



Plant natural products: A lead for nephroprotection

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Abstract



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An extremely dangerous side effect of type I and type II diabetes is diabetic nephropathy (DN). From the early microproteinuria to end-stage renal failure, it progresses. About one in three diabetics in the US suffer from diabetic nephropathy. Chronic hyperglycemia is the primary cause of diabetic ketoacidosis. Hyperglycemia (HG) has the potential to cause humoral mediators and cytokines to be produced by both resident and non-resident renal cells. These substances may interfere with cell growth, alter renal cell and tissue phenotype and function, interact with proteins, produce advanced glycation end products (AGEs), damage tubules and glomeruli, and ultimately cause kidney disease. Poor blood glucose management is thus a significant risk factor for the onset of DN. An alternate course of treatment for DN may use extracts from herbal remedies. Medicinal plants' bioactive components stop DN from progressing. Attention has to be paid to the role that traditional herbs and medications play in the treatment of diabetic nephropathy, particularly in India where several fruits and herbs are believed to provide health benefits. Natural compounds influence the KEAP1/Nrf2/ARE and NFB pathways in addition to having antioxidant and anti-inflammatory properties. The efficacy of entire herbs, plants, or seeds, together with their active components, in treating diabetic nephropathy was investigated in preclinical research. Natural compounds are biologically active substances that come from natural sources and are beneficial for treating specific illnesses. Numerous natural substances, such as glycosides, polysaccharides, terpenoids, alkaloids, flavonoids, and polyphenols, have been shown to enhance DN. The exorbitant expenses associated with contemporary medications suggest that other approaches are necessary for improved DN treatment. Future research on herbal remedies may provide a natural key to open a pharmacy for diabetologists.

Keywords: Diabetic nephropathy; nephroprotective plant; herbal compounds, bioactive compound.

Introduction

Globally, there are around 0.537 billion individuals (20–79 years old) who have diabetes mellitus (DM), and that number is expected to rise to 0.643 billion by 2030 and 0.783 billion by 2045, according to the 2021 International Diabetes Federation (IDF) Diabetes Atlas (10th edition) ¹. As a result, DM has grown to be a significant global public health concern. Prolonged hyperglycemia can cause a serious microvasculopathy that affects the kidney, heart, eyes, nerves, teeth, and other body parts. Diabetic kidney disease (DKD) is a frequent consequence of diabetes. According to clinical study, 20–40% of DM patients acquired DKD, and 80% of those who developed end-stage renal disease did so as a result of hyperglycemia and hypertension interacting ^{2,3}.

One of the most prevalent and dangerous side effects of diabetes mellitus is diabetic nephropathy (DN), which also contributes significantly to end-stage renal disease (ESRD) and chronic kidney disease (CKD) 4–7. Blood pressure, age, genetic background, and blood

glucose levels of patients are all strongly associated with the development and incidence of diabetic ketoacidosis (DN). When macroalbuminuria develops, it does not go away like it does in other renal disorders, making it a leading cause of mortality for diabetic people ⁸. DN patients who are nearing the end of their renal failure are dependent on kidney transplantation and dialysis. As a result, DN prevention and treatment have gained international attention. The primary distinction between the sexes, aside from behavioral patterns, social roles, and psychological cognition, is sex hormones. Sex hormones fluctuate a lot during life, especially in women. These fluctuations occur during pregnancy, adolescence, sexual maturity, perimenopause, and postmenopause. Nonetheless, the fundamental biochemical process via which sex hormones control DN remains incompletely understood. Furthermore, given that sex hormone imbalances contribute to the development of diabetic kidney disease (DN), hormone treatment in diabetic patients may somewhat reduce the damage caused by diabetes

to the kidneys and represents a potentially useful therapeutic approach for DN patients ⁹.

When microalbuminuria occurs, the glomerular basement membrane thickens and a buildup of matrix material occurs in the mesangium. These are the pathological first alterations observed. Then, distinctive nodules form, glomerulosclerosis intensifies (producing high levels of proteinuria), and eventually, glomeruli are gradually eliminated, leading to compromised renal function. One significant predictor of the likelihood of developing diabetic nephropathy is microalbuminuria ¹⁰. An earlier diagnosis of diabetic nephropathy is far more likely to be the cause of steadily rising albuminuria and hypertension. The pathophysiology of diabetic nephropathy (DN) is very intricate and mainly unclear, as it involves the direct impact of elevated extracellular glucose on tubular, glomerular, interstitial, and vascular cells. Consequently, there are poor therapy results for DN. ¹¹ Conventional medicine appears to be ineffectual in stopping the progression of DN to end-stage renal disease (ESRD) and DN-related mortality, even with strict blood pressure and sugar management. DN can also be treated with insulin and antidiabetic medications, such as insulin sensitizers, biguanides, thiazolidinediones, α -glycosidase inhibitors, agonists of glucagon-like peptide, dipeptidyl peptidase-4 inhibitors, incretin-based medications, and sodium-glucose cotransporter inhibitors. Usually, when these medications are given to patients, their GFR is taken into consideration ¹². This tactic, meanwhile, just delays the disease's advancement. As a result, the development of new drugs that address DN disease, such as inflammation and oxidative stress, has taken center stage ¹³. Field surveys have been the mainstay of recent attempts to examine the use of a number of medicinal plants as a treatment for various illnesses, including diabetes. The work's objective is to present an overview of the research on using medicinal plants to treat DN.

Medicinal Plants and Diabetic Nephropathy

Numerous chemical substances, or phytochemicals, with a range of pharmacological actions are found in medicinal plants ¹⁴. An increasing body of research is supporting the use of phytochemicals and their bioactive components as natural modifying agents in the treatment of several illnesses, including DN ¹⁵. Alkaloids, phenolics, flavonoids, terpenoids, and other key phytochemical substances with health benefits are found in medicinal plants ¹⁶. These drugs have a major part in delaying the progression of DN. Recent medical research has shown a great deal of interest in medicinal plants and natural treatments for diabetic nephropathy because of their potential to treat a wide range of illnesses. Over the past 20 years, the pharmaceutical drug business has made significant advancements, yet the quantity of pharmaceuticals. Because they may treat a wide range of illnesses, natural medicines have drawn a lot of attention in medical study in recent years. Even with the previous twenty years, the pharmaceutical drug business has made significant strides, but there are still few drugs that can delay the advancement of diabetic nephropathy. The popularity of herbal

remedies can be attributed to its affordability, ease of use, low occurrence of adverse effects, and high tolerance. The popularity of herbal remedies can be attributed to its affordability, ease of use, low occurrence of adverse effects, and high tolerance.

