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REVIEW ARTICLE

# Effects of Various Herbal leaves Extract and Their Phytoconstituents in the Cure of Diabetic Nephropathy by 'Streptozotocin-induced in Rats' Model - A Review

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## Abstract

The purpose of this study was to collect data for future clinical investigations and research on the safe and efficient use of various herbal medicines to treat hyperglycemia. One of the primary contributing reasons to the onset and progression of diabetic nephropathy is hyperglycemia, and many modern treatments are made from plants since they frequently have fewer side effects than the conventional medications that are now available. The medicinal plants include *Sesbania sesban, Elaeis guineensis, Tecoma stans*, *Aloe barbadensis* miller, *Zingiber officinale* Roscoe, *Olea europaea, Anogeissus acuminata, Juglans regia* L., *Fragaria ananassa*, *Ginkgo biloba, Laurus nobilis* L., *Dryopteris dilatata*, *Moringa oleifera*, *Punica granatum* L., *Lycium chinense*, *Rumex nervous* alkaloids and flavonoids are the primary phytoconstituents that aid in the therapy or cure of diabetic nephropathy. The therapeutic effects of medicinal plant leaf extract may be due to the wide range of bioactive compounds present, including various phytoconstituents such as alkaloids and flavonoids, glycosides, steroids, terpenoids, and phenolics. Alkaloids and flavonoids are the primary phytoconstituents that aid in the therapy or cure of diabetic nephropathy.

**Keywords:** Diabetes Mellitus, Diabetes Nephropathy, Medicinal Plant, Pathogenesis, Streptozotocin-induced in Rats' Model

## 1. Introduction

Hyperglycemia, which is a symptom of diabetes mellites, is caused by either impaired insulin action or impaired insulin synthesis[1]. A significant microvascular consequence that accounts for 30–47 % of instances of end-stage renal diseases is DN. Hyperglycemia is currently the largest contributor to end-stage renal disease in the United States and Europe. ESRD is caused by a variety of causes, including homodynamic abnormalities, inflammation, and hyperglycemia. If left unchecked, micro-albuminuria evolves to extensive proteinuria > 500 mg in 24 hours and presents as DN. Early stages of DN are defined by lower levels of proteinuria or microalbuminuria (albumin excretion of 30–299 mg/24 hours)[2,3].

Chronic hyperglycemia associated with diabetes increases the risk of heart disease (CV) and a few other long-term microvascular problems that can affect the eyes, nerves, and kidney[4]. The kidney enlarges, and the rate of Glomerular Filtration (GFR) is altered when diabetes first appears. All kidney cell types are vulnerable to injury in DN, including mesangial cells, podocytes, and tubulointerstitial cells. There will probably be 439-537 million persons worldwide with diabetes mellitus by 2030 due to the dramatic rise in

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DM mortality and morbidity over the past few years[5-6]. Twenty to thirty per cent of individuals with T2DM have renal impairment[7]. In addition to hypoglycaemia, it also results in hyperlipidemia, oxidative stress, polyuria (excessive urination), ketosis (an increase in ketone bodies), neuropathy (nerve dysfunction), nephropathy, and different heart conditions[8].

### 1.1 Diabetes Mellitus Classification and Other Glucose Regulation Categories

The National Diabetes Data Group established a consensus agreement that unifies the ideas and terminology for diabetes mellitus in 1979[9,10]. The first classification of diabetes mellitus was published first by WHO in 1980, and a revised version was published in 1985. The classifications of diabetic and associated glucose intolerance categories used in 1980 and 1985 included two statistical risk categories as well as clinical classes[11,12].

### 1.2 Type 1 Diabetes (Insulin-Dependent Diabetes)

Type 1 Diabetes Mellitus (T1DM), also known as autoimmune diabetes, is a chronic disease characterized by insulin deficiency due to pancreatic β-cell loss and leads to hyperglycaemia[13]. The incidence of diabetes mellitus type 1 (T1DM) has been rising by 2-5 % globally, with notable regional or continental variability in this diagnosis[14]. These people also frequently have autoimmune diseases such as Graves' disease, vitiligo, pernicious anaemia, celiac sprue, autoimmune hepatitis, Hashimoto's thyroiditis, Addison's disease, and myasthenia gravis[15].

### 1.3 Type II Diabetes (Non-Insulin-Dependent Diabetes)

Type 2 Diabetes Mellitus (T2DM) is an expanding global health problem, closely linked to the epidemic of obesity and this type, either our body does not create enough insulin or human body cells develop insulin resistance[16]. This type of diabetes, which only affects 5–10 % of persons with the condition and was formerly known as insulin-dependent T2D or juvenile-onset diabetes, is brought on by an autoimmune reaction that culminates in the cellular death of the pancreatic beta cells. Type II diabetes has been recorded in up to 95% of patients. Type 2 DM was first described as a component of metabolic syndrome in 1988. Type 2 DM (formed known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycemia, insulin, resistance, and relative insulin deficiency[17].

### 1.4 Gestational Diabetes

Gestational Diabetes Mellitus (GDM) is a form of hyperglycemia. In general, hyperglycemia results from an insulin supply that is inadequate to meet tissue demands for normal blood glucose regulation[18]. Certain pregnant women experience this type of development. Normal recovery from gestational diabetes occurs after childbirth. But, if you have gestational diabetes, you are more likely to later acquire type II diabetes[19]. The International Diabetes Federation (IDF) estimates that in 2019, there were 20 million live births, of which GDM accounted for 75–90 %, and that 16% of viable newborns were afflicted by hyperglycemia in pregnancy[20].

## 2. Introduction of Diabetes Nephropathy

Diabetes type 1 and type 2 are frequently associated with Diabetic Nephropathy (DN), which is another prevalent consequence[21]. The most frequent consequence of diabetes, Diabetic Nephropathy (DN), affects at least 30 per cent of the total of diabetic individuals, placing a significant cost on public health[22]. It is the most common cause of End-Stage Renal Failure (ESRD) worldwide and is also a major factor in the morbidity and mortality of diabetic patients[23,24]. DN, which is also linked to an increase in cardiovascular death, is the most common cause of long-term kidney damage in patients beginning renal replacement treatment[25]. According to the WHO, 370 million people will have diabetes worldwide by 2030[26]. Diabetes-related nephropathy was the cause of 40% of new patients diagnosed with ESRD in 1997. Nephropathy symptoms are present in between twenty-five and thirty per cent of those with both types of diabetes, but only a small proportion of these patients progress to End-Stage Renal Disease in type 2 diabetes (ESRD). Diabetes nephropathy is characterised by a particular set of structural as well as functional kidney abnormalities in diabetic patients[27,28]. The functional change involves a gradual decrease of renal function as well as an early rise in glomerular with intraglomerular hypertension[29,30].

The formation and progression of diabetic nephropathy can be stopped with therapeutic alternatives including rigorous blood pressure or glycaemic management, however, the number of diabetic patients receiving haemodialysis is still rising[31]. The most popular model for researching diabetic nephropathy in rats is the streptozotocin-induced diabetic rat. The rat model of diabetic nephropathy's histological alterations closely resembles human disease[32]. Both microalbuminuria tests and serum indicators of glomerular filtration rate should be used to check for nephropathy in diabetic older persons as they reveal renal damage in subgroups of the diabetics. To detect renal impairment in all diabetics, the American Diabetes Association (ADA) and the National Institutes of Health advise measuring the estimated Glomerular Filtration Rate (eGFR) derived from serum creatinine at least once a year[33]. In recent years, type II diabetic individuals have had an increased risk of developing end-stage renal failure, both in the U.S. and, slightly later, in some European countries[34]. Diabetes is the leading cause of ESRD since diabetic nephropathy occurs in 30 to 40 % of people[35]. The two stages of diabetic nephropathy are macroalbuminuria (UAE>200 g/min) and microalbuminuria (UAE>20 g/min and UAE>199 g/min) respectively[36]. The early phases of the kidney in type 2 diabetes have drawn attention lately. Type I and type II diabetes do not significantly differ in terms of kidney hemodynamics, renal morphology, or the evolution of pre-existing diabetic nephropathy[37]. Although DN has traditionally been thought of primarily as a metabolic illness, mounting evidence points to a significant role in immune response in the development of this condition[38].

## 2.1 Natural History of Diabetes Nephropathy

In contrast to the long-held belief that type 2 diabetes nephropathy is caused by Kimmelstiel-Wilson lesions of the glomerulus and progresses from microalbuminuria to proteinuria and ESRD, it is currently proven beyond a shadow of a question that a nonproteinuric type of diabetic nephropathy is quite common. Microalbuminuria, also known as urine and separation of 30 to 299 mg once daily hours in a 24-hour urine sample, 20 to 199 g/g in and urine sample, or 30 to 299 mg dosage blood urea nitrogen in a spot urine sample on at least two separate occasions within a three to six-month period, is the earliest clinical sign of diabetes renal disease[39]. A greater proportion of people with type-2 diabetes are found to have renal damage and overt nephropathy soon after being diagnosed because it can take a long time for a diagnosis to be made and because biopsy research findings have demonstrated that the presence of albuminuria may be less particular for the presence of kidney disease nephropathy. In people with type 1 diabetes with overt nephropathy, ESRD develops in 50% of cases within 10 years, and in >75% of cases within 20 years. Two years following the diagnosis of diabetes, it is believed that the first histological changes in renal failure become evident[40] and the finding that brain microinfarcts on MRI can foretell the loss of renal function that will follow suggests that this may be the outcome of microvascular illness. The safety of target blood pressures and the applicability (or lack thereof) of RAS blocking in this novel form are clear concerns raised by this novel form[41].

