

Epithelial–mesenchymal transition plays a key role in DN. Recently, it was suggested that curcumin prevents epithelial–mesenchymal transition of podocytes, proteinuria, and kidney injury in DN by suppressing the phosphorylation of caveolin-1, and increasing stabilization of caveolin-1 and β-catenin. Curcumin protects DN by reducing AGE-induced OS and restoring AGE-induced mesangial cell apoptosis. In the treatment of DN in db/db mice, curcumin decreases albuminuria and attenuates glomerular sclerosis by inhibiting phosphorylation of STAT3 and degradation of IkB.[76]

In the clinical setting, it was found that curcumin at the dose of 500 mg/day markedly attenuates urinary microalbumin excretion, reduces plasma MDA level with enhanced the NrF2 system specifically regulated protein, NQO-1, together with other antioxidative enzymes in diabetic patients’ blood lymphocytes. After curcumin administration, there was an increased IkB, an inhibitory protein on inflammatory signaling in patient’s lymphocytes. A recent review of 14 randomized controlled studies showed that curcumin significantly lowers mesangial area, proteinuria, blood urea nitrogen (BUN), and serum creatinine (Scr) and protects the kidneys of rats or mice with diabetes.

Curcumin activates NrF2 and HO-1, and protects the NRK-52E cells from the high glucose-induced epithelial-to-mesenchymal transition of mature tubular epithelial cells. The expression levels of NrF2 and HO-1 protein were elevated to a greater extent in the curcumin-pretreated NRK-52E cells. Furthermore, curcumin effectively attenuates OS, inflammation, and renal fibrosis by modulating NrF2–KEAP1 pathway.

Table 2. Continued.

| Name of the plants/herbs (active ingredients) | Effects on diabetic nephropathy in rate or mice | Mechanism of action | References |
|---------------------------------------------|-----------------------------------------------|---------------------|------------|
| Lycopus lucidus Turcz | Inhibits renal fibrosis | Blocks TGF-β signaling pathway | [265–268] |
| Milk thistle (Flavonolignans) (Silymarin) | Reduces urinary excretion of albumin | Antioxidant and anti-inflammatory effects | [269–274] |

GSTs: Glutathione-s-transferase; OS: oxidative stress; NO: nitric oxide; TNF-α: tumor necrosis factor; GCS: γ-glutamyl-cysteine synthetase; ROS: reactive oxygen species; PKC: protein kinase C; SOD: superoxide dismutase; RNS: reactive nitrogen species; AGEs: advanced glycation end products; NFκB: nuclear factor kappa B; Nrf2: nuclear factor erythroid 2-related factor 2; HO1: heme oxygenase-1; NQO1: NAD(P)H quinone oxidoreductase 1; MCP-1: monococyte chemoattractant protein-1;IKK-β: inhibitor of nuclear factor kappa-B kinase subunit beta;IκBα: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha.
induced Nrf2 and prevents OS, glomerular hypertension, hyperfiltration, and the decrease in antioxidant enzymes in 5/6 nephrectomized rats [81]. Furthermore, curcumin upregulates HO-1 in a rat smooth muscle cell line and it is a potent activator of Nrf2 [82].

**Coenzyme Q10**

Coenzyme Q10 (ubiquinone) is an endogenous lipid and a natural antioxidant and scavenging free radicals. It is an oil-soluble vitamin-like substance that is a component of the electron transport chain. It is found in the membranes of many organelles, and it involves in aerobic cellular respiration as an electron carrier for generating energy. A meta-analysis of clinical studies concluded that coenzyme Q10 had the potential for lowering blood pressure in hypertensive patients [83]. It was suggested that a deficiency in mitochondrial oxidized coenzyme Q10 may be a precipitating factor for DN [84]. Coenzyme Q10 attenuates diabetes-induced decreases in antioxidant defense mechanisms and this effect was potentiated by IGF-1 antagonism [85]. Coenzyme Q10 significantly inhibited leukocyte infiltration, glomerulosclerosis and decreased levels of MDA in serum and kidney content. Another study has found that coenzyme Q10 significantly increased serum levels of GSH, CAT, and SOD in the diabetic animals [86]. Furthermore, coenzyme Q10 decreases leukocyte infiltration and glomerulosclerosis and it exerts beneficial effects on the lipid peroxidation and antioxidant enzymes activity in alloxan-induced type 1 diabetic rats [86]. Data from another study demonstrated that coenzyme Q10 prevents altered mitochondrial function and morphology, glomerular hyperfiltration, and proteinuria in db/db mice [87]. Coenzyme Q10 ameliorated glomerulosclerosis and improved tissue antioxidant enzymes in diabetic rats [88]. It was shown that coenzyme Q10 induces Nrf2 nuclear translocation, augments the cellular antioxidant defense capacity and attenuates H2O2-induced in PC12 cells [89]. Furthermore, solubilized coenzyme Q10 inhibited dimethylnitrosamine-induced liver fibrosis through suppression of TGF-β1 expression via Nrf2/ARE activation in mice [90].

**Green tea**

Green tea (Camellia sinensis L.) has antioxidant and anti-inflammatory properties. It contains strong antioxidative flavonoids. Green tea polyphenols have a beneficial effect on pathological entities related to OS of renal tissues [91]. It protects kidney against gentamycin, cyclosporine, and intravenous contrast [92,93]. In randomized clinical trial, it was found that green tea polyphenol reduces albuminuria in diabetic patients receiving the maximum recommended dose of renin–angiotensin inhibition [94]. In this study, podocyte apoptosis and in vitro albumin permeability were higher in human podocytes exposed to plasma from diabetics compared to podocytes treated with plasma from normal individuals; therefore, it was suggested that reduction in podocyte apoptosis by activation of the WNT pathway may have contributed to the green tea effect.