Ginger

The most widely used family of herbal supplements worldwide is Zingiberaceae, also referred to as *Zingiber officinale*. Although it is often used in cooking, patients seek therapy from it for a range of diseases. More than 50 antioxidants have been identified from the rhizomes of ginger, which exhibits antioxidant activity ¹⁷. In addition, ginger has analgesic, diuretic, anti-inflammatory, anticancer, ant clotting, and antihyperglycemic properties. It lowers blood glucose levels (BGL) in rats with DM caused by STZ ¹⁸. In diabetic rats, the combination of honey and ginger decreased SOD and CAT activity, decreased MDA levels, and boosted GSH levels and the GSH/GSSG ratio back to normal ¹⁹. Ginger interacts with the 5-HT₃ receptor to improve insulin release and sensitivity ²⁰. There are around 115 components in both fresh and dried ginger, according to various analytical techniques. Gingerol is present in high concentrations in fresh ginger. Ginger contains many terpene components, such as β -bisabolene, zingiberene, α -farnesene, β -sesquiphellandrene, and α -curcumene. These components are also known to be the primary active ingredients in ginger essential oil ²¹. Plants have a wide range of therapeutic applications, including as anti-inflammatory, nephroprotective, hepatoprotective, anticancer, antioxidant, and analgesic effects ²²⁻²⁴. Ginger is suggested in Ayurveda for its traditional benefits, which include heart protection, hunger stimulation, anti-asthmatic, and relief from constipation, pain relief, and normalizing blood circulation ²⁵. The most pungent ingredient in ginger, gingerol (100 mg/kg bw), dramatically reduced blood glucose in db/db type 2 diabetic mice as well as lipids and fatty acid ²⁶. According to a different investigation, gingerol restored the plasma insulin level and had a protective impact on pancreatic β -cells. By influencing NF κ B activation, ARE-target gene expression, and KEAP1 interaction, ginger and its derivatives may reduce inflammatory processes in DN and boost antioxidants ²⁷.

An intraperitoneal injection of streptozotocin was used to produce diabetes in a rat used in an experiment by Al Hroob et al., ²⁸. For 45 days, the treatment consisted of 400 or 800 mg/kg/day of *Z. officinale* extract taken orally. Following treatment, a biomarker analysis revealed that the diabetic animal had increased levels of blood urea, nitrogen urea, urine albumin, and serum creatinine, whereas the *Z. officinale*-treated animals showed the opposite effect. The rats who were given the extract had much lower blood glucose and fat levels; however, the rats that were given diabetes showed improvement in both areas. Results from histology, which show that *Z. officinale* therapy lessens histological alterations in the kidneys of diabetic rats, corroborate this conclusion. In chronic hyperglycemia-induced diabetic rats, there was a

notable increase in pro-inflammatory cytokines, Cytochrome C, malondialdehyde, and protein carbonyl, which were reversed by *Z. officinale* therapy²⁹. In light of the study's conclusions, *Z. officinale* rhizome extract protects against diabetes-related kidney impairment by reducing inflammation, oxidative stress, and apoptosis. In *Z. officinalis* Roscoe rhizome, Kato et al.³⁰ investigated the aldose reductase inhibitory (ARI) activity of several phytoconstituents and found that they exhibited good inhibitory efficacy. On the other hand, following a brief time of hyperglycemia, the plant's protective effect on diabetic kidneys was characterized by the avoidance of structural abnormalities induced by raised free radicals. Additionally, it assisted in shielding the kidneys from endothelial dysfunction brought on by membrane glycation.

Garlic

Allium sativum, a synonym for garlic, is a member of the Amaryllidaceae family. Garlic is regarded as an important plant because of its wide variety of use as a traditional spice and a crucial component in folk medicine prescriptions. Much has been discovered about the diverse photochemical properties of garlic^{31, 32}. Garlic has been shown in several recent research to have beneficial effects on cancer and cardiovascular disease^{33, 34}. It has anti-inflammatory, immunomodulatory, antiviral, antioxidant, cardio-protective, anti-diabetic, reno-protective, and anti-hypertensive properties^{35, 36}.

Garlic demonstrated blood pressure stabilization, renal clearance function³⁷, and normalization or attenuation of kidney and plasma levels of ACE-1 and angiotensinogen II in diabetic mice. The renal and hepatic tissues of diabetic rats showed a considerable rise in RAGE, which was associated with mesangial cells in glomeruli showing indications of glomerulosclerosis, mesangial nodule development, and mesangial expansion. Garlic significantly reduced RAGE throughout renal and hepatic regions³⁸. 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 glomerulosclerosis³⁹. After three weeks of therapy, both hypertensive and diabetic rats' blood antioxidant levels rose when they were given garlic. It brought down both systolic and BGL blood pressure⁴⁰. Another study shown that by dramatically reducing BGL, insulin, total triacylglycerol, total cholesterol, and creatinine clearance in rats, fresh garlic homogenate effectively reduced STZ-induced DN. Albumin and acetyl-beta-D-glucosaminidase excretions in the urine were decreased. Furthermore, there was a significant increase in the GSH content of the kidney homogenates. It improved nitrite excretion through the urine⁴¹.

The most prevalent thiol-reactive organosulfur chemical produced by *Allium sativum* in reaction to tissue injury is allicin, also known as diallyl thiosulfinate⁴². In diabetic nerve cell models, allicin exhibits its renoprotective properties by reducing oxidative stress and renal inflammation while also improving the

morphological changes of the kidney caused by diabetes^{43, 44}. Additionally, it inhibits the OS-hypoxiafibrosis pathway, HIF-1, and CTGF to slow down the progression of nephropathy. physiologic changes to the kidney^{45, 44} and the suppression of renal inflammation and oxidative stress⁴³. Additionally, it inhibits the OS-hypoxia fibrosis pathway, HIF-1, and CTGF to slow down the progression of nephropathy⁴⁶.

An antioxidant found in garlic is called S-allylcysteine. Research findings indicate that S-allylcysteine (25 mg/kg) can avert renal damage caused by cisplatin and mitigate its effects on Nrf2 levels, PKC β 2, p47 (phox) and gp91 (phox) expression in the renal cortex and OS, as well as CAT, GPx, and glutathione reductase (GSR) activity in the proximal and distal tubules⁴⁷. Recently, it was shown that S-allylcysteine activates Nrf2 factor in cerebral cortex⁴⁸. The most potent antioxidant in garlic oil is diallyl trisulfide, which is a sulfur-containing molecule. The research showed that diallyl trisulfide inhibits ROS-mediated apoptosis caused by hyperglycemia by upregulating the PI3K/Akt/Nrf2 pathway, which causes Nrf2 to be activated in cardiomyocytes exposed to high glucose⁴⁹.

Cinnamon

Being the second most popular spice in the US and Europe, cinnamon is a well-known spice. Its effects include those of analgesic, antidiabetic, antibacterial, antioxidant, and antiulcerogenic^{50, 51}. Patients suffering from type 2 diabetes might benefit from cinnamon's health benefits⁵². In addition to being used in cooking, it is suggested as a therapeutic for the treatment of respiratory, gynecological, and digestive diseases. The leaves, flowers, fruits, bark, and roots of the cinnamon tree are among its many edible and therapeutic aspects. The diverse chemical compositions of the volatile oils collected from the bark, leaves, and roots suggest that the pharmacological effects of these oils may also differ. This plant contains active ingredients such as camphor, eugenol, and cinnamon aldehyde. The principal applications of cinnamon include the treatment of cancer, inflammation, heart disease, prevention of migraines, Alzheimer's disease, cardio-protective benefits, and antimicrobial properties^{53, 54}.