## 2.2 Symptoms of Diabetes Nephropathy

The main clinical sign of DN, which causes a steady loss in kidney function, is progressive albuminuria. Diabetes nephropathy, "poor blood sugar balance promotes kidney damage", initially has symptoms like high BP, Protein in urea, weight loss, elevated blood of BUN and creatinine, difficulty thinking clearly, and anaemia (low blood count) but this condition worsens[42,43] (Figure 1).

## 2.3 Treatment Intervention in Diabetes Nephropathy

The progression of diabetic nephropathy can be slowed or stopped with treatment, but it cannot be cured. Treatments try to maintain blood - sugar levels within the desirable range through lifestyle modifications. If your renal status worsens and you get ESRD, you will require more invasive therapy like renal replacement, combined therapy targeting hypertension, hyperglycemia, and dyslipidemia example of diagnostic of DN and other treatments in DN shown in Figure 2.

## 2.4 Pathogenesis of Diabetes Nephropathy

Increased levels of lipid hydroperoxides, bioactive carbonyls, and free radicals that cause Oxidative Stress (ROS), but no enzymatic protein glycosylation are also part of the pathophysiology of DN. Radicals Oxidative stress is a common product of many pathways that are involved

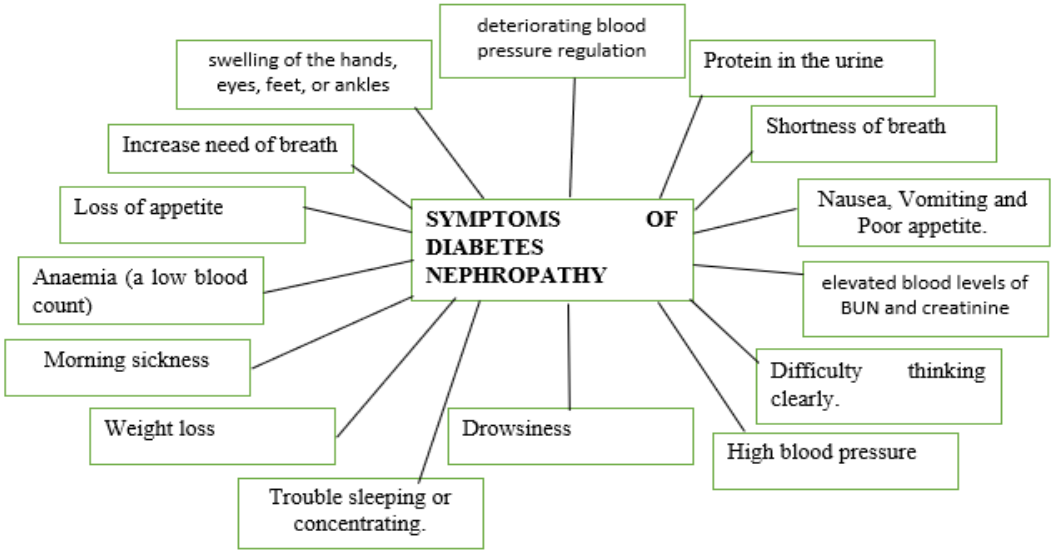



**Figure 1.** Symptoms of diabetes nephropathy.

in the pathogenesis of DN and the role of oxidative stress in DN has been noted by the observation that inhibition of oxidative stress improves a feature associated with streptozotocin-induced Diabetes Nephropathy[44]. Enzymes that combat free radicals help to protect tissues and cells. Differences in free radical generation and antioxidants are believed to be the main factor contributing to the onset of disease. Hemodynamic and digestive system interactions have a significant role in the development of nephropathy. Renal polyol production, Advance Glycated Products (AGEs) build-up, PKC activation, and increased oxidative stress are all caused by the excitation of metabolic pathways in diabetic kidneys. Many cytokine and growth regulators are thus activated. Diabetes types 1 and 2 diabetes share a common DN aetiology. The histological classification of diabetic nephropathy is based on how the glomerulus appears on kidney biopsy. GBM thickening leads to mesangial expansion, nodule glomerulosclerosis, and global glomerulosclerosis as the condition develops[45] (Figure 3).

## 3. Medicinal Plant Leaf Extract Used in Cure Diabetes Nephropathy by STZ-induced Rat Model

Various medicinal like *Sesbania sesban*, *Elaeis guineensis*, *Tecoma stans*, *Aloe barbadensis* miller, *Zingiber officinale* Roscoe, *Olea europaea*, *Anogeissus*

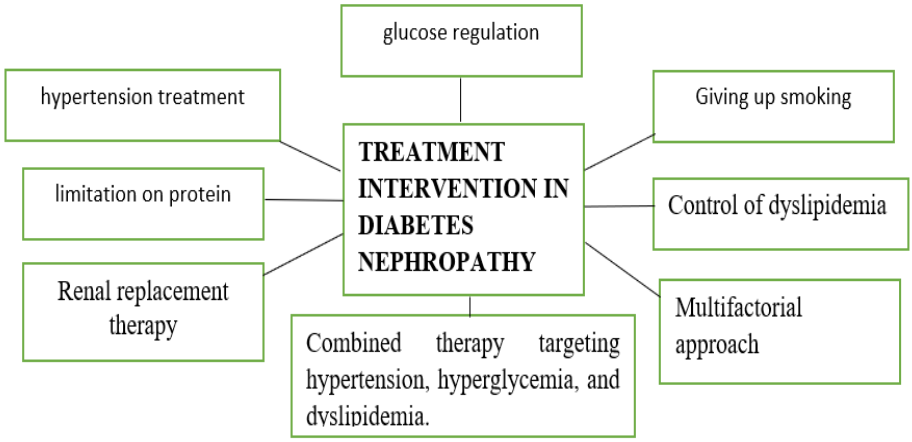



**Figure 2.** Treatment intervention in diabetes nephropathy.

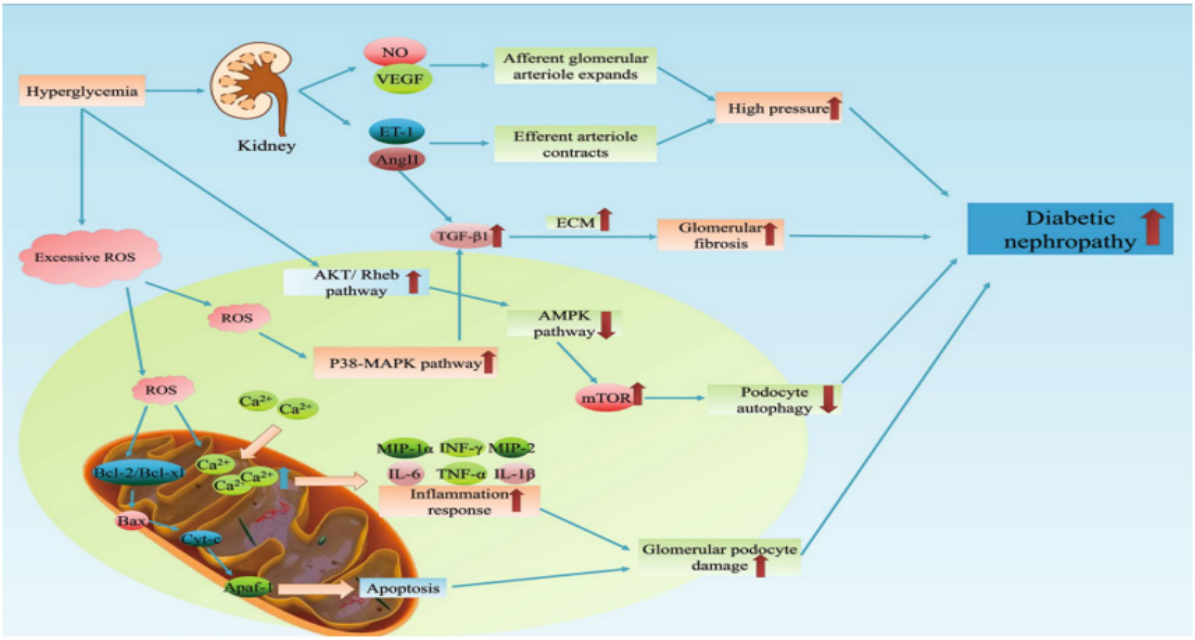



**Figure 3.** Pathogenesis of diabetes nephropathy.

*acuminata*, *Juglans regia* L., *Fragaria ananassa*, *Ginkgo biloba*, *Laurus nobilis* L., *Dryopteris dilatata*, *Moringa oleifera*, *Punica granatum* L., *Lycium chinense*, *Rumex nervous*, *Acacia catechu*, *Croton hookeri*, *Macaranga tanarius*, *Molineria recurvata* leaves extract and phytoconstituents to help cure or treatment of DN by STZ induced rats' model.

### 3.1 *Sesbania sesban* (Family - Fabaceae)

Often called the "*Egyptian river hemp*" or "*Egyptian sesban*", is one of the six species in the genus *Sesbania*. It is a small, slim tree or shrub that can grow as long as 18 cm and as tall as 8 meters. It has leaflets that are 6-27 sets long and oval-shaped (26X5 mm). Antioxidant, antibacterial, antiviral, anthelmintic, antifertility, anti-inflammatory, antidiabetic, anti-hyperlipidemic, anti-cancer, anti-anxiety, and mosquito-repellent characteristics were among the therapeutic potentials of *S. sesban* leaves[46]. The raceme has two to twenty yellow flowers with petal striations that are black or brown. *S. sesban* has five however, botanical varieties, however, these variations have little impact on how prolific they are[47]. Crude extract from the leaf of *Sesbania sesban* stops the progression of diabetes nephropathy and lower proteinuria, albuminuria, fat, and glycosylated haemoglobin (HbA1c) in stz - induced diabetic rats[48].