Green tea treatment significantly reduced BGL, glycosylated protein (HbA1c), SCr, and BUN in diabetic rats. In addition, the green tea-treated group showed a significant higher creatinine clearance compared with the untreated diabetic rat and green tea also prevented glycogen accumulation in the renal tubules [95]. Another study showed that green tea polyphenols increased the activity of SOD in the kidney rats that had been subjected to subtotal nephrectomy and injection of STZ [96]. In mice, green tea extract increased Nrf2 and NQO1 mRNA, and lowered hepatic steatosis, MDA, lipid uptake and lipogenic gene expression, and NFκB-dependent inflammation [97].

The green tea catechins have potent anti-inflammatory and antioxidant agents. They inhibit chelate transition metals, leukocyte chemotaxis, quench free radicals, and lipid peroxidation chain reaction [98]. It has been demonstrated that high doses of catechins-rich OPLE for 4 weeks in STZ-induced diabetic rats attenuate proteinuria, hyperfiltration, glomerulosclerosis, and tubulointerstitial fibrosis and causes suppression of 8-hydroxy-2′-deoxyguanosine, lipid peroxides, and TGF-β1 [99]. Another study showed that catechin has renoprotective properties comparable with renin–angiotensin inhibition, and co-administration with enalapril might be useful in reducing albumin excretion as well as improving endothelial function [100].

Epigallocatechin-3-gallate is the most abundant and most active catechin polyphenol extracted from green tea. It could restore unilateral ureteral obstruction-induced renal dysfunction, and prevent unilateral ureteral obstruction-induced OS in inflammatory responses in the obstructed kidney. Furthermore, epigallocatechin-3-gallate could induce both NfkB and Nrf2 nuclear translocation in the unilateral ureteral obstruction kidney and promote HO-1 production [101]. Epigallocatechin 3-O-gallate reversed an increase in the levels of BGL, BUN, SCr, and urine protein in STZ-induced DN in mice [102]. Therefore, epigallocatechin 3-O-gallate might provide an effective protection against STZ-induced DN in mice by osteopontin suppression [102].

Epigallocatechin-3-gallate activates Nrf2–ARE and peroxisome proliferator-activated receptor pathway, diminishes AKT/ERK/NFkB pathways to reduce OS and inflammation, and activates Sirt1 in mice with crescentic glomerulonephritis [103]. Moreover, it upregulates Nrf2 signaling and ameliorates cisplatin-induced acute kidney injury and lupus nephritis in animal models [104,105].

**Guava (Psidium guajava)**

Guava (Psidium guajava) is one of the popular tropical fruits rich in vitamin C, fiber, and phenolic compounds. Psidium cattleianum Sabine (Myrtacea) is rich in vitamin C and phenolic compounds, including epicatechin and gallic acid as the main components. It was considered as a good source of natural antioxidants [106]. Psidium guajava is an evergreen small tree or shrub whose origin is America. Its extract contains caffeic acid, myricetin, and quercetin, coumarin and ferulic acids [107]. This fruit extract dose-dependently reserved GSH content, retained activity of CTA and GPx, and decreased ROS, IL-6, TNF-α, and IL-1β levels in the kidney and therefore, it can protect the kidney against diabetic progression via its antioxidative, anti-inflammatory, and anti-glycative effects [107]. Extract of Psidium guajava possesses a significant free radical scavenging and antioxidant activities [108]. Total triterpenoids from Psidium guajava leaves decrease the level of BGL of diabetic rats, increase the insulin sensitivity index, and protect renal lesions in diabetic rats [109]. It also suppressed renal activity of aldose reductase. The levels of BUN and SCr were decreased and the renal
structural damages were improved with the use of *Psidium guajava* leaves in STZ-induced diabetic rats [109].

It was found that the flavonoid fraction of guava leaf extract inhibits LPS-induced NO and PGE2 production, TNF-α, IL-1β, IL-10, INOS, COX-2, and LPS-induced NfκB transcriptional activity in diabetic mice [107]. The flavonoid fraction of guava leaf extract suppresses the expression of inflammatory mediators that involves the inhibition of NfκB activation through the suppression of LPS-induced IkB-α degradation [110].

**Rosa laevigata Michx**

*Rosa laevigata Michx* is a well-known medicinal plant, and it has been widely used in China for a long time. Previous studies revealed that the total flavonoids fraction from the *Rosa laevigata Michx* has potent antioxidant, hypolipidemic, hepatoprotective, and antithrombotic activities through attenuating inflammation, suppression of apoptosis, and altering mitogen-activated protein kinase signaling pathways [111]. Another study showed that *Rosa laevigata Michx* significantly ameliorates renal dysfunction in diabetic rats [112]. The protection involves increasing the activity of SOD and total antioxidant capacity, decreasing the levels of MDA and ROS, and inhibiting the expression of NfκB p65 and MCP-1 at both the protein and mRNA levels with an increase in the expression of the IkBa protein [112].

Total flavonoids from *Rosa laevigata Michx* fruit attenuated cell injury and decreased Scr and BUN levels in rats with ischemia/reperfusion injury [113]. They also decreased the levels of MDA, SOD, GSH and GPx, and ROS, upregulated the levels of Nrf2, Sirt1, and HO-1, downregulated the levels of KEAP1 and NfκB p65, and increased the mRNA levels of IL-6, IL-1β, and TNF-α. Furthermore, inhibiting Sirt1 attenuated the protecting effect of the total flavonoids on renal ischemia/reperfusion injury, suggesting that the effect of the extract depended on Sirt1. Therefore, the total flavonoids have nephroprotective effect against ischemia/reperfusion injury by affecting Sirt1/Nrf2/NfκB signaling pathway [116].

**Garlic**

Large data from human and animal studies have reported the health-promoting properties of garlic (*Allium sativum* L.), a widely used condiment and spice. Many studies have shown that fresh garlic has the anti-diabetic properties. Raw garlic extract is active in reducing hyperglycemia and alleviating dyslipidemia and OS in both animal models and humans [114–117].