Due to its antioxidant and anti-diabetic properties, cinnamon oil has been shown to mitigate the symptoms of early-stage diabetic nephropathy as compared to alloxan (150 mg/kg I.P.)-induced diabetic nephropathy. Through the elimination of hyaline casts, the reduction of tubular dilatations, and the reduction of glomerular enlargement, histological investigations of the kidney demonstrated the protective impact of cinnamon oil. The findings showed that more than 98% of the volatile oil extracted from cinnamon was cinnamaldehyde, and that it provides dose-dependently large protection against kidney damage caused by alloxan. At a dosage of 20 mg/kg, the greatest reduction in fasting blood glucose has been attained⁵⁵.

In vitro, cinnamon and its procyanidin-B2 (PCB2) enriched fraction effectively suppress the production of AGE in diabetic nephropathic rats. For a

duration of 12 weeks, rats with streptozotocin-induced diabetes were administered either 3% cinnamon or 0.002% PCB-fraction. Biochemical examination of the participants' blood and urine was done at the conclusion of the experiment. The renal biomarkers were evaluated using immunohistochemistry, immunoblotting, and reverse transcription polymerase chain reaction (RT-PCR) as measures of renal function. Suppression of glycation-mediated red blood cells-immunoglobulin G (RBC-IgG) cross-links and HbA1c augmentation in cinnamon and PCB2 treated diabetic mice was observed. It also reduced the significantly advanced glycated end product, N-carboxymethyl lysine (CML), from accumulating in diabetic kidneys. Treatment with cinnamon inhibited the advanced glycation end product mediated decrease of the expression of glomerular podocyte proteins, including nephrin and podocin. Treatment with cinnamon and the PCB2 fraction reduced urinary albumin and creatinine, thus ameliorating renal malfunction. In conclusion, cinnamon reduced AGE formation in diabetic rat kidneys and improved DN pathogenesis. On the other hand, the plant's protective impact on the diabetic kidney was demonstrated by its ability to prevent nephrin expression deficiency. Nephrin is thought to be an instrument for glomerular function. It was shown that cinnamon inhibited the kidney receptor for advanced glycation end products (AGE-RAGE), activated monocyte chemo attractant protein-1, and protein kinase C- α (PKC- α). This modulated the production of podocin and nephrin, which are the slit diaphragm proteins⁵⁶. The conservation of nephrin expression in clinical settings such as DN has great potential for the treatment of a range of renal diseases in which nephrin loss is a risk factor. This is because nephrin expression is considered a critical indicator of glomerular function. The study by Muthenna P et al. suggests that 57 RAGE may be involved in controlling nephrin expression. The conservation of nephrin expression in clinical settings such as DN has great potential for the treatment of a range of renal diseases in which nephrin loss is a risk factor. This is because nephrin expression is considered a critical indicator of glomerular function. The study by Muthenna P et al. suggests that 57 RAGE may be involved in controlling nephrin expression.

Cinnamomum zeylanicum L. oils and extracts have potent antioxidant qualities due to the phenolic and polyphenolic components they contain. 58%. As a potential treatment for diabetes mellitus, *Cinnamomum zeylanicum* exhibited many positive benefits in vitro and in animal. It also showed benefits against diabetic neuropathy and DN⁵⁹. Additionally, research revealed that cinnamon's polyphenols have the biological ability to enhance insulin both in vitro and in vivo⁶⁰. More than 98% of the volatile oil derived from cinnamon is known to include cinnamonaldehyde, and studies have shown that it significantly protects against alloxan-induced kidney damage at different doses⁶¹. The procyanidin-B2 portion of cinnamon can suppress AGE and, in animals, reduce urine albumin and creatinine to improve diabetes-induced renal dysfunction⁶². An inducer of Nrf2 transcriptional

activity was discovered to be trans-cinnamic aldehyde, also known as cinnamonaldehyde, the primary flavoring of cinnamon essential. After being exposed to cinnamon aldehyde, cellular protein levels of Nrf2, GSH, HO-1, and gamma-glutamyl-cysteine synthetase are increased. Pretreatment with cinnamon aldehyde significantly increases the levels of GSH within cells and shields HCT116 cells from the oxidative damage and genotoxicity caused by H₂O₂ in cultivated human epithelial colon cells⁶³. With almost 98% cinnamaldehyde, the volatile oil from cinnamon provides considerable, dose-dependent protection against kidney damage caused by alloxan⁶⁴. Cinnamaldehyde pretreatment inhibited I κ B α , preventing NF κ B activation in vascular endothelial cells treated with TNF- α , leading to decreased expression of VCAM-1 and ICAM-1⁶⁵. By preventing the inhibitory protein I κ B α from degrading and by inducing Nrf2-related genes like HO-1, cinnamonaldehyde reduces inflammation. Moreover, cinnamon aldehyde stimulates Nrf2, upregulates ARE-luciferase activity, and stimulates another Nrf2-related gene called thioredoxin reductase-1.

Turmeric

Turmeric is a rhizomatous herbaceous perennial plant related to ginger that has garnered interest in science and culinary circles⁶⁶. The majority of studies come to the conclusion that curcumin, the active ingredient in turmeric, is primarily responsible for its therapeutic properties. It is mostly grown in nations like China and India, and it is primarily grown in tropical and subtropical regions of the world. The primary naturally occurring polyphenol in the rhizome of *Curcuma longa*, or turmeric, is known as diferuloyl methane and is also referred to as curcumin. Treatment for diabetic wounds, rheumatism, anti-cancer, anti-hyperlipidemia, inflammatory treatment, antimicrobial, anti-fertility, anti-venom, liver toxicity, renal injury, skin disease, and anti-platelets are only a few of its many medical qualities. For ages, Asian nations have utilized *Curcuma longa* as a therapeutic herb due to its antibacterial, anti-inflammatory, anti-mutagenic, antioxidant, and anticancer properties⁶⁷⁻⁷⁰. A study on curcumin was looked into by Lu M. et al.,⁷¹ and it shown good DN inhibitory effect. By suppressing the NLR family pyrin domain containing three inflammasome signaling (NLRP3), curcumin improves diabetic neuropathic pain. By reducing NLRP3 inflammasome signaling in lipopolysaccharide-induced septic shock, curcumin has been shown to have renoprotective action in rats with streptozotocin-induced diabetic nephropathy. Curcumin has been demonstrated to decrease NLRP3 inflammasome activation and IL-1 β (Interleukins-1 β) production. It has also been demonstrated that DN is associated with both NLRP3 inflammasomes and IL-1 β , a pro-inflammatory cytokine. Further evidence has indicated that the NLRP3 inflammasome is the primary regulator of inflammation and tissue damage in both acute and chronic renal diseases⁷². Curcumin medication is thought to prevent DN by reducing the level of gene expression, according to a different study on the drug by Sun LN et al.,⁷³.

Reversing caveolin-1 Tyr 14 phosphorylation, which affected Toll-like receptor-4 activation, is how this activity is carried out ⁷⁴. The primary emphasis of the study was on how curcumin administration affected DN in db/db (diabetes) mice and how it affected HK-2 cells. According to study results, administering curcumin to db/db mice results in reduced renal hypertrophy, enhanced renal function, and lessened renal histological changes. According to a curcumin study's RT-PCR results, curcumin may slow the advancement of DN by lessening the NLRP3 inflammasome's activation ⁷⁵.