### 3.2 *Elaeis guineensis* (Family - Arecaceae)

Commonly known as the oil palm. Active phytochemical components include phenolic compounds, alkaloids, steroids, terpenoids, saponins, flavonoids, and carbohydrates. Most experts agree that the oil palm, Guineensis Arid to semi-arid, originated in the Gulf region of Africa's tropical rain forest, close to the equator. Palm oil and palm kernel oil are the two types of oil that the African oil palm produces. The leaf is also used to treat kidney disease, cardiovascular disease, cancer, and wound healing[49]. In experimental diabetic nephropathy, palm oil *(Elaeis guineensis)* leaf extract displays both antioxidant and pro-oxidant actions, with a duration-dependent outcome and reduced kidney production of p22phox and p67phox NADPH oxidase subunits[50].

### 3.3 *Tecoma stans* L. (Family - Bignoniaceae)

It is also called *kusi urakame,* and timboco, is a plant that is indigenous to high-altitude areas of South America and a steroid, alkaloids, saponins, phenols, flavonoids, steroids, anthraquinones, and tannins were found by phytochemical examination. Analgesic, antibacterial, antispasmodic, immunomodulatory, wound healing and hepatoprotective activities have been identified by pharmacological research. The primary bioactive elements that contribute to its

medicinal advantages are alkaloids, phenolic acids, flavonoids, and fatty acids[41]. Understanding *Tecoma stans* leaf extract's neuroprotective role in STZ-induced DN and observing the disease's effectiveness and improvements as well as the drop in MDA levels[52].

### 3.4 *Aloe barbadensis* miller (Family - Liliaceae)

It is also known as *Aloe barbadense* miller. It belongs to the genus Aloe, which has over 420 species and is the most important plant family within the Alliaceae phylum. The name Aloe vera is derived from the Arabic "Alloeh", which means "shining bitter material," and the Latin "vera1", which means "true". *Aloe barbadense* miller is a frequent name for this plant[53]. Aloe vera has been used for a long time to treat skin injuries and stomach problems because of its anti-inflammatory, antibacterial, and wound-healing properties (eczemas, burns, wounds, and insect bites). New pharmacological data research indicates that most studies concentrate on skin and digestive system protection activity, and antibacterial capabilities, anti-cancer activity[54]. Analyze the effects of aloe vera leaf extract in rats with stz-induced DN nephropathy and note changes in body weight, kidney weight, food intake, and water consumption[55].

### 3.5 *Zingiber officinale* Roscoe (Family - Zingiberaceae)

It is also known as *Zingiber officinale* Roscoe. It has been a popular medicinal plant in Chinese, Ayurvedic, and Tibb-Unani herbal remedies for several unrelated illnesses since ancient times, including joint pain, sprains, muscular aches and pains, hypertension, cramps, constipation, vomiting, dementia, indigestion, fever, rheumatoid arthritis, infectious diseases, and helminthiasis[56]. Ginger lowers fasting blood glucose levels, protects mice from diabetic nephropathy, and lessens the oxidative stress, inflammation, and apoptosis that hyperglycemia induces[57].

### 3.6 *Olea europaea* (Family - Oleaceae)

It is also known as Olive. But the genus Olea got its name from the Greek "elaia" and the Latin "oleum". From *O. europaea*, secondary metabolites belonging to the secoiridoids, iridoids, flavanones, triterpenes, flavonoids, benzoic acid derivatives, isochromans, and other classes had been isolated by phytochemical research. A wide range of *in vitro* and *in vivo* pharmacological activities, including anticonvulsant, antioxidant, anti-inflammatory, immunomodulatory, analgesic, antimicrobial, antiviral, antihypertensive, anticancer, antihyperglycemic, antidiabetic, antinociceptive, gastroprotective, and wound healing activities, have been demonstrated by plant materials and isolated components[58]. Effects of *Olea europaea* leaf extract on streptozotocin-induced diabetes in albino male rats and observation of changes in body weight, renal weight, dietary intake, and consumption of water as well as a reduction in HDL-C level and an increase in LDL and VLDL[59].

### 3.7 *Anogeissus acuminata* (Family - Combretaceae)

It is also known as also known as Button tree. These secondary metabolites can be very significant for humans because they can help treat a wide range of diseases, including eczema, headache, skin ulcers, menstrual cramps, rheumatoid arthritis, TB, dermatitis, and medications, even though the organic ingredients produced by plants may not be essential for their life or normal physiology[60]. On experimentally created diabetic nephropathy, *Anogeissus acuminata* leaf extract was investigated for its anti-diabetic and renoprotective activities. The greater urinary volume and decreased protein excretion in urine were signs of improved urinary functionality, according to data[61].

### 3.8 *Juglans regia* L. (Family - Juglandaceae)

It is popularly known as the Persian walnut, Circassian walnut, and English walnut. It is most common in Southeast Europe, but it can also be found in the Himalayas and Southwest China. This plant is indigenous to Kyrgyzstan, where walnut trees can reach elevations of 1,000–2,000 meters (3000–7000 feet). An extensive body of research has demonstrated that *Juglans regia* possesses a few therapeutic properties, including anti-fertility, antioxidant, bronchodilator, analgesic, anti-diabetic, hepatoprotective, immunomodulatory, anti-microbial, anti-inflammatory, anticancer, wound healing, anti-histaminic[62]. A study using immunohistochemistry was done to determine whether *Juglans regia* L. leaf extract inhibits the development of DN in experimental diabetes. Following GRL ingestion, lipid peroxidation was seen in diabetic rats ($P = 0.01$)[63].

### 3.9 *Fragaria ananassa* (Family - Rosaceae)

It is also known as the *Genus fragaria*. Flavonols, a class of phytochemicals that also includes ellagitannin, chlorogenic acid, salicylic acid, and caffeine acid, have several positive health effects, including the regulation of heart function, gastric cancer[64]. When strawberry (*Fragaria ananassa*) leaves were extracted and tested for effects on DN in rats, it was discovered that both insulin and blood glucose levels increased[65].

### 3.10 *Ginkgo biloba* (Family - Ginkgoaceae)

It is also known as Maidenhair tree. The maidenhair tree *Ginkgo biloba* L. also referred to as a living fossil, is indigenous to China, Japan, and Korea and has experienced relatively few evolutionary changes over the course of 200 million years. For more than 5000 years, traditional Chinese medicine has employed medicinal preparations of dried leaves for a variety of uses. Alzheimer's Disease (AD), neurodegenerative diseases, cerebral insufficiencies, neurosensory issues (such as tinnitus, and vertigo), eye conditions, vascular insufficiencies, time of life memory deficits, and oxidative stress have all benefited greatly from its use[66]. By the inhibition of tissue transglutaminase, *Ginkgo biloba* extract of the leaf has been shown to prevent diabetic nephropathy, as evidenced by lower kidney weights and lower levels of 24-hour urinary albumin excretion[67].

### 3.11 *Laurus nobilis* L. (Family - Lauraceae)

It is also known as Bay laurel or laurel. The laurel fruit was used to separate a variety of phytoconstituents, including monoterpenes, sesquiterpenes, fatty acids, flavonoids, phenolic acid, and certain minerals. Its antioxidant, antibacterial, antiproliferative, antinociceptive, and anti-inflammatory effects have been the subject of numerous pharmacological research[68,69]. The Aspartate Aminotransferase (AST), Gamma-Glutamyl Transferase (GGT), and Alanine Aminotransferase (ALT) enzyme levels were significantly reduced, and glucose concentration decreased in *Laurus nobilis* L. leaf extract on vital organs in streptozotocin-induced diabetic rats[70].

### 3.12 *Dryopteris dilatata* (Family - Dryopteridaceae)

It is also known as Broad buckler fern. These healing plants include naturally occurring bioactive substances known as phytochemicals in all their sections, including sugars, alkaloids, phenols, flavonoids, steroids, terpenoids, and tannins[71]. It was discovered that *Dryopteris dilatata* leaf extract has beneficial effects on STZ-induced diabetic nephropathy in male Wistar rats[72].

### 3.13 *Moringa oleifera* (Family Moringaceae)

It is also known as drumstick tree. *Moringa oleifera* Lam. is a plant that is often consumed as a food supplement and has been proven to have beneficial pharmacological benefits, such as CNS activity, anti-ulcer, anti-cancer, anti-inflammatory, anti-microbial, antioxidant, hepatoprotective, and antipyretic action[73]. *Moringa oleifera* extract was found to have anti-inflammatory and anti-angiogenesis properties as well as reduce levels of glycemia, cholesterol, and triglycerides in the early stages of STZ-induced DN in rats[74].

### 3.14 *Punica granatum* L. (Family - Punicaceae)

It is also known as the pomegranate. Anti-fibrotic, anti-tumour, anti-bacterial, anti-diabetic, anti-fungal and pharmacological action. Pomegranate has been used to isolate the phytoconstituents such as alkaloids, sterols, flavonoids, terpenoids, proanthocyanidins and xanthonoids that are present in this plant[75]. In STZ-induced diabetic mice, *Punica granatum* Linn. leaf extracts prevented diabetic nephropathy and it was discovered that the mice had larger body weights and lower blood glucose levels[76].