In diabetic rats, garlic showed normalization or attenuation in plasma and kidney ACE-1 and angiotensinogen II, normalization of blood pressure, and renal clearance function [114]. RAGE was significantly increased in renal and hepatic tissues of diabetic rats, which involved mesangial cells in glomeruli exhibiting signs of mesangial expansion, mesangial nodule formation, and glomerulosclerosis. Garlic significantly reduced RAGE throughout renal and hepatic regions [118]. In diabetic rats, the use of the garlic extract (500 mg/kg body weight) caused a significant decrease in the expression of VEGF and extracellular signal-regulated kinase-1 compared to diabetic rats, and attenuating mesangial expansion and glomerulosclerosis [119].

Garlic increased the serum antioxidant levels after 3 weeks of treatment in both diabetic and hypertensive rats. It decreased BGL and lowered systolic blood pressure [116]. Another study showed that fresh garlic homogenate significantly attenuated STZ-induced DN by attenuation of BGL, insulin, total triacylglycerol, total cholesterol, and creatinine clearance in rats. Urinary excretions of albumin and N-acetyl-beta-D-glucosaminidase were reduced. In addition, a marked improvement of GSH content in the kidney homogenates was also observed. It enhanced urinary excretion of nitrates [120].

Aged garlic extract is produced by storing sliced and macerated fresh garlic at room temperature for 20 months. Aged garlic extract contains many of the bioactive compounds found in fresh garlic including flavonoids and sapo-nins, the water-soluble allyl amino acid derivatives, stable lipid-soluble allyl sulfides, and S-allylcysteine and S-allylmercaptocysteine [121]. Aged garlic extract exhibits a dose-dependent ameliorative action on indicators of DM including serum insulin, total antioxidant level, and CAT activity in the serum, kidney, and liver in STZ-induced diabetic rats [122]. In animal models, it was found that aged garlic extract lowers OS by increasing endogenous antioxidant enzymes, such as CAT and GPx, and lowering xanthine oxidase and NADPH oxidase [123,124]. Aged garlic extract reduces the formation of superoxide and lipid peroxidation [125]. Aged garlic activated the Nrf2–ARE signaling pathway and induced the expression of antioxidant enzymes HO-1 and GCL modifier subunit [126].

Allicin is a major biologically active component of garlic. A study showed that allicin treatment for 12 weeks ameliorated diabetes-induced morphological alterations of the kidney and decreased BGL, Scr, triglyceride, and 24 h urine albumin excretion in diabetic rats. It decreased the expression levels of collagen I, TGF-β1, and p-ERK1/2 [127].

S-allylcysteine is a garlic-derived antioxidant. Data showed that S-allylcysteine (25 mg/kg) prevents the cisplatin-induced renal damage and attenuates cisplatin-induced decrease in Nrf2 levels and increase in PKCβ2, p47(phox) and gp91(phox) expression in renal cortex and OS, and decrease in the activity of CAT, GPx, and glutathione reductase (GSR) in the proximal and distal tubules [128]. Recently, it was shown that S-allylcysteine activates Nrf2 factor in cerebral cortex [129]. Diallyl trisulfide is the most powerful antioxidant among the sulfur-containing compounds in garlic oil. The study demonstrated that diallyl trisulfide protects against hyperglycemia-induced ROS-mediated apoptosis by upregulating the PI3K/Akt/Nrf2 pathway, which activates Nrf2 in cardiomyocytes exposed to high glucose [130].

**Black seed (Nigella sativa)**

Black seed is composed of fixed and essential oil. Dihomo-γ-linolenic acid presents in the fixed oil of seeds and it has a powerful antioxidant [131]. It contains vitamin E, vitamin A, β-carotene, and thymoquinone. It was found that ethanol extract of *Nigella sativa* seeds to STZ-induced diabetic rats for 30 days significantly reduced the elevated levels of BGL, and improved levels of CAT, SOD, reduced GST and GPx in the liver and kidney [132]. Results showed that vitamin C and *Nigella sativa* oil lowered the Scr, BUN, and antioxidant activity as compared to gentamicin control group values. When these were given as combination, they have synergistic nephroprotective effect [133]. Pretreatment with black seed for 3 weeks prior to ischemia reperfusion injury improved
renal function and reduced renal inflammation and oxidative injury [134]. It was suggested that the anti-diabetic properties of *Nigella sativa* seeds may be mediated by stimulated insulin release [135]. In STZ-induced diabetic rats, black seed oils significantly induced the gene expression of insulin receptor and they upregulated the expression of IGF-1. Also they significantly reduced BGL, OS parameters, serum insulin/insulin receptor ratio, and TNF-α [136].

Thymoquinone, an active quinone, that is the main component of black seed, has antioxidant, anti-inflammatory, and anti-diabetic effects. A study showed that thymoquinone has markedly reduced renal damage induced by doxorubicin with the restoration of decrease in IL-10 levels, Nrf2 mRNA levels towards normal values [137]. Thymoquinone is effective in protecting rats against N(omega)-nitro-L-arginine methyl esters-induced HTN and renal damage [138].

Thymoquinone decreased MDA and 8-isoprostanol levels in renal tissues and reduced levels of SCr and BUN concentration [139]. It was found that the protective effect of thymoquinone in STZ-induced diabetic rats is mediated via inhibiting the phosphorylation of mitogen-activated protein kinases production of NO by iNOS enzyme [140]. In a model of vancomycin- or gentamycin-induced nephrotoxicity in rats, thymoquinone caused reversal of the increase in BUN, SCr, and lipid peroxides [141,142].

Thymoquinone significantly abolished LPS-induced pro-inflammatory cytokines, such as IL-1β, TNF-α, COX-2, and prostaglandin E2 [143]. Oral administration of thymoquinone (80 mg/kg) to diabetic rats for 45 days reversed the decreased activities of CAT, Gpx, and glutathione S-transferase (GST), and increased GSH and vitamins C and E [144]. *Nigella sativa* oil and thymoquinone prevented diabetes-induced down-regulation of mRNA expression of the podocyte-specific marker and the mRNA over expression of collagen IV, TGF-β1, and VEGF in the diabetic kidney, and ameliorated albuminuria [145]. It was suggested that the anti-inflammatory activities of black seed and thymoquinone may be mediated through the suppression of NfκB activation [146].