Coriander

Coriandrum sativum L., also referred to as coriander, is a member of the Apiaceae family. Alkaloids, flavones, tannins, resins, sugars, anthraquinones, and fixed oil sterols are the principal phytoconstituents found in coriander ^{76, 77}. Coriander fruit is primarily composed of fatty oil and essential oil. The fatty acids that are found in coriander include linoleic acid (18:2), oleic acid (18:1), petroselinic acid (cis-6-octadecenoic acid, 18:1), and palmitic acid (16:0). Along with being low in cholesterol and saturated fat and high in zinc, thiamine, and dietary fiber, coriander is a good source of vitamins, minerals, and iron, just like other leafy green vegetables ^{78, 89}. Kajal A., et al., ⁸⁰ gave *Coriandrum sativum* doses of 100, 200, 300, and 400/kg of petroleum ether extract (CPE) for 45 days in order to conduct a study on the plant. The levels of biochemical markers like creatinine, lipids, and serum glucose decreased. Additional characteristics that were considerably reduced in the kidneys included the production of advanced glycation end products, lipid peroxidation, and thiobarbituric acid reactive species. Understanding the mechanism involved using a molecular docking method. Consequently, these findings suggested that coriander's active ingredients may slow the development of diabetic nephropathy further.

Fenugreek

One of the earliest plants in India and Northern Africa, it is also known by the common name *Trigonella foenum graecum* L. It is a member of the Fabaceae family. Its leaves and seeds, which have therapeutic properties, are ground into powders and extracted. It has been incorporated into daily diets for the general public, utilized to make bread, and supplemented with wheat and maize flour ^{81, 82}. Extracts from fenugreek seeds have been shown to have anti-diabetic, hypocholesterolemic, and antioxidant qualities in numerous pre-clinical and clinical investigations. It has been shown that fenugreek seed powder (FSP) has antioxidant enzymes because of its capacity to repair oxidative damage caused by oxygen-free radicals. This suggests that FSP may have antioxidant qualities. Reduced ROS generation and antioxidant enzyme activation have resulted in decreased AGE formation and activated NF-kB. In diabetic rats treated with FSP, there is a marked decrease in IL-6 and inflammation, which may be linked to an increase in antioxidant enzymes ⁸³. Glutathione (GSH) was found to be significantly elevated and malondialdehyde (MDA) was found to be significantly reduced in the renal tissue of

diabetic rats treated with fructose syrup. Additionally, catalase and SOD levels rise in response to FSP therapy. After FSP administration, IL-6 and inflammation levels in diabetic rats are significantly lower, indicating that FSP may have antioxidant or anti-inflammatory properties. The expression of genes that NF-kB regulates, such IL-6, is lowered when NF-kB is blocked. In the diabetic untreated group, there were elevations in blood glucose levels, ROS, interleukin-6, and DN. Histopathology results validated the above results. According to the findings acquired, FSP might shield the kidneys from oxidative and inflammatory damage ⁸⁵.

Red Sandal Wood

Red Sandal Wood *Pterocarpus santalinus*, a member of the Fabaceae family, was used to treat patients whose blood sugar levels were significantly lower and their glucose tolerance tests improved. Red sandalwood extract decreased MDA levels, demonstrating its antioxidant properties. A thiobarbituric acid reactive material was used to measure the extract's effects on antioxidants, catalase superoxide dismutase, and lipid peroxidase production. Serum creatinine and urine albumin were reduced after the treatment. Following treatment, there was a decrease in serum creatinine and urine albumin. The results were corroborated by a histology analysis of the kidney for diabetic rats, which showed that after 16 weeks of combination therapy, the animals' lipid profiles decreased and their high density lipoprotein cholesterol increased ^{87, 88}.

Guava

One of the more well-liked tropical fruits, guava (*Psidium guajava*) is high in fiber, vitamin C, and phenolic compounds. Gallic acid and epicatechin are two of the primary phenolic compounds found in *Psidium cattleianum* Sabine (Myrtaceae) that are rich in vitamin C. It was regarded as an excellent natural antioxidant source ⁸⁹. *Originating in America*, *Psidium guajava* is a tiny, evergreen tree or shrub. Myricetin, ferulic, coumaric, and caffeic acids are all included in the extract detailed by Gutiérrez et al., ⁹⁰. These included its usage for diabetes, cough, inflammation, heart problems, pain, and liver illnesses. It also had an affinity for free radicals and was harmful to normal cells. Through its anti-oxidative, anti-inflammatory, and anti-glycative properties, this fruit extract can protect the kidney against the progression of diabetes by reserving GSH content, maintaining CTA and GPx activity, and lowering ROS, IL-6, TNF- α , and IL-1 β levels in the kidney in a dose-dependent manner ⁹¹. Significant antioxidant and free radical scavenging properties are present in *Psidium guajava* extract ⁹². In diabetic rats, total triterpenoids from *Psidium guajava* leaves raise the insulin sensitivity index, lower the BGL level, and shield renal lesions ⁹³. Moreover, it reduced aldose reductase renal activity. In STZ-induced diabetic rats, *Psidium guajava* leaves showed improvements in kidney structural damages and lowered levels of BUN ⁹³.

Lin C.Y., et al., ⁹⁴ measured the concentrations of phenolic acid and flavonoids in guava fruit extracts to

evaluate the renal protective effects of guava aqueous extract (GAE) and ethanol extract (GEE) in diabetic mice. Higher concentrations of myricetin, caffeic acid, and quercetin were found in GAE, and the study's findings showed that GAE lowered the kidney's levels of IL-1, reactive oxygen species, interleukin (IL)-6, and tumor necrosis factor. The kidneys' levels of fructose, N-(carboxymethyl) lysine, and pentosidine were lowered by 2% GAE and GEE treatments. These results show that its anti-oxidative qualities provide kidney protective effect.

Green Tea

Green tea, sometimes referred to as *Camellia sinensis* and a member of the Theaceae family, has been used for centuries and has a variety of medicinal uses. Anti-inflammatory, anti-arthritic, anti-bacterial, anti-viral, anti-angiogenic, anti-oxidative, neuroprotective, and anti-hyperlipidemic qualities are among its many attributes⁹⁵⁻¹⁰⁰. It shields the kidneys from intravenous contrast, cyclosporine, and gentamycin. Green tea flavonoids possess anti-oxidative and anti-inflammatory characteristics. This is because polyphenols and flavonoids are present, which shield the kidney from renal oxidative stress brought on by diabetes and hypertension. Following treatment with green tea polyphenol, albuminuria had decreased in diabetic individuals receiving the maximum recommended dose of rennin-angiotensin system inhibitor. This action might result from the wingless-related integration site (WNT) pathway being activated, which inhibits podocyte death. The study's findings validate that, in a clinical setting, green tea can decrease podocyte apoptosis and activate the WNT pathway, which can both lessen albuminuria in DN¹⁰¹. Mozaffari K., et al.¹⁰² examined the lowering effect of sour tea and green tea on blood pressure in patients with type II diabetes in a randomized clinical trial involving 100 people with mild hypertension. They discovered that patients who were less hypertensive and drank three cups of sour and green tea every day for four weeks had significantly lower systolic and diastolic blood pressure. Consequently, our research implies that giving green tea to diabetic hypertensive people may shield their kidneys.