### 3.15 *Lycium chinense* (Family - Nightshade)

It is also known as Chinese boxthorn. The leaves of *Lycium chinense* Mill. were once employed in traditional Chinese medication to nourish the kidneys and improve vision, but they are now largely discarded. Goji leaves have a similar nutritional profile to Goji berries, however, some nutrients, such as flavonoids, are present in greater quantities in the former[77]. By reducing renal oxidative stress and inflammation caused by hyperglycemia and reducing serum levels of creatinine, albumin, and BUN, TGF-1, *Lycium chinense* leaves extract improves diabetic nephropathy[78].

### 3.16 *Rumex nervous* (Family - Polygonaceae)

It is also known as Magnoliopsida. The carbon-based secondary metabolites include terpenoids,

phenolics, steroid glycosides, flavonoids, fatty acids, vitamin C, saponins, and others. Investigations into a range of pharmacological properties, including anti-inflammatory, anti-microbial, antioxidant, wound-healing, and anti-plasmodial activities[79]. By triggering Nrf2 signalling, *Rumex nervosus* was able to reduce the effects of streptozotocin-induced diabetic nephropathy in rats. It was found that serum albumin levels, urinary output and flow, and urinary creatinine levels were all significantly lower, whereas serum urea and creatinine, as well as urinary albumin and the albumin/Cr ratio, were both significantly higher[80].

### 3.17 *Acacia catechu* (Family - Fabaceae)

It is also known as black cutch. The plant contained a variety of compounds, such as ascorbic acid, terpenoids, triterpenoids, alkaloids, and tannins. Anti-diabetic, antioxidant, anti-microbial, anti-cancer, anti-diarrheal, anti-inflammatory, antiviral, hepatoprotective, and immunomodulatory are a few of their properties[81]. *Acacia catechu* leaves ameliorate Streptozotocin-induced diabetic rats' nephropathy Moderate-to-severe degenerative characteristics, such as dilated tubules, degraded tubules, glomerular congestion, interstitial inflammatory infiltration, and atrophy of the glomerulus seen with dilated glomerular space, were visible in the extract and observation[82].

### 3.18 *Croton hookeri* (Family- Euphorbiaceae)

It is also known as croton. The plant included several different substances, including tannin, terpenoids, triterpenoids, and alkaloids[83]. In this work, rats with diabetes produced by streptozotocin were examined for the protective effects of *Croton hookeri* extract on renal injury. It was discovered that this extract dramatically decreased fasting blood glucose levels and kidney weight[84].

### 3.19 *Macaranga tanarius* (Family - Euphorbiaceae)

It is also known as Parasol leaf tree. Propolis contains about 300 active ingredients, including flavonoids, terpenes, and phenolic acids. Depending on the source, propolis has different chemical compositions. They include anti-Alzheimer's, anti-cancer, anti-diabetic, anti-microbial, longevity-extending, and anti-inflammatory properties[85]. Revealed the therapeutic potential of a leaf extract from *Macaranga tanarius* (MTE) and the greater glucose-induced fibronectin in DN[86].

### 3.20 *Molineria recurvata* (Family - Hypoxidaceae)

It is also known as palm grass. The plant included several substances, including saponins, tannins, steroids, glycosides, flavonoids, and alkaloids, according to a phytochemical examination[87]. They include antioxidant, anti-inflammatory, antibacterial, and osteoporosis[88]. *Molineria recurvata* Ameliorates streptozotocin-induced diabetes nephropathy through antioxidant and anti-inflammatory pathways and observed that decreased fasting blood glucose levels and kidney weight[89].

All medicinal plants leave extract cure or treatment of DN by STZ-induced rats' model shown in Table 1.

## 4. Role of Flavonoids and Alkaloids to Cure or Treatment of Diabetic Nephropathy

All the medicinal plants included in the table contain phytochemicals, but the flavonoids quercetin, myricetin, and kaempferol, as well as the alkaloids berberine, magnoflorine, trigonelline, and oxymatrine, are particularly important in the care of diabetes nephropathy. Compared to other phytochemicals, flavonoids and alkaloids are more effective at treating diabetes nephropathy. The flavonoid targets the nucleus by targeting the TNF-beta, AGEs, and ROS pathways shown in Figure 4 and in the case of alkaloids target the TGF-**β** /$Smad_3$, NF-$_K$B, $TLR_4$/NF-**β**, TNF-**β**, CTGF, PPAR-γ/GLUT4-leptin/TNF-**α** signalling pathways this function is equivalent to that of flavonoids and alkaloids[90,91]. Furthermore, as shown in Table 2, every medicinal herb has phytochemical components such as alkaloids, flavonoids, glycosides, steroids, terpenoids, and phenolics that can treat diabetes nephropathy. And the chemical structures of flavonoids and alkaloids are indicated in the table, together with phytochemical components found in medicinal plants used to treat diabetes and nephropathy (Table 3).

**Table 1.** Various herbal plants leaves extract in cure of diabetic nephropathy by 'streptozotocin-induced rats' model

| Sr. No. | Medicinal Plant Name | Family | Common Name | Animal/Cell Model and STZ dose mg/kg | Parts used | Extraction method | Parameter | Ref. |
|---|---|---|---|---|---|---|---|---|
| 1. | *Sesbania sesban* | Fabaceae | Egyptian river hemp or 'Egyptian Sesban' | streptozotocin-induced diabetic in rat (55 mg/kg) | leaves | Aqueous | Reduce fat, protein, albumin, and glycated haemoglobin levels (HbA1c) | 45 |
| 2. | *Elaeis guineensis* | Arecaceae | Oil palm | streptozotocin-induced diabetic in rat (60 mg/kg) | leaves | ethanol | Reduce p22phox and p67phox NADPH oxidase subunit expression in the kidneys | 47 |
| 3. | *Tecoma stans* | Bignoniaceae | Yellow bells | streptozotocin-induced diabetic in rat (45 mg/kg) | leaves | methanol | effectiveness in fighting the illness and lowering the MDA level. | 49 |
| 4. | *Aloe barbadense* miller | Liliaceae | Alov vera | streptozotocin-induced diabetic in rat (60 mg/kg) | leaves | ethanol | decreased body weight and value increases of the kidneys, food, and fluids | 52 |
| 5. | *Ginger officinale* Roscoe | Zingiberaceae | Ginger | streptozotocin-induced diabetic in rat (50 mg/kg) | leaves | ethanol | Reduced fasting blood glucose levels | 54 |
| 6. | *Olea europaea* | Oleaceae | Olive | streptozotocin-induced diabetic in rat (60 mg/kg) | leaves | Aqueous | reduction in HDL-C level and an increase in LDL and VLDL levels. | 56 |
| 7. | *Anogeissus acuminata* | Combretaceae | Button tree | streptozotocin-induced diabetic in rat (50 mg/kg) | leaves | methanol | better urine volume and less protein excretion in the urine, both indicators of improved urinary function. | 58 |
| 8. | *Juglans regia* L. | Juglandaceae | Persian walnut | streptozotocin-induced diabetic in rat (55 mg/kg) | leaves | methanol | After consuming GRL, diabetic rats showed hyperglycemic effects and lipid peroxidation ($P = 0.01$). | 60 |
| 9. | *Genus fragaria* | Rosaceae | Strawberry | streptozotocin-induced diabetic in rat (45 mg/kg) | leaves | water | reduced blood sugar and elevated insulin levels | 62 |
| 10. | *Ginkgo biloba* | Ginkgoaceae | Maidenhair tree | streptozotocin-induced diabetic in rat (50 mg/kg) | leaves | ethanol | reduced kidney weights and reduced 24 h urine albumin excretion levels | 64 |

**Table 1.** *to be Continued...*

| Sr. No. | Medicinal Plant Name | Family | Common Name | Animal/Cell Model and STZ dose mg/kg | Parts used | Extraction method | Parameter | Ref. |
|---|---|---|---|---|---|---|---|---|
| 11. | *Laurus nobilis* L. | Lauraceae | Lauraceae | streptozotocin-induced diabetic in rat (70 mg/kg) | leaves | ethanol | Aminotransferase (AST), Gamma-Glutamyl Transferase (GGT), and Alanine Aminotransferase (ALT) enzyme levels were significantly reduced | 67 |
| 12. | *Dryopteris dilatata* | Dryopteridaceae | Broad buckler fern | streptozotocin-induced diabetic in rat (60 mg/kg) | leaves | methanol | Organ weight decreased, and hyperglycemia and corticosterone were restored | 69 |
| 13. | *Moringa oleifera* | Moringaceae | Drumstick tree | streptozotocin-induced diabetic in rat (50 mg/kg) | leaves | water | reduced levels of triglycerides, cholesterol, and glucose | 71 |
| 14. | *Punica granatum* L. | Punicaceae | Pomegranate | streptozotocin-induced diabetic in rat (45 mg/kg) | leaves | methanol | rise in body weight and a decline in blood sugar levels | 73 |
| 15. | *Lycium chinense* | Nightshade | Chinese boxthorn | streptozotocin-induced diabetic in rat (65 mg/kg) | leaves | methanol | reductions in serum levels of TGF-1, albumin, BUN, and creatinine. | 75 |
| 16. | *Rumex nervous* | Polygonaceae | Magnoliopsida | streptozotocin-induced diabetic in rat (35 mg/kg) | leaves | Methanol | serum albumin levels, urinary output and flow, and urinary creatinine levels were all significantly lower, whereas serum urea and creatinine, as well as urinary albumin and the albumin/Cr ratio, were both significantly higher | 77 |
| 17. | *Acacia catechu* | Fabaceae | Black cutch | streptozotocin-induced diabetic in rat (75 mg/kg) | leaves | ethanol | shown moderate-to-severe degenerative features like dilated tubules, degenerated tubules, glomerular congestion, interstitial inflammatory infiltration, and atrophy of glomerulus seen with dilated glomerular space | 79 |