**Panax ginseng**

The root of *Panax ginseng* has been widely used for the management of many diseases, including cancer, DM, and CVD for thousands of years [147,148]. Ginsenosides, main pharmacologically active constituents of ginseng and the secondary metabolites of the *Panax* species, have antioxidants and free radicals scavenging properties [149]. It reduced the cisplatin-induced nephrotoxicity in cultured renal proximal tubular epithelial cells in a dose-dependent manner [150]. North American ginseng has preventive effects on DN and it works through its anti-hyperglycemic and antioxidant activities [151].

In type 1 insulin-dependent DN animal models induced by STZ, it was found that sun ginseng, heat-processed American ginseng, and 20(S)-ginsenoside Rg3 ameliorated hyperglycemia and renal damage [152]. In type 2 insulin-independent DN animal models, ginsenoside Rg3 decreased hyperglycemia and proteinuria and augmented creatinine clearance [111].

Panaxytriol, an active component of red ginseng extracts, is a potent ARE inducer. The upregulation of aldo–keto reductase enzymes, induced by chemically homogeneous panaxytriol, was partially dependent on PKC and PI3K kinases. Aldo–keto reductase enzymes play an important role in the transformation and detoxification of aldehydes and ketones generated during drug detoxification and xenobiotic metabolism. This cellular mechanism may account for panaxytriol’s neuroprotective, neuroprotective, and anti-cancer properties [153]. It has been shown that ginseng induces NQO1, a phase 2 detoxification enzyme protect against carcinogenesis and OS, and the most potent inducing red ginseng extract has the highest panaxytriol content [154].

**Fenugreek (Trigonella foenum-graecum)**

Fenugreek (*Trigonella foenum-graecum*) is used as a daily diet of the general population in many countries. It was found that extractions from fenugreek seed have anti-diabetic and antioxidant effects. Fenugreek has a favorable function on peripheral glucose utilization and insulin secretagogue actions [155]. Furthermore, another study showed that fenugreek ameliorates SCr in diabetic animals [156]. In diabetic rats, treatment with fenugreek for 12 weeks reduces the high levels of glucose, BUN, SCr, and IL-6. It also reduced the levels of MDA and IL-6 in the kidney homogenate and increased the concentration of GSH and the activity of both SOD and CAT. These results suggest a therapeutic potential of fenugreek against DN by its antioxidative/anti-inflammatory properties [156]. In STZ-induced DN in rats, fenugreek treatment significantly reduced BGL, improved renal functions, suppressed ECM accumulation, and it relieved OS with the restrained TGF-β1/CTGF signaling pathway [157]. Cisplatin administration triggered inflammatory responses and apoptosis in rat livers and kidneys by increased expression of pro-inflammatory cytokine, TNF-α, and apoptotic marker p38 mitogen-activated protein kinases; results of overproduction of ROS. Fenugreek significantly attenuated the cisplatin-induced biochemical and histopathological alterations, inflammation, and apoptosis in rat kidneys. The results suggested that fenugreek has a powerful antioxidant effect [158].

Acrylamide intoxication significantly increased serum levels of LDH, AST, ALT, APL, γ-GT, cholesterol, uric acid, BUN, SCr, 8-oxo-2′-deoxyguanosine, IL-1β, IL-6, and TNF-α. Fenugreek oil supplementation normalized the altered serum parameters, prevented lipid peroxidation, and enhanced the antioxidant biomarker concentrations and activities in the hepatic, renal, and brain tissues in a dose-dependent manner [159].

Treatment with GII, a water-soluble compound purified from fenugreek seeds, for 15 days in the subdiabetic and moderately diabetic rabbits and for 30 days in the severely diabetic rabbits decreased the elevated TC, TG, LDL, VLDL and increased the decreased HDL, increased the decreased SOD and Gpx. Therefore, the treatment with GII compound corrects the altered polyol pathway and antioxidant enzymes [160].

Another study showed that *Trigonella foenum-graecum* seed aqueous extract confers protection against functional and morphologic injuries in the kidneys of diabetic rats by increasing activities of antioxidants and inhibiting the accumulation of oxidized DNA in the kidney [161]. In addition, glycosides fenugreek seed extract showed anti-fibrotic efficacy through induction of Nrf2 in rats with bleomycin-induced pulmonary fibrosis [162].

**Rosmarinus officinalis**

Rosmarinic acid is a polyphenolic phytochemical, found in *Perilla*, rosemary and mint; it is the main constituent of
Rosmarinus officinalis. It has antioxidant and anti-inflammatory properties [163]. Rosmarinic acid exerts an early renal protective role to DN by inhibiting CTGF [164]. It significantly decreased focal glomerular necrosis, dilatation of Bowman’s capsule, degeneration of tubular epithelium, necrosis in tubular epithelium, and tubular dilatation [165]. DM caused a significant decrease in the activity of SOD and CAT in rats. The treatment with rosmarinic acid (10 mg/kg) prevented the alteration in SOD and CAT activity and it reversed the decrease in ascorbic acid and non-protein-thiol levels in diabetic rats [166].

Rosmarinic acid has antioxidant and anti-inflammatory activity [163,167,168]. It prevented ischemia/reperfusion injury in the kidneys by decreasing OS [165]. Furthermore, rosmarinic acid was found to reduce NfκB, and increase glutathione transferase, anti Bcl-2 activity, and scavenger of peroxynitrite [169,170]. It conserves the glomerular number in diabetic rats and ameliorates glomerulosclerosis [171]. Furthermore, it was found that rosemary extract can inhibit the increased serum MDA in treated diabetic rats [172]. Other studies showed that rosmarinic acid improves activity of kidney antioxidants, such as SOD, GPx, and CAT, in gentamicin-induced nephrotoxicity and ameliorated DN in rats [173].