Clove

Due to its antibacterial and antioxidant qualities, clove, also known as *Syzygium aromaticum*, is a rare spice that is a member of the Mirtaceae family and has been used for ages in medicine and food preservation. It is filled with a variety of volatile oils. Clove contains phenolic acids, including ellagic, salicylic, ferulic, and caffeic acids. Additionally, it has flavonoids including kaempferol and quercetin (figure1). Due to its antibacterial and antioxidant qualities, clove, also known as *Syzygium aromaticum*, is a rare spice that is a member of the Mirtaceae family and has been used for ages in medicine and food preservation. It is filled with a variety of volatile oils. Clove contains phenolic acids, including ellagic, salicylic, ferulic, and caffeic acids. Additionally, it has flavonoids including kaempferol and quercetin¹⁰³⁻¹⁰⁵. A

study on the assessment of renal function in streptozotocin-induced diabetic albino rats was examined by Joshua et al.¹⁰⁶. Cloves have the antioxidant quality and their active ingredient, eugenol, decreases DN substantially. According to this study, either taken on its own or in conjunction with metformin, clove extract dramatically lowered blood glucose levels and their associated consequences, such as nephropathy, or kidney disease. Additionally, this investigation revealed a noteworthy variation in creatinine and urea. The intended outcome was achieved when the kidney parameters in the treatment-administered group were considerably lower than those in the positive diabetic control group ($p < 0.0001$). Additionally, compared to diabetic rats, clove-treated diabetic rats showed a 21% decrease in necrotic cells in their bodies. This work is consistent with previous studies since it demonstrated a regenerative effect in comparison to the degree of repair on Kupffer cells in the kidney and liver compared to the group of diabetics, who displayed many cell differentiations and alterations as shown by histology. Eugenol inhibits cytokine release and lipid peroxidation, which may lead to the restoration of closer levels of liver and kidney function.

Panax ginseng

For thousands of years, the root of Panax ginseng has been widely utilized to treat a variety of illnesses, such as cancer, diabetes, and cardiovascular disease (CVD)¹⁰⁷⁻¹⁰⁸. The primary chemically active components of ginseng and the secondary metabolites of the Panax species are called ginsenosides, and they have the ability to scavenge free radicals and serve as antioxidants¹⁰⁹. In cultured renal proximal tubular epithelial cells, it decreased the nephrotoxicity caused by cisplatin in a dose-dependent way¹¹⁰. North American ginseng prevents diabetic peripheral neuropathy (DN) by acting as an antioxidant and antihyperglycemic¹¹¹. It was discovered that sun ginseng, heat-processed American ginseng, and 20(S)-ginsenoside Rg3 alleviated hyperglycemia and renal damage in type 1 insulin-dependent DN animal models produced by STZ¹¹². Ginsenoside Rg3 reduced hyperglycemia, proteinuria, and hyperglycemia in type 2 insulin-independent diabetic neuropathic mice while increasing creatinine clearance¹¹³.

Black seed (*Nigella sativa*)

Black seed consists of essential and fixed oils. The fixed oil of seeds contains dihomog- γ -lignoleic acid, which has a potent antioxidant value of¹¹⁴. It has thymoquinone, vitamin A, β -carotene, and vitamin E. *Nigella sativa* seed ethanol extract was reported to dramatically lower high BGL levels in STZ-induced diabetic rats after 30 days of treatment. It also improved CAT and SOD levels and decreased GST and GPx in the liver and kidney¹¹⁵. The findings demonstrated that, in comparison to the values of the gentamicin control group, vitamin C and *Nigella sativa* oil decreased the SCr, BUN, and antioxidant activity. These have a synergistic nephroprotective effect when administered in combination¹¹⁶. Renal function was enhanced and renal inflammation and oxidative damage were

decreased by pretreating with black seed three weeks before ischemia reperfusion injury ¹¹⁷. It was proposed that increased insulin release may operate as a mediator for the anti-diabetic effects of *Nigella sativa* seeds ¹¹⁸. The primary ingredient in black seed, thymoquinone, is an active quinone with anti-inflammatory, anti-diabetic, and antioxidant properties. Thymoquinone significantly lessened the kidney damage caused by doxorubicin, according to a study, and Nrf2 mRNA levels were restored to normal levels along with a decrease in IL-10 levels. Rats exposed to N(omega)-nitro-L-arginine methyl esters are protected against HTN and renal injury by thymoquinone ¹²⁰.

Rosmarinus officinalis

The primary component of *Rosmarinus officinalis*, rosmarinic acid is a polyphenolic phytochemical that can be found in perilla, rosemary, and mint. Its anti-inflammatory and antioxidant qualities number ¹²¹. By blocking CTGF ¹²², rosmarinic acid protects the kidneys from damage early on in DN. Significant reductions were observed in focal glomerular necrosis, Bowman's capsule dilatation, tubular epithelium degeneration, tubular epithelium necrosis, and tubular dilatation ¹²³. The activity of SOD and CAT in rats was significantly reduced by DM. In diabetic rats, the administration of 10 mg/kg rosmarinic acid reversed the decline in non-protein-thiol and ascorbic acid levels and prevented changes in SOD and CAT activity ¹²⁴ in addition. The antioxidant and anti-inflammatory properties of rosmarinic acid are known ¹²⁵⁻¹²⁷. By lowering OS it protected the kidneys from ischemia/reperfusion damage ¹²⁸. In addition, it has been observed that rosmarinic acid decreases NFκB and increases glutathione transferase, anti-Bcl-2 activity, and peroxynitrite scavenger activity ^{129, 130}. It improves glomerulosclerosis ¹³¹ and maintains the glomerular number in diabetic mice. Additionally, in treated diabetic rats, rosemary extract was discovered to be able to reduce the increasing levels of serum MDA ¹³². According to other research, rosmarinic acid prevents gentamicin-induced nephrotoxicity in rats and enhances the activity of kidney antioxidants like SOD, GPx, and CAT ¹³³.

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 ¹³⁴⁻¹³⁵. Furthermore, it was found that carnosic acid activated Nrf2 through modulation of PI3K/Akt pathway resulting in increased levels of antioxidant enzymes ¹³⁶. Carnosic acid prevented methyl glyoxal dependent neurotoxicity by activating the PI3K/Akt/Nrf2 signaling pathway and the antioxidant enzymes modulated by Nrf2 transcription factor ¹³⁷.

Gooseberry

Gooseberry formally called *Phyllanthus emblica*, the Indian gooseberry, or Amla, is a member of the Grossulariaceae family of plants. Most tropical regions

of Southeast Asia are where it is grown. Obesity, constipation, diabetes, cancer, and pain have all been treated with the fruit and its extract ¹³⁸. As a mild laxative, it is also frequently used.

Oats

Consuming a lot of whole-grain meals, including oats, is mostly linked to a decreased risk of type-2 diabetes and cardiovascular problems. Oats were the subject of an anti-diabetic investigation. This study's streptozotocin (STZ)-induced diabetic rats developed DN, as evidenced by increased 24-hour urine albumin, serum blood urea nitrogen (BUN), creatinine, and creatinine clearance. A 21-week oat supplementation period significantly enhanced renal function and had a hypoglycemic effect, which helped reverse diabetic kidney disease ¹³⁹.