**Table 1.** *to be Continued...*

| Sr. No. | Medicinal Plant Name | Family | Common Name | Animal/Cell Model and STZ dose mg/kg | Parts used | Extraction method | Parameter | Ref. |
|---|---|---|---|---|---|---|---|---|
| 18. | *Croton hookeri* | *Euphorbiaceae* | *Croton* | streptozotocin-induced diabetic in rat (45 mg/kg) | leaves | methanol | reduced the fasting blood glucose level and kidney weight significantly | 81 |
| 19. | *Macaranga tanarius* | Euphorbiaceae | Parasol leaf tree | streptozotocin-induced diabetic in rat (35 mg/kg) | leaves | Acetone | Increase glucose-induced fibronectin | 83 |
| 20. | *Molineria recurvata* | Hypoxidaceae | Palm grass | streptozotocin-induced diabetic in rat (45 mg/kg) | leaves | methanol | reduced the organ weight and blood glucose levels | 86 |

**Table 2.** Phytochemical constituents present in medicinal plants used to cure diabetes nephropathy

| Species | F | A | C | Ta | Se | Te | Ph | Pr | G | M | R |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *Sesbania sesban* | + | + | - | - | + | + | + | - | - | - | - |
| *Elaeis guineensis* | + | + | + | + | + | + | + | + | + | - | + |
| *Tecoma stans* | + | + | + | + | + | + | + | + | + | - | - |
| *Aloe barbadensis* miller | + | + | + | + | + | + | + | + | + | - | - |
| *Zingiber officinale* Roscoe | + | + | - | + | - | - | + | - | + | - | - |
| *Olea europaea* | + | + | + | - | - | - | + | - | - | - | - |
| *Anogeissus acuminata* | + | + | + | + | + | + | + | + | + | - | + |
| *Juglans regia* L. | + | + | - | - | + | + | + | + | + | - | - |
| *Fragaria ananassa* | + | + | + | + | + | + | + | + | - | - | - |
| *Ginkgo biloba* | + | + | + | - | + | + | + | - | - | - | - |
| *Laurus nobilis* L. | + | + | + | + | + | - | + | + | - | - | - |
| *Dryopteris dilatata* | + | + | + | + | - | - | + | + | - | - | - |
| *Moringa oleifera* | + | + | + | + | - | + | - | + | - | - | - |
| *Punica granatum* L. | + | + | + | + | + | - | + | - | + | - | - |
| *Lycium chinense* | + | + | + | + | + | + | - | + | - | - | - |
| *Rumex nervous* | + | + | + | + | - | + | - | - | - | - | - |
| *Acacia catechu* | + | + | + | + | + | - | + | - | - | - | - |
| *Croton hookeri* | + | + | + | + | + | - | - | - | + | + | - |
| *Macaranga tanarius* | + | + | + | + | + | + | - | - | + | + | - |
| *Molineria recurvata* | + | + | + | + | + | + | + | - | + | - | - |

**Pr**-(protein), **G**-(glycoside), **M**-(mucilage's), **R-(**resin), **(+)** present, **(-)** not present.

**Table 3.** Chemical structure of flavonoids and alkaloids to help cure diabetes nephropathy

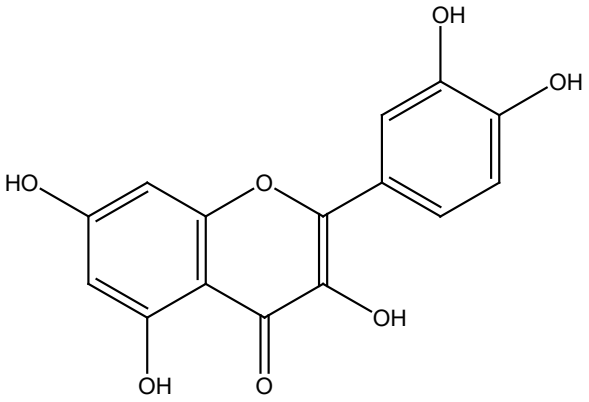
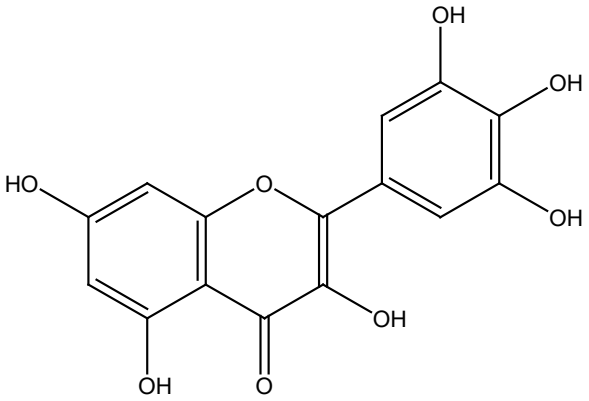
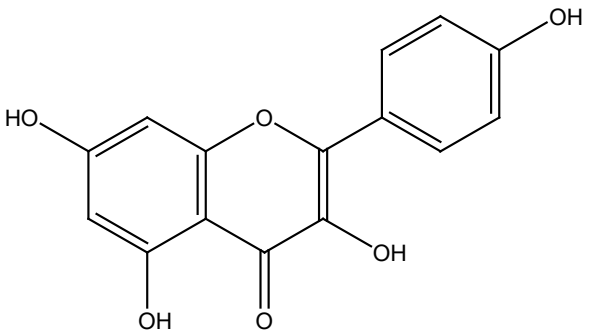
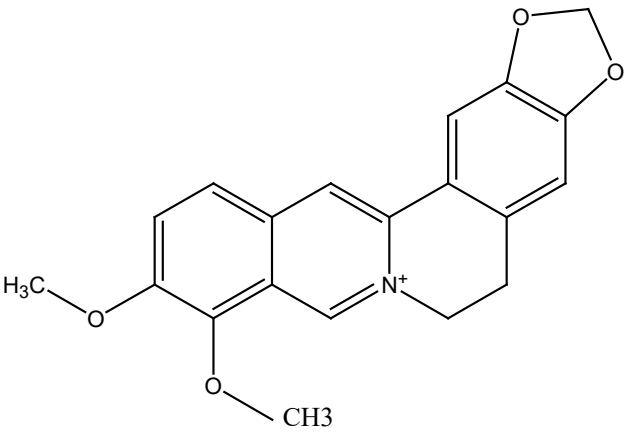
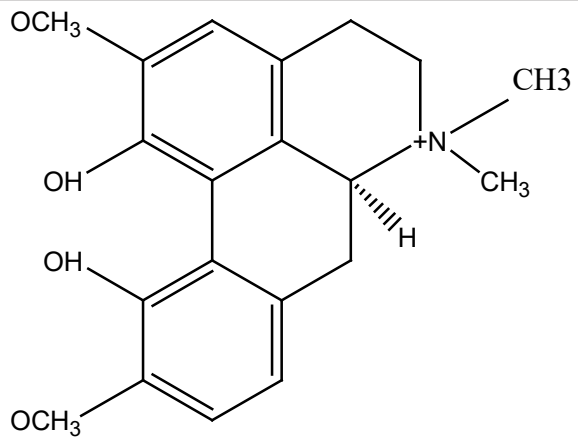
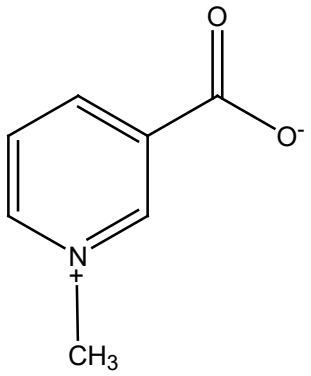
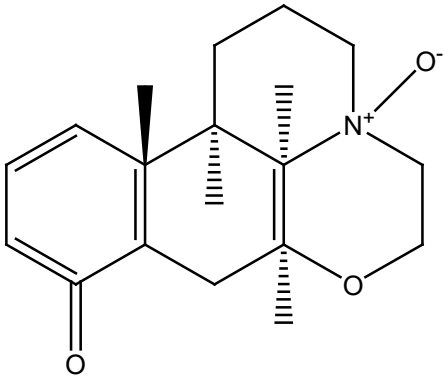
| Chemical Name | Chemical Structure |
|---|---|
| Quercetin |  |
| Myricetin |  |
| Kaempferol |  |
| Berberine |  |

**Table 3.** *to be Continued...*

| | |
|---|---|
| Magnoflorine |  |
| Trigonelline |  |
| Oxymatrine |  |

## 5. Conclusion

The results of this review suggest that because stress and free radical generation are two major contributors to diabetic nephropathy, traditional medicines with antioxidant characteristics could be used in the treatment of the condition. As a result of the broad antioxidant qualities of essential oils, flavonoids, and polyphenols we can deduce from our research that the medicinal herbs we've just described can effectively reduce diabetes and its consequences with little to no adverse effects. Overall, phytochemical components from plants may appear to be a good and secure substitute, offering tremendous opportunities for study and learning. The medicinal plant like *Sesbania sesban, Elaeis guineensis, Tecoma stans, Aloe barbadensis* miller, *Zingiber officinale* Roscoe, *Olea europaea, Anogeissus acuminata, Juglans regia* L., *Fragaria ananassa, Ginkgo biloba, Laurus nobilis* L., *Dryopteris dilatata, Moringa oleifera, Punica granatum* L., *Lycium chinense, Rumex*