Carnosic acid, a phenolic diterpene isolated from Rosmarinus officinalis, exerts anti-inflammatory, antioxidant, and anticarcinogenic activities. It was found to cross the blood-brain barrier to support neuronal growth, and upregulates the production of neural protection factors in an Nrf2-dependent manner [174,175]. Furthermore, it was found that carnosic acid activated Nrf2 through modulation of PI3K/Akt pathway resulting in increased levels of antioxidant enzymes [176]. Carnosic acid prevented methylglyoxal-dependent neurotoxicity by activating the PI3K/Akt/Nrf2 signaling pathway and the antioxidant enzymes modulated by Nrf2 transcription factor [177].

Grape seed

Whole grape-based diet increased cardiac GSH and GSR activity in hypertensive rats [178]. Grape-derived phytochemicals, resveratrol and pterostilbene, were both protective against azoxymethane-induced colon carcinoma by inhibiting NFκB activation and subsequent iNOS and COX-2 expression, concomitant with increased ARE-responsive HO-1 and GSR [179].

Grape seed proanthocyanidin extract, a polyphenol compound derived from grape seeds, has antioxidant, anti-inflammatory, and antitumor activities, and it mediates resistance to free radicals and has protection from CVD [180,181]. Its antioxidant activity is 50 times higher than that of vitamin E and 20 times higher than that of vitamin C. It has been shown that this extract could downregulate OS proteins and increase renal antioxidant enzyme activity and ameliorate DN [182,183]. Another study showed that it can decrease proteinuria, attenuating the progression of nephropathy in diabetic rats that are correlated with suppression on AGEs/RAGE axis, and downregulating expression of CTGF [184]. Furthermore, it was found that proanthocyanidins protect the kidney of diabetic rats by increasing the renal antioxidative ability [185].

A recent study showed that proanthocyanidins decreases fasting BGL, serum insulin, HbA1c, and systolic blood pressure, improves renal function parameters, reduces the expression of tissue inhibitor of metalloproteinase1 and increases the activity of matrix metalloproteinase in diabetic rats. It also increased the activity of antioxidant enzymes and reduced the levels of CRP and the expression of TNF-α, MCP-1, and ICAM-1 in the kidney [186]. It was found that proanthocyanidin significantly decreases lipid peroxidation and augments the activities of antioxidant enzymes in the kidney of DN rats and also reduces albuminuria. It was suggested that these results were due to the reduction of the OS and increase in renal antioxidant enzyme activity [182]. In rat mesangial cells treated with high-dose glucosamine, the administration of grape seed procyanidin B2 significantly increased the viability of mesangial cells, inhibited apoptosis, and suppressed OS. It activated the protein expression of PPARγ co-activator-1α, SIRT1, and AMP-activated protein kinase in mesangial cells. It was suggested that grape seed procyanidin B2 ameliorates mitochondrial dysfunction and inhibits apoptosis due to the activation of the AMPK-SIRT1-PGC-1α axis [187].

Grape seed proanthocyanidin causes a significant improvement in renal OS markers in the kidneys of cadmium-treated rats, decreases the amount of iNOS, NFκB, TNF-α, caspase-3, and Bax and increases the levels of Bcl-2 protein expression. Furthermore, it normalizes the renal expression of NfκB/Keap1 and its downstream regulatory proteins. These results suggested that proanthocyanidin ameliorates renal dysfunction and OS through the activation of the Nrf2 pathway in cadmium-intoxicated rats [188].

Ginkgo biloba

Ginkgo biloba has a number of benefits including scavenging ROS [189]. Extract of Ginkgo biloba could inhibit AGEs production and downregulate RAGE expressions by reducing OS, and improve the renal tissue structure and renal functions of DN rats [190]. Furthermore, Ginkgo biloba extract has a protective property against glomerulosclerosis of mesangial cells in DN [191]. Data showed that Ginkgo biloba decreased BGL, SCR, BUN, urine protein, and the intensity of the OS in DN rats. It reduced AGE, collagen IV, laminin, TGF-β1 mRNA, CTGF, mesangium hyperplasia, and thickness of GBM [192]. A systemic review of randomized controlled trials conducted on adults with early DN showed that Ginkgo biloba extract decreased the urinary albumin excretion, BGL, SCR, and BUN [193].

Endothelial progenitor cells are precursor cells that can differentiate into vascular endothelial to form new blood vessels. These cells could be damaged by OS in DM [194]. It was found that Ginkgo biloba can improve SOD activity and reduce the rate of apoptosis of endothelial progenitor cells within the peripheral blood of diabetic patients [195].

In mouse C2C12 myoblasts, Ginkgo biloba extract shows that cytoprotective effects from OS induced by alcohol depend on the transcriptional upregulation of HO-1 via the major mitogen-activated protein kinases/Nrf2 pathway. Furthermore, Ginkgo biloba extract produced an increase in Nrf2 and upregulation of HO-1 [196]. It could inhibit cyto-kine-induced endothelial adheriveness by inducing HO-1 expression via the activation of p38 and Nrf2 pathways. Ginkgo biloba extract might exert its anti-atherogenesis and vascular protective effects by inducing vascular HO-1 expression [197]. It could reduce leukocyte adherence to injured arteries, and enhance HO-1 expression in circulating monocytes and in blood vessels.
**Flaxseed (Linum usitatissimum)**

Flaxseed (*Linum usitatissimum*) contains plenty of omega-3 fatty acid. Therefore, flaxseed oil may prevent many diseases such as CVD, HTN, cancer, skin diseases, renal failure, rheumatoid arthritis, and multiple sclerosis [198]. Data showed that it has favorable effects on renal injury [199]. Flaxseed also prevents heavy metals-induced nephrotoxicity and OS damage [200]. It was found that flaxseed can reduce proteinuria and glomerular and tubulointerstitial lesions in obese SHR/N-cp rats [201]. It was found that flaxseed may have beneficial effects on DN by reducing the levels of the OS and increasing the antioxidant defense systems [202]. Flaxseed and Pumpkin seed mixture supplemented in diet may be helpful to prevent DM and its complications in diabetic rats [203].