Tulasi

Ocimum sanctum, which belongs to the Labiatae family, is the scientific name for tulasi. Its therapeutic qualities are also well-known. Native American medicine makes use of the healing plant. The major components of the leaf aqueous extract include eugenol, geraneol, ocimene, carvacrol, urosolic acid, rosmarinic acid, linalool, β-caryophyllene, eugenol, and geraneol ¹⁴⁰. The plant is known to have various health benefits, including its ability to reduce stress, improve asthma, fight infections, fight cancer, boost the immune system, stimulate the stomach, and prevent mutagenic reactions. Furthermore, rheumatoid arthritis, diabetes, cataracts, hypertension, diarrhea, cardiac toxicity, allergic hypercholesterolemia, depression, thyroid, and neurotoxicity have all been treated with these herbs. Analgesic, antipyretic, memory-enhancing, anti-tussive, anti-fertility, anti-emetic, anti-spasmodic, anti-stress, anti-coagulant, antibacterial, anti-inflammatory, radioprotective, and anti-carcinogenic are some of the other therapeutic qualities ¹⁴¹. Based on antioxidant and anti-inflammatory mechanisms similar to those discovered in statins and angiotensin receptor blockers (ARBs), the study suggests that *Ocimum sanctum* protects the kidneys. *Ocimum sanctum's* antioxidant properties may reduce the amount of AGEs that are produced as a result of diabetes. Inflammatory cell infiltration, prolonged hypoxia, AGE production, oxidative stress, and iron buildup are all linked to DN. The breakdown of oxidative matrix proteins, the invasion of inflammatory cells, and AGE alterations all contribute to the acceleration of tissue fibrosis, which is caused by chronic hypoxia, which turns tubular cells into myo-fibroblasts ¹⁴².

Plant secondary metabolites targeting diabetic nephropathy

Andrographolide

A variety of medical uses, including anti-diabetic ¹⁴³, are associated with andrographolide (figure 1), a labdane diterpenoid produced from *Andrographis paniculata*. This substance lowers renal oxidative stress and inflammation brought on by

hyperglycemia through the Akt/NF- κ B pathway in the treatment of diabetic kidney disease.¹⁴⁴

Astragaloside

Astragaloside IV, a tetracyclic triterpenoid saponin derived from lanolin alcohol, is the primary active component of *Astragalus membranaceus*. Significant protective effects on the kidneys have been shown in animal models of diabetic renal disease¹⁴⁵. Astragaloside IV can reduce kidney damage in db/db mice by having a renoprotective effect that may be mediated by mitochondrial quality control network repair and inflammation suppression caused by the NLRP3 inflammasome¹⁴⁶⁻¹⁴⁷.

Berberine

A variety of plants, including *Arcangelisia flava*, *Berberis aquifolium*, *Berberis aristata*, *Berberis vulgaris*, and *Hydrastis canadensis*¹⁴⁸, are sources of berberine, an isoquinoline alkaloid quaternary ammonium salt derived from plants. Researcher observations have indicated that berberine protects the kidneys. TGF- β /Smad3-mediated renal fibrosis and NF- κ B-induced renal inflammation are inhibited by this drug, protecting the kidney from damage¹⁴⁹. It inhibits the TLR4/NF- κ B pathway¹⁵⁰, so reducing renal damage, inflammation, and podocyte death. Additionally, by blocking hyperglycemia-induced EMT through NLRP3 inflammasome inactivation, berberine lessens renal tubulointerstitial fibrosis.¹⁵¹

Catechin

Plants use the secondary metabolite catechin, a flavanol, for antioxidant purposes (Figure 1). Research using db/db mice showed that catechin uses methylglyoxal trapping to block the inflammatory process and prevent the development of AGEs¹⁵². Catechin increases the expression of insulin signal-transduction pathway-related proteins and liver glucose-metabolism enzymes in diabetic rats¹⁵³.

Genistein

A phytoestrogen derived mostly from legumes, genistein is an isoflavone flavonoid¹⁵⁴. Genistein prevents renal fibrosis by preventing the production of fibrosis-related markers, according to a study done on diabetic mice¹⁵⁵. Genistein decreases oxidative stress by activating the Nrf2-HO-1/NQO1 pathway and ameliorates renal fibrosis in diabetic Sprague-Dawley rats via controlling the TGF- β /Smad3 pathway¹⁵⁶.

Gallic Acid

Belonging to the subclasses of phenolic acid, gallic acid is a phenolic chemical. In diabetics, it inhibits TGF- β 's renal expression, increased glyoxalase 1 (GLO1) activity, Nrf2 adjustment, and decreased microRNA-associated fibrosis and endoplasmic reticulum (ER) stress in diabetic NMRI mice (Sprague-Dawley rats)¹⁵⁷⁻¹⁵⁸.

Hesperetin

Hesperetin is one of the most prevalent flavonoids found in citrus fruits, and it is a member of

the flavanones flavonoid class¹⁵⁹. One of this compound's many pharmacological properties is its capacity to decrease the growth of diabetic neuropathy. Hesperetin was discovered by Chen et al.,¹⁵⁹ to modulate the course of diabetic DN in diabetic Sprague-Dawley rats by upregulating Glo-1, suppressing the AGE/RAGE axis, and reducing inflammation.

Kaempferol

The flavonoid kaempferol shares a chemical structure with quercetin¹⁶⁰. Research has been done on kaempferol's potential as a DN treatment. Kaempferol reduces renal fibrosis in diabetic C57BL/6 mice by blocking fibrogenesis via RhoA/Rho kinase¹⁶¹. According to another study, kaempferol activates the Nrf-2/HO-1/antioxidant axis, which lowers the oxidative stress of diabetic rats¹⁶².

Luteolin

Several fruits and vegetables naturally contain the flavone luteolin in a glycosylated form. Lutein slows the apoptotic death, removal, and integration of podocytes while also protecting the filtration function of the basement membrane in diabetic Sprague-Dawley rats by upregulating Nphs2 protein expression¹⁶³. Lutein lowers oxidative stress and the inflammatory response in C57BL/6 J db/db and C57BL/6 J db/m mice by blocking the signal transducer and activator of transcription 3 (STAT3) pathway.

Magnoflorine

The bark, roots, rhizomes, and stems of various medicinally important plants, such as *Thalictrum isopyroides* C.A. Mey.¹⁶⁵, *Magnolia officinalis* Rehder & E.H. Wilson, *P. amurense*, *S. acutum*, and *Berberis kansuensis* C.K. Schneid., contain the important quaternary aporphine alkaloid magnoflorine. Because it makes lysine-specific demethylase 3A (KDM3A) more consistently produced, this metabolite reduces DN and inhibits inflammatory reactions and fibrosis¹⁶⁷.

Mangiferin

The mango fruit's peel, stalks, leaves, bark, kernels, and stones all contain high concentrations of the xanthone mangiferin, which is also present in higher plants. Numerous therapeutic actions are associated with it, such as anti-diabetic and antioxidant qualities¹⁶⁸. Mangiferin decreases cell apoptosis and oxidative stress in diabetic rats undergoing DN therapy¹⁶⁹. Using the AMPK-mTOR-ULK1 pathway to increase autophagy, mangiferin also shields podocytes in diabetic rats¹⁷⁰.