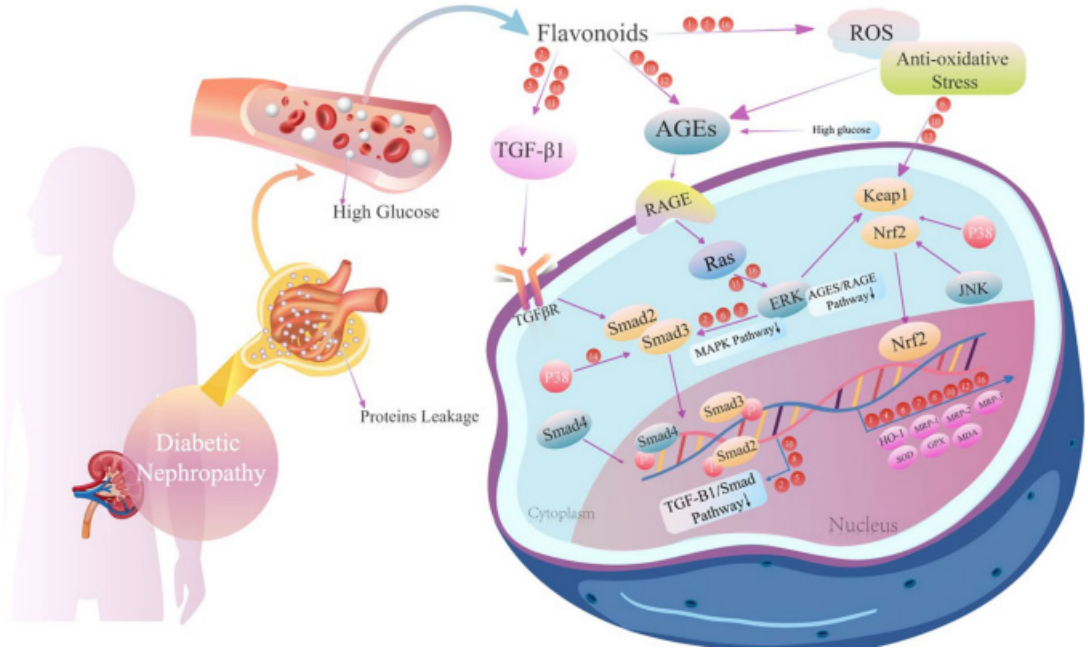



**Figure 4.** Role of flavonoid to treat diabetes nephropathy by different signalling pathways.

*nervous, Acacia catechu, Croton hookeri, Macaranga tanarius, Molineria recurvata* has alkaloids and flavonoids in its leaves, which aid in the cure of DN. Many phytoconstituents such alkaloids and terpenoids, fatty acids, glycosides, sterols, terpenoids, esters, and flavonoids, as well as a few other bioactive compounds, may be responsible for the therapeutic advantages of medicinal plant leaf extract.

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## 7. References

1. Ayodele OE, Alebiosu CO, Salako BL. Diabetic nephropathy - A review of the natural history, burden, risk factors and treatment. J Natl Med Assoc. 2004; 96(11):1445-54. PMID 15586648. PMCID PMC2568593
2. Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH, *et al.* Nephropathy in diabetes. Diabetes Care. 2004; 27(Suppl 1):S79-83. https://doi.org/10.2337/diacare.27.2007.S79 PMid:14693934
3. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes estimates for the year 2000 and projections for 2030. Diabetes Care. 2004; 27(5):1047-53. https://doi.org/10.2337/diacare.27.5.1047 PMid:15111519
4. Sharma D, Bhattacharya P, Kalia K, Tiwari V, Tiwari V. Diabetic nephropathy: new insights into established therapeutic paradigms and novel molecular targets. Diabetes Res Clin Pract. 2017; 128:91-108. https://doi.org/10.1016/j.diabres.2017.04.010 PMid:28453961
5. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010; 87(1):4-14. https://doi.org/10.1016/j.diabres.2009.10.007 PMid:19896746
6. Oliveira RSM, Rebocho A, Ahmadpour E, Nissapatorn V, Pereira DM, Pereira DM. Type 1 diabetes mellitus: a review on advances and challenges in creating insulin-producing devices. Micromachines. 2023; 14(1):151. https://doi.org/10.3390/mi14010151 PMid:36677212 PMCid: PMC9867263
7. Tsai IT, Wu CC, Hung WC, Lee TL, Hsuan CF, Wei CT, *et al.* FABP1 and FABP2 as markers of diabetic nephropathy. Int J Med Sci. 2020; 17(15):2338-45. https://doi.org/10.7150/ijms.49078 PMid:32922199 PMCid:PMC7484639
8. Hajam YA, Rani R, Malik JA, Pandita A, Sharma R, Kumar R. Diabetes mellitus: signs and symptoms, epidemiology, current prevention, management therapies, and treatments. In: Antidiabetic potential of plants in the era of omics.

Apple Academic Press; 2023. pp. 31-77. https://doi.org/10.1201/9781003282860-3
9. Mayfield JA. Diagnosis and classification of diabetes mellitus: new criteria. Am Fam Phys. 1998; 58(6):1355-62. PMID 9803200.
10. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group. Diabetes. 1979; 28(12):1039-57. https://doi.org/10.2337/diab.28.12.1039 PMid:510803
11. Magliano DJ, Zimmet P, Shaw JE. Classification of diabetes mellitus and other categories of glucose intolerance. Int Textbook Diabetes Mellitus. 2015; p. 1-6. https://doi.org/10.1002/9781118387658
12. Hajam YA, Malik JA, Pandita D, Rani R. Diabetes mellitus: history, diagnosis, classification, pathophysiology, and risk factors. In: Antidiabetic potential of plants in the era of omics. Apple Academic Press; 2023. p. 3-29. https://doi.org/10.1201/9781003282860-2
13. Katsarou A, Gudbjörnsdottir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, *et al.* Type 1 diabetes mellitus. Nat Rev Dis Primers. 2017; 3(1):17016. https://doi.org/10.1038/nrdp.2017.16 PMid:28358037
14. Oliveira RSM, Rebocho A, Ahmadpour E, Nissapatorn V, Pereira DM, Pereira DM. Type 1 diabetes mellitus: a review on advances and challenges in creating insulin-producing devices. Micromachines. 2023; 14(1):151. https://doi.org/10.3390/mi14010151 PMid:36677212 PMCid: PMC9867263
15. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2013; 36(Suppl 1):S67-74. https://doi.org/10.2337/dc13-S067 PMid:23264425 PMCid:PMC3537273
16. DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, *et al.* Type 2 diabetes mellitus. Nat Rev Dis Primers. 2015; 1(1):15019. https://doi.org/10.1038/nrdp.2015.19 PMid:27189025
17. Olokoba AB, Obateru OA, Olokoba LB. Type 2 diabetes mellitus: a review of current trends. Oman Med J. 2012; 27(4):269-73. https://doi.org/10.5001/omj.2012.68 PMid:23071876 PMCid:PMC3464757
18. Buchanan TA, Xiang AH. Gestational diabetes mellitus. J Clin Invest. 2005; 115(3):485-91. https://doi.org/10.1172/JCI24531 PMid:15765129 PMCid: PMC1052018
19. Xiang AH, Peters RK, Trigo E, Kjos SL, Lee WP, Buchanan TA. Multiple metabolic defects during late pregnancy in women at high risk for type 2 diabetes mellitus. Diabetes. 1999; 48(4):848-54. https://doi.org/10.2337/diabetes.48.4.848 PMid:10102703
20. Dinesen S, El-Faitarouni A, Dalgaard LT, Dalgaard LT. Circulating microRNAs associated with gestational diabetes mellitus: useful biomarkers? J Endocrinol. 2023; 256(1). https://doi.org/10.1530/JOE-22-0170 PMid:36346274
21. Pillai A, Fulmali D, Fulmali D. A narrative review of new treatment options for diabetic nephropathy. Cureus. 2023; 15(1):e33235. https://doi.org/10.7759/cureus.33235
22. Kanter JE, Bornfeldt KE. Impact of diabetes mellitus. Arterioscler Thromb Vasc Biol. 2016; 36(6):1049-53. https://doi.org/10.1161/ATVBAHA.116.307302 PMid:27225786 PMCid: PMC4972454
23. Duran-Salgado MB, Rubio-Guerra AF. Diabetic nephropathy and inflammation. World J Diabetes. 2014; 5(3):393-8. https://doi.org/10.4239/wjd.v5.i3.393 PMid:24936261 PMCid: PMC4058744
24. Yamagishi SI, Matsui T. Advanced glycation end products, oxidative stress, and diabetic nephropathy. Oxid Med Cell Longev. 2010; 3(2):101-8. https://doi.org/10.4161/oxim.3.2.11148 PMid:20716934 PMCid: PMC2952094
25. Collins AJ. Cardiovascular mortality in end-stage renal disease. Am J Med Sci. 2003; 325(4):163-7. https://doi.org/10.1097/00000441-200304000-00002 PMid:12695721
26. Valmadrid CT, Klein R, Moss SE, Klein BE. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. Arch Intern Med. 2000; 160(8):1093-100. https://doi.org/10.1001/archinte.160.8.1093 PMid:10789601
27. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes estimates for the year 2000 and projections for 2030. Diabetes Care. 2004; 27(5):1047-53. https://doi.org/10.2337/diacare.27.5.1047 PMid:15111519
28. American Diabetes Association, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH, *et al.* Nephropathy in diabetes. Diabetes Care. 2004; 27(Suppl 1):s79-83. https://doi.org/10.2337/diacare.27.2007.S79 PMid:14693934
29. Reeves WB, Andreoli TE. Transforming growth factor b contributes to progressive diabetic nephropathy. Proc Natl Acad Sci U S A. Proceedings of the National Academy of Sciences. Proceedings of the NatI Acad sci USA. 2000; 97(14):7667-9. https://doi.org/10.1073/pnas.97.14.7667 PMid:10884396 PMCid: PMC33997
30. Ayodele OE, Alebiosu CO, Salako BL. Diabetic nephropathy - A review of the natural history, burden, risk factors and treatment. J Natl Med Assoc. 2004; 96(11):1445-54. PMID 15586648. PMCID PMC2568593
31. Hostetter TH, Troy JL, Brenner BM. Glomerular hemodynamics in experimental diabetes mellitus. Kidney Int. 1981; 19(3):410-5. https://doi.org/10.1038/ki.1981.33 PMid:7241881
32. Hostetter TH, Rennke HG, Brenner BM. The case for intrarenal hypertension in the initiation and progression of diabetic and other glomerulopathies. Am J Med. 1982; 72(3):375-80. https://doi.org/10.1016/0002-9343(82)90490-9 PMid:7036732