Flax seed, walnuts, and fish oil contain omega 3. Omega-3 fatty acids, such as α-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid, are polyunsaturated fatty acids that have anti-inflammatory and antioxidant activity. Omega-3 has antithrombotic, antihyperlipidemic, antiatherogenic, and anti-inflammatory actions [204,205]. Omega-3 can slow disease progression in human and experimental DN. It was suggested that omega-3 can ameliorate glomerular lesions by the inhibition of thromboxan A2 and B, prostaglandin E, and prostaglandin I, activating protein-1, MCP-1, and mitogen-activated protein kinase/extracellular signal-regulated kinase signaling [205,206]. The omega-3 polyunsaturated fatty acids docosahexaenoic acid and/or eicosapentaenoic acid protect rodents against ischemic acute renal failure, IgA- or cyclosporine A-induced nephrotoxicity, and STZ-induced type 1 and type 2 DN [207,208]. It was found that TAK-085, a concentrated formulation of omega-3 polyunsaturated fatty acids, can attenuate albuminuria and renal dysfunction in type 2 diabetic db/db mice [209]. The omega-3 polyunsaturated fatty acids protect against DN by inhibiting inflammation [210]. During tarcolumus use, it was suggested that renoprotective effects of long-chain omega-3 fatty acids derived from fish oil may be attributed to decreased production of inflammatory mediators, decreasing the generation and expression of proinflammatory cytokines, and a block of angiotensin II signaling in the kidney [211]. Another study demonstrated that omega-3 fatty acids lowered several components of OS and markers of inflammatory and fibrotic response and they attenuated tubulointerstitial fibrosis and inflammation in the remnant kidney [212].

**Cinnamon (Cinnamomum zeylanicum)**

Cinnamon is a well-known spice and it is the second most important spice used in the USA and European markets. It has antimicrobial, antioxidant, antiulcerogenic, antiobiotic, and analgesic effects [213,214]. Cinnamon is beneficial for the health of patients with type 2 diabetes [215].

The oils and extracts from *Cinnamomum zeylanicum* L. possess a powerful antioxidant activity due to the presence of phenolic and polyphenolic substances [216]. *Cinnamomum zeylanicum* demonstrated numerous beneficial effects both in vitro and in vivo as a potential therapeutic agent for DM, and it also showed beneficial effects against diabetic neuropathy and DN [217]. It reduces BSL. Furthermore, studies showed that polyphenols from cinnamon have in vitro and in vivo insulin-enhancing biological activity [218]. The volatile oil from cinnamon contains more than 98% cinnamaldehyde and that it showed a dose-dependent significant protection against alloxan-induced renal damage [219]. Cinnamon can inhibit AGE, and its procyanidin-B2 fraction ameliorates the diabetes-mediated renal malfunction in rats by reducing urinary albumin and creatinine [220].

Trans-cinnamaldehyde (cinnamaldehyde), the key flavor compound in cinnamon essential, was found to be an inducer of Nrf2 transcriptional activity. Cinnamaldehyde treatment upregulates cellular protein levels of Nrf2, GSH levels, and HO-1 and gamma-glutamyl-cysteine synthetase. Cinnamaldehyde pretreatment strongly upregulates cellular GHS levels and protected HCT116 cells against H2O2-induced genotoxicity and arsenic-induced oxidative insult in cultured human epithelial colon cells [221]. The volatile oil from cinnamon contains more than 98% cinnamaldehyde and that shows a dose-dependent, significant protection against alloxan-induced renal damage [219]. In vascular endothelial cells treated with TNF-α, cinnamaldehyde pretreatment prevented NFκB activation by inhibiting IκBα, resulting in reduced expression of VCAM-1 and ICAM-1 [222]. Cinnamaldehyde exerts its anti-inflammatory effects by blocking the degradation of the inhibitory protein IκBα, and by the induction of Nrf2-related genes, including HO-1. In addition, cinnamaldehyde upregulates Nrf2, increases ARE-luciferase activity, and upregulates thioredoxin reductase-1, another Nrf2-related gene.

**Astragalus membranaceus**

*Astragalus membranaceus* is a flowering plant in the family *Fabaceae* which is commonly used in traditional Chinese medicine. It is used to strengthen immune system and help wound healing.

It has anti-inflammatory and antioxidant activity [223,224]. A meta-analysis comprising 25 studies showed that *Astragalus* had a therapeutic effect in DN patients, such as decreasing BUN, Scr, and urine protein and improving creatinine clearance and serum albumin level [225]. A review of 13 reports focusing on animal models showed that the *Astragalus membranaceus* are effective in reducing BGL and albuminuria, in reversing the glomerular hyperfiltration state, and in ameliorating the pathological changes of early DN in rat models [226].

*Radix astragali*, the dried root of perennial herbs *Astragalus membranaceus*, was reported to upregulate c-met (a receptor tyrosine kinase) expression in human kidney fibroblasts to delay the progression of DN [227]. Two major isoflavonoids in radix astragali, calycosin and calycosin-7-O-beta-glucoside, could inhibit high glucose-induced mesangial cell early proliferation and AGES-mediated cell apoptosis [228]. Astragaloside IV, active constituent in radix astragali, inhibits human tubular epithelial cells apoptosis and reduces TGF-β1 expression probably by the inhibition of p38 MAPK pathway activation [229].