Oxymatrine

Strong pharmacological effects are exhibited by oxymatrine, a quinolizidine alkaloid that is naturally present in the roots of *Sophora flavescens* Ait.¹⁷¹. Oxymatrine significantly reduces oxidative stress and kidney-related levels of AGEs, TGF- β 1, CTGF, and inflammatory cytokines in diabetic rats¹⁷². Oxymatrine also inhibits twist-mediated renal tubulointerstitial fibrosis by upregulating Id2 expression¹⁷³.

Silymarin

Through ribonucleic acid (RNA) polymerase I stimulation, silymarin promotes protein synthesis and cellular regeneration in the kidney epithelium. Silibinin, Lysiluk, and silichristin are considered to be the main culprits for these effects; silidianin appears to have less impact. In instances where the renal epithelium is necrotic¹⁷⁴, silymarin may be particularly helpful, the report suggests. Silymarin bioflavonoid causes protein synthesis, inhibits lipid peroxidation, leukotriene and prostaglandin production, and neutrophil migration in addition to its anti-inflammatory and antioxidant qualities¹⁷⁵⁻¹⁷⁷. Silymarin therapy for people with renal insufficiency may be useful. According to recent research, giving silymarin either by itself or in conjunction with vitamin E to hemodialysis patients lowers their plasma MDA levels while raising their blood levels of hemoglobin and glutathione peroxidase¹⁷⁸. Treatment with silymarin reduced kidney damage and restored glutathione peroxidase, catalase, and superoxide dismutase activity in rats with diabetes caused by alloxan. In streptozotocin-induced diabetic rats, milk thistle extract prevents diabetic renal damage. This effect is likely due to increased glutathione peroxidase and catalase activity as well as decreased lipid peroxidation in the renal tissue¹⁷⁹. It is believed that a reduction in proteinuria is associated with silymarin's anti-inflammatory and free radical scavenging properties. Additionally, silymarin was reported to decrease albumin, TNF- α , and MDA excretion in patients with diabetic renal disease¹⁸⁰.

Syringaresinol

A kind of lignan called syringaresinol is found naturally in plants like flax seed, sesame seed, Brassica vegetables, and cereals¹⁸¹. Its ameliorative action against the advancement of diabetic neuropathic pain is demonstrated in diabetic rats and is mediated by Nrf2 activation and TGF- β 1/Smad pathway inhibition. By stimulating the Nrf2 antioxidant pathway, syringaresinol prevents pyroptosis in diabetic C57BL/6 mice¹⁸².

Resveratrol

A phytoalexin called resveratrol is produced spontaneously by certain spermatophytes in response to injury¹⁸³. Resveratrol has been shown in numerous animal studies to help treat diabetes in a number of ways. By reducing oxidative stress and downregulating the expression of the receptor for advanced glycation end product (RAGE), resveratrol slows the progression of diabetic neuropathic pain (DN) and reduces the accumulation of amyloid (AGE), oxidative damage, apoptosis, and NADPH oxidase 4 (NOX4)¹⁸⁴.

Quercetin

Quercetin is a flavonoid chemical that is a member of the flavonol subclasses. Quercetin modulates TGF- β 1 expression to reduce oxidative damage in diabetic rats¹⁸⁵⁻¹⁸⁶. Quercetin was found to reduce podocyte death by blocking the EGFR signaling pathway in C57BL/KSJ db/db mice. By decreasing the expression

of snail1 and increasing the amount of autophagy mediated by beclin-1, quercetin improves kidney fibrosis in diabetic mice¹⁸⁷.

Ursolic Acid

A naturally occurring pentacyclic triterpenoid, ursolic acid is present in several therapeutic plants, such as *Fructus ligustris*, hawthorn, and bearfruit. Due to its diverse pharmacological properties, this substance has garnered a great deal of attention lately¹⁸⁸. Ursolic acid reduces oxidative stress and inflammation, prevents the build-up of extracellular matrix and renal fibrosis, and prevents the development of AGEs in the kidney and plasma in DN animal models¹⁸⁹.

Lupeol

Natural triterpenoid luteol is widely distributed and found in many different plants (e.g., licorice, *Emblica officinalis*), fruits (mango, strawberry), and vegetables (white cabbage, pepper)¹⁹⁰. By boosting the activities of antioxidant enzymes (GSH, CAT, and SOD), which in turn lower oxidative stress, it demonstrates renoprotective efficacy in the DN animal model.

Astragaloside

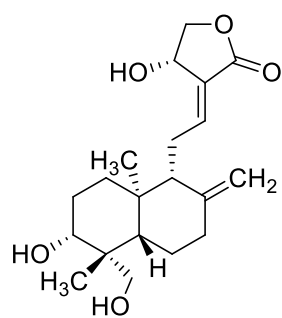
A tetracyclic triterpenoid saponin, astragaloside IV is the active ingredient in *Astragalus membranaceus*. It is produced from lanolin alcohol¹⁹¹⁻¹⁹² and has demonstrated substantial protective benefits on the kidneys of DN animal models. Astragaloside IV's renoprotective effects may be due to two mechanisms: the prevention of inflammation mediated by the NLRP3 inflammasome and the restoration of the mitochondrial quality control network, which can lessen kidney damage in db/db mice¹⁹³.

Conclusions

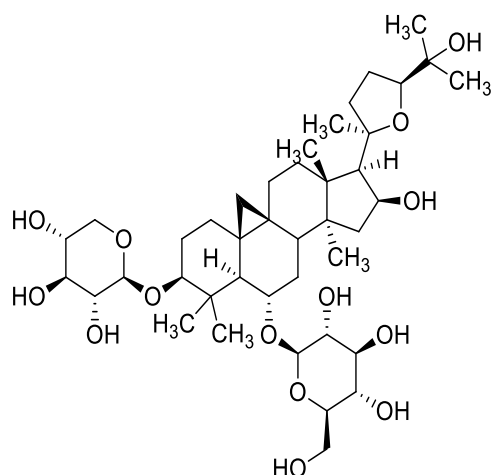
People of all ages can be affected by diabetes mellitus, an endocrine illness. Prolonged hyperglycemia is the primary factor causing changes in kidney function in people with diabetes mellitus. Increased advanced glycation end products and polyol pathway activation in hyperglycemia result in oxidative stress due to inflammation and kidney damage. AGEs promote an increase in the production of extracellular matrix proteins by kidney macrophages, mesangial cells, and endothelial cells. It has also been demonstrated that the extracellular matrix proteins' cross-linking reduces the flexibility of the matrix proteins, leading to an unbalanced interaction with other matrix components. Many underdeveloped countries, including India, rely heavily on traditional medicine, and medicinal plants play a major part in this field of practice. The study indicates that diabetes and its aftereffects have developed into significant health problems in India. The current review illustrates how different pharmacological pathways have an impact on the therapeutic effects of medicinal plants used for diabetes treatment and prevention. For instance, ginger increased plasma's antioxidant capacity and decreased lipid peroxidation, which both slowed the development of diabetic nephropathy. Because of their antioxidant qualities, most plants—including guava, pepper,

coriander, gooseberry, and green tea—are used to treat DN. The results of this review show that plants lead a very diverse lifestyle. Since the development of stress and free radicals is a major cause of diabetes nephropathy, traditional medicines with antioxidant qualities may be used to treat the condition. Based on the broad antioxidant capabilities of polyphenols, flavonoids, and essential oils, it can be concluded from

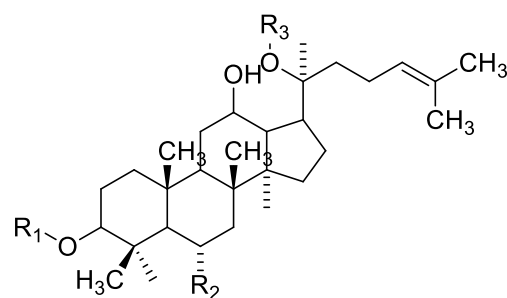
our study that the medicinal plants indicated above have the potential to control diabetes and its complications while having minimal adverse effects. All things considered, phytochemical components found in herbs can appear like a suitable and secure substitute, offering a wealth of opportunities for investigation and learning.