33. Fukami K, Yamagishi SI, Ueda S, Okuda S. Role of AGEs in diabetic nephropathy. Curr Pharm Des. 2008; 14(10):946-52. https://doi.org/10.2174/138161208784139710 PMid:18473844
34. Pourghasem M, Shafi H, Babazadeh Z. Histological changes of kidney in diabetic nephropathy. Caspian J Intern Med. 2015; 6(3):120-7. PMID 26644877. PMCID PMC4650785
35. Dabla PK. Renal function in diabetic nephropathy. World J Diabetes. 2010; 1(2):48-56. https://doi.org/10.4239/wjd.v1.i2.48 PMid:21537427 PMCid: PMC3083882
36. Ritz E, Stefanski A. Diabetic nephropathy in type II diabetes. Am J Kidney Dis. 1996; 27(2):167-94. https://doi.org/10.1016/S0272-6386(96)90538-7PMid:8659491
37. Schena FP, Gesualdo L. Pathogenetic mechanisms of diabetic nephropathy. J Am Soc Nephrol. 2005; 16(Suppl 1):S30-3. https://doi.org/10.1681/ASN.2004110970PMid:15938030
38. Ruiz-Ortega M, Rodrigues-Diez RR, Lavoz C, Rayego-Mateos S. Special Issue "Diabetic Nephropathy: Diagnosis, Prevention and Treatment". J Clin Med. 2020; 9(3):813. https://doi.org/10.3390/jcm9030813 PMid:32192024 PMCid: PMC7141346
39. Remuzzi G, Schieppati A, Ruggenenti P. Nephropathy in patients with type-2 diabetes. N Engl J Med. 2002; 346(15):1145-51. https://doi.org/10.1056/NEJMcp011773 PMid:11948275
40. Ritz E, Zeng XX, Rychlík I. Clinical manifestation, and natural history of diabetic nephropathy. Diabetes Kidney. 2011; 170:19-27. https://doi.org/10.1159/000324939 PMid:21659754
41. Pourghasem M, Shafi H, Babazadeh Z. Histological changes of kidney in diabetic nephropathy. Caspian J Intern Med. 2015; 6(3):120-7. PMID 26644877 PMCID PMC4650785
42. Guo J, Zheng W, Liu Y, Zhou M, Shi Y, Lei M, *et al*. Long non-coding RNA DLX6-AS1 is the key mediator of glomerular podocyte injury and albuminuria in diabetic nephropathy by targeting the miR-346/GSK-3β signalling pathway. Cell Death Dis. 2023; 14(2):172. https://doi.org/10.1038/s41419-023-05695-2 PMid:36854759 PMCid: PMC9975222
43. John S. Complication in diabetic nephropathy. Diabetes Metab Syndr Clin Res Rev. 2016; 10(4):247-9. https://doi.org/10.1016/j.dsx.2016.06.005 PMid:27389078
44. Samsu N. Diabetic nephropathy: challenges in pathogenesis, diagnosis, and treatment. BioMed Res Int. 2021; 2021:1497449. https://doi.org/10.1155/2021/1497449 PMid:34307650 PMCid: PMC8285185
45. Shahin DH, Sultana R, Farooq J, Taj T, Khaiser UF, Alanazi NSA, *et al.* Insights into the uses of traditional plants for diabetes nephropathy: a review. Curr Issues Mol Biol. 2022; 44(7):2887-902. https://doi.org/10.3390/cimb44070199 PMid:35877423 PMCid: PMC9316237
46. Abdelgawad SM, Hetta MH, Ibrahim MA, Fawzy GA, El-Askary HI, Ross SA. A holistic overview of the phytoconstituents and pharmacological activities of Egyptian Riverhemp [*Sesbania sesban* (L.) Merr.]: A review. Nat Prod Commun. 2023; 18(3):1934578X231160882. https://doi.org/10.1177/1934578X231160882
47. Gomase PV. *Sesbania sesban* Linn: A review on its ethnobotany, phytochemical and pharmacological profile. Asian J Biomed PharmSci. 2012; 2(12):11.
48. Pandhare RB, Sangameswaran B, Mohite PB, Khanage SG. Aqueous extracts of the leaves of *Sesbania sesban* reduces the development of diabetic nephropathy in streptozotocin-induced diabetic rat. Bangladesh J Pharmacol. 2010; 5(2):103-6. https://doi.org/10.3329/bjp.v5i2.7592
49. Owoyele BV, Owolabi GO. Traditional oil palm (*Elaeis guineensis* jacq.) and its medicinal uses: a review. CELLMED. 2014; 4(3):e16. https://doi.org/10.5667/tang.2014.0004
50. Varatharajan R, Sattar MZ, Chung I, Abdulla MA, Kassim NM, Abdullah NA. Antioxidant and pro-oxidant effects of oil palm (*Elaeis guineensis*) leaves extract in experimental diabetic nephropathy: a duration-dependent outcome. BMC Complement Altern Med. 2013; 13(1):242. https://doi.org/10.1186/1472-6882-13-242 PMid:24074026 PMCid: PMC3829664
51. Anand M, Basavaraju R. A review on phytochemistry and pharmacological uses of *Tecoma stans* (L.) Juss. ex Kunth. J Ethnopharmacol. 2021; 265:113270. https://doi.org/10.1016/j.jep.2020.113270 PMid:32822823
52. Gupta A, Behl T, Sehgal A, Singh S, Sharma N, Yadav S, *et al*. Elucidating the neuroprotective Effect of *Tecoma stans* Leaf Extract in STZ-Induced Diabetic Neuropathy. Evid Based Complement Alternat Med. 2022; 2022:3833392. https://doi.org/10.1155/2022/3833392 PMid:35795278 PMCid: PMC9251095
53. Kumar S, Yadav JP. Ethnobotanical and pharmacological properties of Aloe vera: A review. J Med Plants Res. 2014; 48(8):1387-98.
54. Sánchez M, González-Burgos E, Iglesias I, Gómez-Serranillos MP. Pharmacological update properties of Aloe vera and its major active constituents. Molecules. 2020; 25(6):1324. https://doi.org/10.3390/molecules25061324 PMid:32183224 PMCid: PMC7144722
55. Dangi NB, Gyanwali M, Gyanwali P, Sapkota HP, Pandey A, Shrestha A. Evaluation of aloe vera leaves extract in streptozotocin-induced diabetic nephropathy in the rat. J Chitwan Med Coll. 2015; 5(4):55-63. https://doi.org/10.3126/jcmc.v5i4.16555
56. Ali BH, Blunden G, Tanira MO, Nemmar A. Some phytochemical, pharmacological and toxicological properties of ginger (*Zingiber officinale* Roscoe): a review of recent research. Food Chem Toxicol. 2008; 46(2):409-20. https://doi.org/10.1016/j.fct.2007.09.085PMid:17950516
57. Al Hroob AM, Abukhalil MH, Alghonmeen RD, Mahmoud AM. Ginger alleviates hyperglycemia-induced oxidative stress, inflammation and apoptosis and protects rats against diabetic nephropathy. Biomed Pharmacother. 2018;