The mechanisms of *Astragalus membranaceus* action in DN are based on the reduction in the mRNA level of NFκB, and an increase in inhibitory NFκB protein mRNA expression in the renal cortex [230,231]. *Astragalus* may protect diabetic rats’ kidney by downregulation of Tie-2 (a receptor tyrosine kinase of the Tie family), a receptor for angiopoietin 1 [232]. Furthermore, it was suggested that the modulation of TGF-β/Smad signaling could be a potential mechanism to prevent DN in KK-Ay mice [233].
Vitamin C and E

Vitamin C plays a major role in the antioxidant defense system and in the apoptosis. The decrease in vitamin C was observed in patients with DN [234]. In diabetes, it was demonstrated that vitamin C depletion from tubular epithelial cells, through the competition of glucose and dehydroascorbate for a common transport mechanism, would deprive the cells of antioxidant ability and could lead to ROS accumulation [235]. Another study showed that in diabetic rats the administration of vitamin C can protect podocyte by increasing antioxidative capacity and ameliorating the renal OS [236,237]. In addition, vitamin C decreased lipid peroxidation and augmented the activities of antioxidant enzymes, SOD, CAT, and GPx and reduced albuminuria, and GBM thickness in the kidneys of diabetic rats [238]. Vitamin C decreased BUN, SCr, and urinary albumin excretion rate as well as increased creatinine clearance rate in DN rats. Furthermore, the expressions of collagen type IV were significantly downregulated in treatment groups. It was found that vitamin C protects renal lesions in DN by inhibiting expression of type IV collagen [239]. It has been shown that vitamin C increases HO-1 protein expression in a concentration- and time-dependent manner via Nrf2 activation in RAW 264.7 cells [240].

In a double-blind study, 4 weeks’ treatment with vitamin C and E in pharmacological doses lowers albuminuria in type 2 diabetic patients with micro/macroulurinuria [241]. A combination of metformin and vitamin C significantly reduced HbA1c levels in diabetic patients as compared to metformin alone [242]. Another study showed that administering vitamin C with antidiabetic drugs enhanced antioxidant defenses and reduced oxidative damage [243].

Studies showed that vitamin E and tocotrienol ameliorate SCr in diabetic animals [244,245]. In a clinical setting, oral vitamin E normalized elevated baseline creatinine clearance in type 1 diabetic patients without much effect on glycemie control in an 8-month randomized double-blind placebo-controlled trial [246]. Vitamin E reduced HbA1c levels in type 2 diabetes [247]. It was shown that vitamin E and C combination improved renal function and reduced albuminuria in patients with type 2 diabetes [241]. In 19 diabetic patients, the treatment with vitamin E decreased microalbuminuria, and it showed nephroprotective effect that was mediated by the antioxidant action and the decrease of thromboxane A2 production [248]. Tocotrienol, a member of the vitamin E family, reduced proximal tubular injury and renal LPO, increased GSH level and CAT activity and improved the index of NO²⁻/NO³⁻ generation [249]. However, vitamin E did not show a beneficial effect on diabetic complication including albuminuria [250].

At the early stage of nitrosomethylbenzylamine-induced esophageal cancer, α-tocopherol could block the initiation of carcinogenesis through suppressing the activation of NFκB signaling pathway [251]. This might be a case in DN though no study was conducted to show such effect.

Zinc

Zinc is an essential trace metal that has important physiological functions and it acts as a cofactor for many enzymes and proteins. Furthermore, it is an essential component of numerous proteins involved in the defense system against the OS. It was known that patients with DM often have zinc deficiency because of the increased urinary excretion and the restricted certain food intake [252].

Meta-analyses showed that zinc supplementation has a favorable effect on glycemic control in diabetic patients [253]. Furthermore, zinc supplementation in diabetic mice and rats significantly reduce diabetes-induced renal damage [254]. In STZ-induced diabetic rats, zinc supplementation can attenuate diabetes-induced renal pathological changes likely through prevention of hyperglycemia-induced CTGF expression by zinc-induced cardiac metallothionein in renal tubular cells [255]. It was found also that supplementation of zinc improved the effectiveness of hypoglycemic agents and may be beneficial in decreasing BSL, triglyceride, urinary albumin excretion, and inflammation in type 2 diabetic nephropathy patients [256]. A recent study showed that zinc has a protective effect against diabetic damage through stimulation of metallothionein synthesis, a potent antioxidant, and regulation of the OS [255].

Zinc upregulates Nrf2 function via activating Akt-mediated inhibition of Fyn function, Nrf2 nuclear exporter. Treatment of diabetic mice with TPEN, zinc chelator, decreased renal zinc level and Nrf2 expression and transcription, with an exacerbation of renal oxidative damage, inflammation and fibrosis. These results suggest that zinc is essential for Nrf2 expression and transcription function [257]. Zinc has antioxidant properties that may be mediated by the upregulation of Nrf2 [258]. Zinc treatment of diabetic mice for 3 months significantly upregulated the expression and function of Nrf2 and the expression of metallothionein [259].

Oats

Oats are a source of several natural antioxidants [260]. Oat downregulates the TGF-β1 and receptors for AGE expression at mRNA levels and it can suppress DN in rats and may slow down renal fibrosis by the disruption of the detrimental receptors for AGE-NFκB axis [261]. After 12 weeks of diabetes in rats, oat treatment reduced BGL, HbA1c, and OS markers, and normalized NFκB activation and TNF-α expression. Furthermore, it reduced VEGF in the diabetic retina by 43% (P < 0.001). Oat β-D-glucan had a strong hypoglycemic effect in streptozotocin-nicotinamide-induced mice [262]. Meta-analysis of four articles dealing with 350 type 2 DM patients showed that the administrated oat β-D-glucan from 2.5 to 3.5 g/day for 3–8 weeks caused significantly lowered concentrations in BSL and HbA1c [263]. Avenanthramides, unique group of alkaloids in oat that contain a phenolic group, could significantly increase HO-1 expression in both a dose- and time-dependent manner which was mediated by Nrf2 translocation in HK-2 cells [264]. They have antioxidant and anti-inflammatory activities.

