

A Review on Phytochemical and Nephroprotective Properties of Lamiaceae Species against Diabetic Nephropathy

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Abstract:

Diabetic nephropathy (DN) is one of the most severe microvascular complications of diabetes mellitus and a leading cause of chronic kidney disease and end-stage renal failure worldwide. Persistent hyperglycaemia induces oxidative stress, inflammation, glomerular damage, and renal fibrosis, ultimately resulting in progressive loss of kidney function. Current therapeutic approaches mainly include strict glycaemic control, antihypertensive therapy, renin–angiotensin–aldosterone system inhibitors, SGLT2 inhibitors, and lifestyle modifications. However, these treatments are often associated with limited efficacy and adverse effects, creating a need for safer and more effective alternatives. Medicinal plants from the Lamiaceae family have gained considerable attention because of their rich phytochemical composition and broad pharmacological activities. Species such as *Ocimum sanctum*, *Rosmarinus officinalis*, *Salvia officinalis*, and *Teucrium polium* possess antioxidant, anti-inflammatory, hypoglycaemic, and renal protective properties. Various in vitro studies, including high glucose-induced mesangial cell injury and podocyte apoptosis assays, along with in vivo streptozotocin-induced diabetic nephropathy models, have demonstrated the potential of these plants to reduce oxidative stress, improve renal biomarkers, and prevent kidney damage. Bioactive compounds such as rosmarinic acid, flavonoids, terpenoids, and phenolic acids contribute significantly to these protective effects. This review highlights the therapeutic potential of Lamiaceae species in the management of diabetic nephropathy and emphasizes their importance as promising candidates for the development of novel plant-based nephroprotective agents.

Keywords:

Diabetic nephropathy, Lamiaceae family, Medicinal plants, Nephroprotection, oxidative stress, Renal fibrosis, phytochemicals, chronic kidney diseases.

Introduction:

Diabetic Nephropathy is one of the most prevalent and severe complications of Diabetes Mellitus and a major cause of end-stage renal disease in the world [1,2]. It affects approximately 30% of diabetic patients, making it a significant public health problem [2,3]. Blood glucose and blood pressure control are critical to the management of the disease and microalbuminuria is a useful marker of disease progression [2,3]. The current treatments are primarily aimed at blocking the renin–angiotensin system with ACE inhibitors and Angiotensin Receptor Blockers, as well as glucose-lowering drugs such as SGLT2 inhibitors and GLP-1 receptor agonists, which have also been found to be beneficial in reducing proteinuria and slowing disease progression, respectively, through dietary approaches including low-protein, low-glycaemic, low-calorie, and low-salt diets.[4-7] In recent years, new therapies have been developed, including mesenchymal stem cell and renal autologous cell therapies, which have shown promise as treatment options [1,2]. Nevertheless, there are still a number of patients that are difficult to treat, and new therapeutic targets and innovative treatment strategies are needed [1,2].

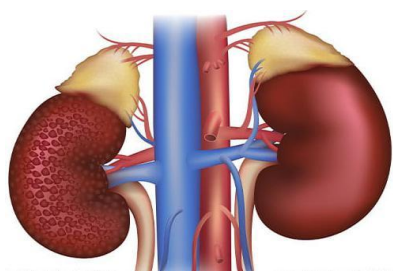


Figure 1: Anatomical Structure of the Human Kidneys

Epidemiology

Diabetic nephropathy is the most common cause of end stage renal disease (ESRD) and affects almost 30-40% of all diabetic patients globally. Its incidence has increased dramatically in recent decades, due to the increasing incidence of diabetes. DN also contributes significantly to cardiovascular morbidity, mortality and overall healthcare burden [10-13]. Diabetic nephropathy is a progressive kidney disease due to long-term diabetic mellitus. It is one of the most common causes of chronic kidney disease and end-stage renal failure in the world [14-18].

1. Hyperfiltration
2. Silent stage
3. Microalbuminuria (incipient)
4. Macroalbuminuria (overt nephropathy)
5. End stage renal disease

Development and Progression of the Disease: [Pharmacological Aspects]

Diabetic nephropathy is one of the most common complications of type 1 and type 2 diabetes mellitus [19]. Type 1 diabetes is an autoimmune disease in which the pancreas β -cells are destroyed, leading to a lack of insulin. Peripheral insulin resistance is a characteristic of type 2 diabetes. In both cases, the outcome is chronic hyperglycaemia [19]. In the presence of chronic hyperglycemia, oxidative stress, inflammation and hypertension all contribute to the damage of renal tissues. Hyperglycaemia increases the production of reactive oxygen species and advanced glycation end products leading to endothelial dysfunction and thickening of the glomerular basement membrane [20]. Haemodynamic changes are also involved in mesangial expansion, podocyte injury and glomerulosclerosis, in addition to the effects of inflammatory cytokines [21]. Hypertension aggravates renal injury by elevating the intraglomerular pressure [19]. As kidney injury progresses, albuminuria and glomerulopathy are seen, which is typical of diabetic nephropathy [21]. Progressive cellular dysfunction and fibrosis cause a progressive reduction in renal filtration capacity, and hence reduced kidney function [20,21]. Diabetic nephropathy may progress to end-stage renal failure, which necessitates dialysis or kidney transplantation, if not treated or if it progresses [19,21].