106:381-9. https://doi.org/10.1016/j.biopha.2018.06.148 PMid:29966984
58. Hashmi MA, Khan A, Hanif M, Farooq U, Perveen S. Traditional uses, phytochemistry, and pharmacology of *Olea europaea* (olive). Evid Based Complement Alternat Med. 2015; 2015:541591. https://doi.org/10.1155/2015/541591 PMid:25802541 PMCid: PMC4352757
59. Al-Attar AM, Alsalmi FA. Effect of *Olea europaea* leaves extract on streptozotocin-induced diabetes in male albino rats. Saudi J Biol Sci. 2019; 26(1):118-28. https://doi.org/10.1016/j.sjbs.2017.03.002 PMid:30622415 PMCid: PMC6318816
60. Yadav VK, Irchhiaya R, Ghosh AK. Phytochemical and pharmacognostic studies of *Anogeissus acuminata*. J Drug Deliv Ther. 2019; 9:450-7(4-A). https://doi.org/10.22270/jddt.v9i4-A.3507
61. Navale AM, Paranjape A. Antidiabetic and renoprotective effect of *Anogeissus acuminata* leaf extract on experimentally induced diabetic nephropathy. J Basic Clin Physiol Pharmacol. 2018; 29(4):359-64. https://doi.org/10.1515/jbcpp-2017-0190 PMid:29617268
62. Panth N, Paudel KR, Karki R. Phytochemical profile and biological activity of *Juglans regia*. J Integr Med. 2016; 14(5):359-73. https://doi.org/10.1016/S2095-4964(16)60274-1 PMid:27641607
63. Nasiry D, Khalatbary AR, Ahmadvand H, Talebpour Amiri FT. *Juglans regia* L. leaf extract attenuates diabetic nephropathy progression in experimental diabetes: an immunohistochemical study. Iran J Med Sci. 2019; 44(1):44-52. PMID 30666075.
64. Rapuru R, Bathula S, Kaliappan I. Phytochemical constituents and pharmacological activities of strawberry. In: Strawberries. IntechOpen; 2022. https://doi.org/10.5772/intechopen.103973 PMid:37547003 PMCid: PMC10402039
65. Ibrahim DS, Abd El-Maksoud MA. Effect of strawberry (*Fragaria ananassa*) leaf extract on diabetic nephropathy in rats. Int J Exp Pathol. 2015; 96(2):87-93. https://doi.org/10.1111/iep.12116 PMid:25645466 PMCid:PMC4459800
66. Mohanta TK, Tamboli Y, Zubaidha PK. Phytochemical, and medicinal importance of *Ginkgo biloba* L. Nat Prod Res. 2014; 28(10):746-52. https://doi.org/10.1080/14786419.2013.879303 PMid:24499319
67. Yu X, Su Q, Geng J, Liu H, Liu Y, Liu J, *et al*. *Ginkgo biloba* leaf extract prevents diabetic nephropathy through the suppression of tissue transglutaminase. Exp Ther Med. 2021; 21(4):333. https://doi.org/10.3892/etm.2021.9764 PMid:33732306 PMCid: PMC7903480
68. USMANI QI, Ahmad A, Jamaldeen FN. *Laurus nobilis* L., (Habb-ul-Ghar), A Review on phytochemistry, pharmacology and ethnomedicinal uses. J Drug Deliv Ther. 2021; 11(5):136-44. https://doi.org/10.22270/jddt.v11i5.5021
69. Anzano A, de Falco B, Grauso L, Motti R, Lanzotti V. Laurel, *Laurus nobilis* L.: A review of its botany, traditional uses, phytochemistry and pharmacology. Phytochem Rev. 2022; 21(2):565-615. https://doi.org/10.1007/s11101-021-09791-z
70. Mohammed RR, Omer AK, Yener Z, Uyar A, Ahmed AK. Biomedical effects of *Laurus nobilis* L. leaf extract on vital organs in streptozotocin-induced diabetic rats: experimental research. Ann Med Surg (Lond). 2021; 61:188-97. https://doi.org/10.1016/j.amsu.2020.11.051 PMid:33520200 PMCid: PMC7817776
71. Akpotu A, Ani C, Agiopu T, Okeke A, Agu F, Ugwuchukwu N, *et al*. Phytochemical and *in vitro* antioxidant properties of ethyl acetate leave extract of *Dryopteris dilatata* on Wistar rats. Afr J Biotechnol. 2021; 20(8):318-24. https://doi.org/10.5897/AJB2021.17339
72. Asiwe JN, Moke EG, Asiwe N, Yovwin GD, Nwogueze BC, Daubry TME. *Dryopteris dilatata* leaf extract ameliorates streptozotocin-induced diabetic nephropathy in male Wistar rats. Nutrire. 2022; 48(1):1. https://doi.org/10.1186/s41110-022-00186-4
73. Paikra BK, Dhongade HKJ, Gidwani B. Phytochemistry and pharmacology of *Moringa oleifera* Lam. J Pharmacopuncture. 2017; 20(3):194-200. https://doi.org/10.3831/KPI.2017.20.022 PMid:30087795 PMCid: PMC5633671
74. Thongrung R, Senggunprai L, Hipkaeo W, Tangsucharit P, Pannangpetch P. Anti-angiogenesis, and anti-inflammatory effects of *Moringa oleifera* leaf extract in the early stages of streptozotocin-induced diabetic nephropathy in rats. Asian Pac J Trop Biomed. 2022; 12(7):290. https://doi.org/10.4103/2221-1691.350177
75. Maphetu N, Unuofin JO, Masuku NP, Olisah C, Lebelo SL. Medicinal uses, pharmacological activities, phytochemistry, and the molecular mechanisms of *Punica granatum* L. (pomegranate) plant extracts: a review. Biomed Pharmacother. 2022; 153:113256. https://doi.org/10.1016/j.biopha.2022.113256 PMid:36076615
76. Mestry SN, Dhodi JB, Kumbhar SB, Juvekar AR. Attenuation of diabetic nephropathy in streptozotocin-induced diabetic rats by *Punica granatum* Linn. leaves extract. J Trad Complement Med. 2017; 7(3):273-80. https://doi.org/10.1016/j.jtcme.2016.06.008 PMid:28725620 PMCid: PMC5506633
77. Lei Z, Chen X, Cao F, Guo Q, Wang J. Phytochemicals, and bioactivities of *Goji (Lycium barbarum* L. and *Lycium chinense* Mill.) leaves and their potential applications in the food industry: a review. Int J Food Sci Technol. 2022; 57(3):1451-61. https://doi.org/10.1111/ijfs.15507
78. Olatunji OJ, Chen H, Zhou Y. *Lycium chinense* leaves extract ameliorates diabetic nephropathy by suppressing hyperglycemia mediated renal oxidative stress and inflammation. Biomed Pharmacother. 2018;

102:1145-51. https://doi.org/10.1016/j.biopha.2018.03.037 PMid:29710532

79. Gonfa YH, Beshah F, Tadesse MG, Bachheti A, Bachheti RK. Phytochemical investigation and potential pharmacologically active compounds of *Rumex nepalensis*: an appraisal. Beni Suef Univ J Basic Appl Sci. 2021; 10(1):1. https://doi.org/10.1186/s43088-021-00110-1
80. AlMousa LA, AlFaris NA, Alshammari GM, Alsayadi MM, ALTamimi JZ, Alagal RI, *et al*. *Rumex nervosus* could alleviate streptozotocin-induced diabetic nephropathy in rats by activating Nrf2 signalling. Sci Prog. 2022; 105(2): 00368504221102751:368504221102751. https://doi.org/10.1177/00368504221102751 PMid:35619568 PMCid: PMC10358522
81. Adhikari B, Aryal B, Bhattarai BR. A comprehensive review of the chemical composition and pharmacological activities of *Acacia catechu* (Lf) Willed. J Chem. 2021; 2021:1. https://doi.org/10.1155/2021/2575598
82. D'souza P, Holla R, Swamy G. Amelioration of diabetic nephropathy in streptozotocin-induced diabetic rats by *Acacia catechu* leaves extract. J Health Allied Sci Nu. 2019; 09(3):116-20. https://doi.org/10.1055/s-0039-3402084
83. Junior JI, Ferreira MR, de Oliveira AM, Soares LA. Croton sp.: A review about popular uses, biological activities and chemical composition. Res Soc Dev. 2022; 11(2): e57311225306. https://doi.org/10.33448/rsd-v11i2.25306
84. Kundu A, Dey P, Sarkar P, Karmakar S, Tae IH, Kim KS, *et al.* Protective effects of *Croton hookeri* on streptozotocin-induced diabetic nephropathy. Food Chem Toxicol. 2020; 135:110873. https://doi.org/10.1016/j.fct.2019.110873 PMid:31600566
85. Shahinozzaman M, Obanda DN, Tawata S. Chemical composition and pharmacological properties of Macaranga-type Pacific propolis: a review. Phytother Res. 2021; 35(1):207-22. https://doi.org/10.1002/ptr.6819 PMid:32776610
86. Hsu YC, Chang CC, Hsieh CC, Shih YH, Chang HC, Lin CL. Therapeutic potential of extracts from *Macaranga Tanarius* (MTE) in diabetic nephropathy. Plants (Basel). 2023; 12(3):656. https://doi.org/10.3390/plants12030656 PMid:36771740 PMCid: PMC9920382
87. Dey P, Mukherjee M, Bhakta T, Ghosh TK. Preliminary phytochemical studies of leaf extracts of *Molineria recurvata*. J Chem Pharm Res. 2012; 4(7):3727-0.
88. Wang Y, Li J, Li N. Phytochemistry and pharmacological activity of plants of genus Curculigo: an updated review since 2013. Molecules. 2021; 26(11):3396. https://doi.org/10.3390/molecules26113396 PMid:34205154 PMCid: PMC8199960
89. Dey P, Kundu A, Lee HE, Kar B, Vishal V, Dash S, *et al*. *Molineria recurvata* ameliorates streptozotocin-induced diabetic nephropathy through antioxidant and anti-inflammatory pathways. Molecules. 2022; 27(15):4985. https://doi.org/10.3390/molecules27154985 PMid:35956936 PMCid: PMC9370403
90. Hu Q, Qu C, Xiao X, Zhang W, Jiang Y, Wu Z, *et al*. Flavonoids on diabetic nephropathy: advances and therapeutic opportunities. Chin Med. 2021; 16(1):74. https://doi.org/10.1186/s13020-021-00485-4 PMid:34364389 PMCid: PMC8349014
91. Putra IMWA, Fakhruddin N, Nurrochmad A, Wahyuono S. A review of medicinal plants with renoprotective activity in diabetic nephropathy animal models. Life (Basel). 2023; 13(2):560. https://doi.org/10.3390/life13020560 PMid:36836916 PMCid: PMC9963806