Lycopus lucidus Turcz

*Lycopus lucidus Turcz* has been widely used as a traditional oriental medicine and it contains antioxidant phenol. It was shown that *Lycopus* can inhibit renal fibrosis by blocking TGF-β signaling pathway and it has a protective effect on renal damage of STZ-induced DN in rats [265]. In primary cultured human umbilical vein endothelial cells, it was found that high glucose induces H₂O₂ production and ROS formation; however, pretreatment with aqueous extract of the leaves of *L. lucidus Turcz* inhibited the high
glucose-induced ROS formation. In addition, the aqueous extract suppressed the translocation and promoter transcriptional activity of NFκB that was increased by high glucose [266]. Furthermore, administration of lycopene decreased the levels of MDA content and expression of CTGF, increased protein kinase (Akt/PKB) phosphorylation and SOD activity in diabetic renal tissues in rats. It was proposed that lycopene prevents development of DN and ameliorates renal function through improving OS and regulating p-Akt and CTGF [267].

Lycopus suppressed rhTGF-β1-induced Smad2 and ERK1/2 activation, downregulated the expression of TGF-βRI, TGF-βRII, Smad4 and Smad7 in SV40 MES13 cells [268]. In STZ-induced DN rat’s model, Lycopus inhibited Smad2 phosphorylation, reduced mRNA level of TGF-β1, ameliorated expansion of the mesangial area and decreased SCR, BUN and reduced the SOD activity. Therefore, it was suggested that by blocking TGF-β signaling pathway, Lycopus is a novel inhibitor of renal fibrosis [268].

**Milk thistle**

Milk thistle has been known as a remedy for a variety of disorders. *Silybum marianum*, the Latin term for the plant and its seeds, contains flavonolignans and silymarin is a dry mixture of these compounds. Silymarin has antioxidant and anti-inflammatory effects. It reduces urinary excretion of albumin, TNF-α, and MDA in patients with DN [269]. Silybin, the active constituent of silymarin, was tested on cultures of mouse podocytes and in the OVE26 mouse, a model of type 1 DM and DN [270]. The results showed a protective effect of silybin against high glucose-induced podocyte injury. Another study showed that silymarin lowers levels of BSL, HbA1c, urine volume, SCr, serum uric acid, and urine albumin, and the histopathological studies strongly supported the protective effect of silymarin [271]. In diabetic rats, silibinin decreased levels of HbA1c, serum triglyceride, cholesterol, BGL, and the apoptosis ratio of pancreatic β-cells. Interestingly, silibinin reversed STZ-induced downregulation of Sirt-1 expression. Silibinin may reverse hyperglycemia and repair damaged pancreatic β-cells by promoting Sirt-1 expression [272].

In a randomized, triple-blinded, placebo-controlled clinical trial, 40 type 2 diabetes patients were treated with silymarin supplementation which increased SOD, GPx activity and total antioxidant capacity, reduced CRP levels, and decreased MDA concentration [273]. In another randomized, double-blind, placebo-controlled, 2-arm parallel trial, 60 patients with type 2 diabetes with macroaluminuria despite treatment with the maximum dose of a renin–angiotensin system inhibitor were randomly assigned to two equal groups to receive three 140-mg tablets of silymarin or three tablets of placebo daily for 3 months. The results showed that the urinary albumin–creatinine ratio, urinary levels of TNF-α, and urinary and serum levels of MDA decreased significantly in the silymarin compared with the placebo group [269]. It increases CAT, albumin, and hemoglobin in ESRD [274]. Silibinin decreased the NADPH oxidase, iNOS and NFκB over expression by arsenic and upregulated the Nrf2 expression in the renal tissue [275]. Furthermore, it caused a decrease in lipid peroxidation and an increase in the level of renal antioxidant defense system.

**Conclusion**

This review shows that many natural products have antioxidant and anti-inflammatory properties, and they have potential therapeutic properties in DM and DN. Data showed that the natural substances or their active ingredients modulate Keap1/Nrf2/ARE pathway and NFκB. They upregulate Keap1/Nrf2/ARE pathway and stimulate antioxidant status of living cells and tissue. And by downregulating NFκB, the natural substances decrease productions and activities of chemokines, growth factors, cytokines, and adhesion molecules, and ameliorate inflammatory response. Most of the studies, preclinical as well as clinical, included the introduction of herbs, plants or their active ingredient after the establishment of DM and DN. The results showed the obvious therapeutic outcome in preclinical studies that used whole natural substances or the active ingredients, but there is little evidence in clinical settings that taking single antioxidant has a therapeutic effect. There is a lack of randomized controlled trials using whole natural products or combined antioxidants in the management of DN. Furthermore, there was no consistency and subsequent studies following a positive result in animals’ experiments. Also the effective doses of the plants or their derivatives or extracts are still to be determined. Therefore, it is suggested that the use of combined antioxidants or whole natural plant products might demonstrate the expected beneficial results in patients with DM and DN.

A finding of new successful therapeutic intervention for the management of DN is demanded. However, prevention of DM complication such as DN is very important. The natural substances might have strong preventive properties. Such data exploring this potential property are lacking in preclinical and clinical settings. Therefore, studies on using natural substances in the prevention of DM complications and DN are important. We believe that using natural substances in prediabetic status of disease and before development of DN will explore more beneficial outcome in clinical trials.

Since biological systems always are under oxidative and inflammatory insults due to the change in lifestyle and pollution, antioxidant and anti-inflammatory pathways play a major role in keeping healthy environments for cells and organs. Therefore, using natural substances augments antioxidants and anti-inflammatory system before establishment or appearance of diseases. It is important to stress that the future work should include using natural substances as supplementary interventions besides standard therapeutic interventions, using natural substances before the appearance of disease or complication such as DN, and focusing on the development of new ingredients that work directly in Keap1/Nrf2/ARE/NFκB pathways.

**Disclaimer statement**

No potential conflict of interest was reported by the authors.

**Funding**

This work was supported by None.

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