Andrographolide



Astragaloside IV

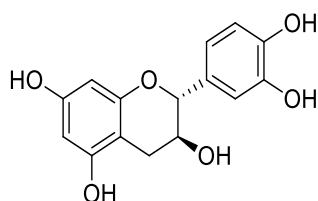


Ginsenoside Rb1

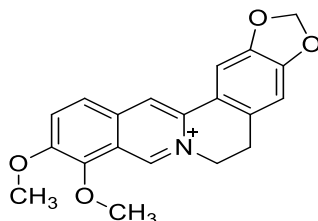
R1 = Glu-Glu

R2 = H

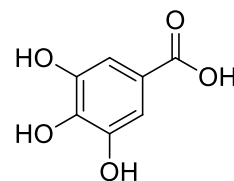
R3 = Glu-Glu



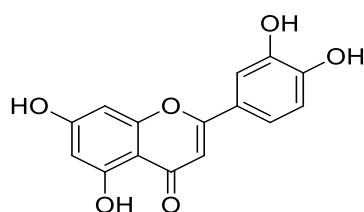
Catechin



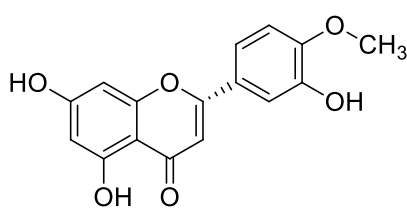
Berberine



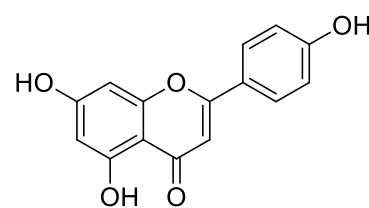
Gallic acid



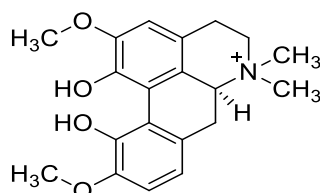
Luteolin



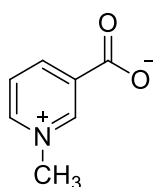
Hesperetin



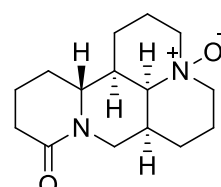
Genistein



Magnoflorine



Trigonelline



Oxymatrine

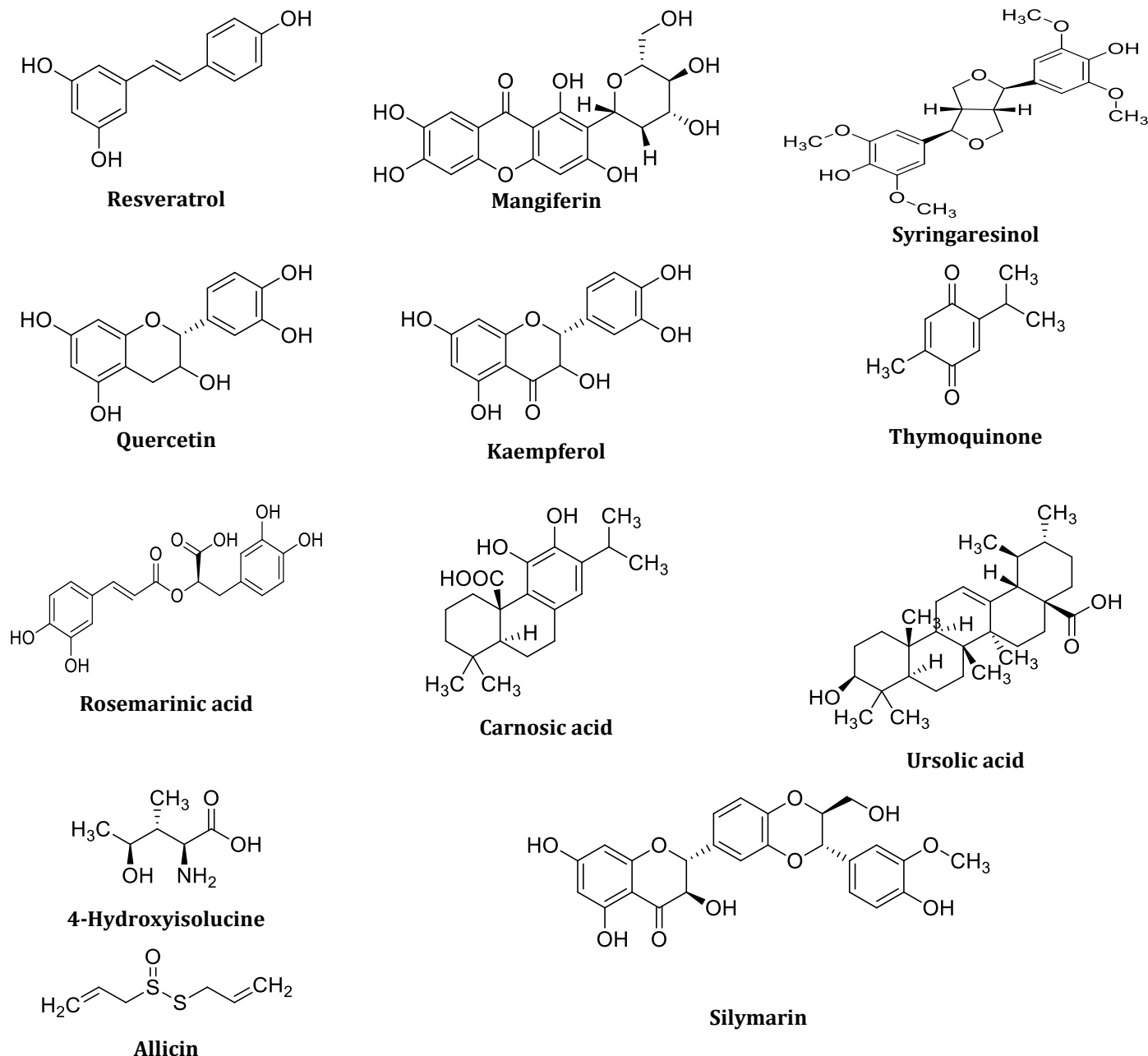


Figure 1. Chemical structure of bioactive phytoconstituents for diabetic nephropathy

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