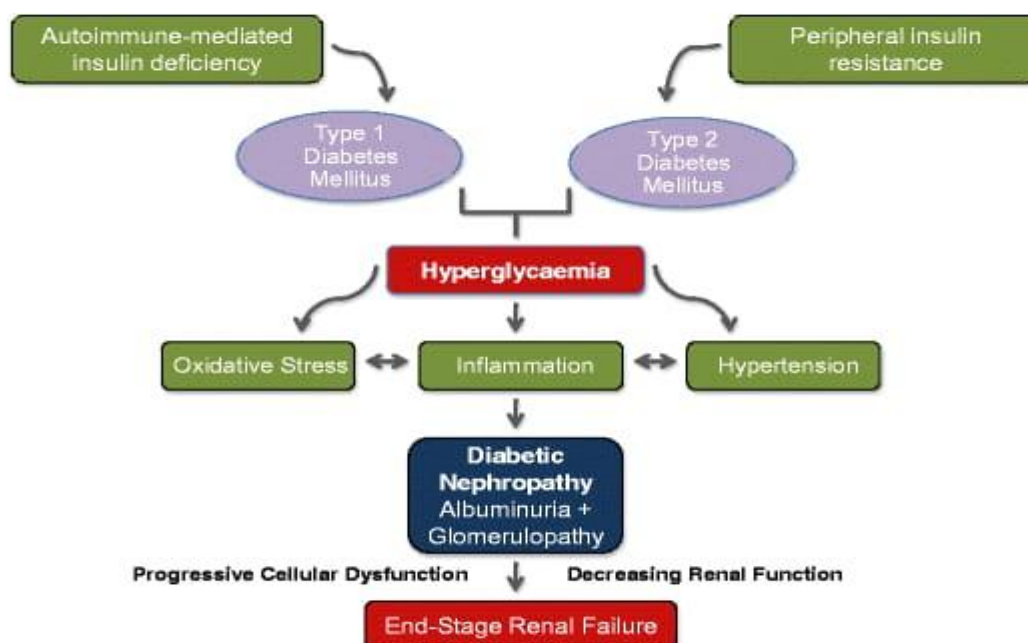


Figure 2: Pathophysiology of diabetic nephropathy

Drug Based Management of Diabetic Renal Disease

Table 1: List of drugs: [22-24]

RENIN - ANGIOTENSIN ALDOSTERONE SYSTEM (RASS)	ANTI DIABETIC DRUGS USED TO CONTROL HYPERGLYCAEMIA AND REDUCE PROGRESSION OF NEPHROPATHY	MINERALOCORTICOID RECEPTORS ANTAGONISTS REDUCE INFLAMMATION AND FIBROSIS IN KIDNEY	ANTI HYPERTENSIVE AGENTS HELP CONTROL BLOOD PRESSURE & PROTECT RENAL FUNCTION	LIPID- LOWERING AGENTS
ACE Inhibitors - Enalapril - Lisinopril - Ramipril Angiotensin II Receptor blockers (ARBs) - Losartan - Valsartan - Irbesartan	SGLT2 Inhibitors - Empagliflozin - Dapagliflozin - Canagliflozin GLP-1 Receptor Agonists - Liraglutide - Semaglutide - Biguanides - Metformin Insulin preparation - Insulin Glargine - Insulin lispro	- Finerenone - Spironolactone	Calcium channel blockers - Amlodipine Diuretics - Furosemide - Hydrochlorothiazide	- Atorvastatin - Rosuvastatin

Phytochemical Aspects:

The Lamiaceae family has been rich in phytochemicals such as flavonoids, phenolic acids, terpenoids, tannins and essential oils. These bioactive compounds have antioxidant, anti-inflammatory, antimicrobial, antidiabetic and nephroprotective activities. The Lamiaceae plants contain important constituents such as rosmarinic acid, thymol, menthol and eugenol, which give them their medicinal properties.

Overview Of Lamiaceae

The Lamiaceae or mint family is a cosmopolitan family of flowering plants with approximately 7136 species in 236 genera, most of which are herbaceous or shrubby, and trees are rare. The best known genus is *Salvia* (900), followed by *Scutellaria* (360), *Stachys* (300), *Plectranthus* (300), *Hyptis* (280), *Teucrium* (250), *Vitex* (250), *Thymus* (220), *Nepeta* (200), and *Clerodendrum* (150) [25]. These compounds are pharmacologically active terpenoids and play important roles in the development of novel bioactive products in the cosmeceutical, nutraceutical and pharmaceutical industries [26]. The species of Lamiaceae also have antispasmodic, antiseptic, antimicrobial, calmative and antidiabetic activities [27]. Lamiaceae species have been used as antidiabetic agents since time immemorial due to their curative abilities in the folk medicine of different communities, regions and tribes in the African sub-region and the world [28]. The present study reviews the traditional use of Lamiaceae species for the treatment of diabetes worldwide and reports the isolated antidiabetic compounds and their pharmacological actions from Lamiaceae species [28].

Table 2: List Of Lamiaceae Species In The Management Of Diabetic Nephropathy [29]

PLANT SPECIES	PART OF THE PLANT	MODE OF PREPARATION	PHYTO-CONSTITUENTS	ANTI NEPHROPATHIC ACTIVITY
<i>Ajuga iva</i> (L.) Schreb	Aerial parts (leaf and steam)	Decoction Infusion Raw powder	Flavonoids, Steroids, Terpenoids, Fatty acids	Hypoglycaemic, hypolipidemic, and alpha-amylase activity
<i>Ballota nigra</i> L.	Aerial part	Decoction Infusion Raw powder	Ballonigrin, Ballotinine, ballotenol	Hypoglycaemic activity
<i>Becium grandiflorum</i> (Lam.) pic. serm	leaves	Powder	8-O-glucoside	Antihyperglycaemic activity
<i>Calamintha officinalis</i> Moench	Seeds, stem and leaves	Decoction	Chlorogenic, Caffeic, Hydroxycinnamic and rosmarinic acid	Hypoglycaemic activity
<i>Coleus forskohlii</i> (Willd.) Briq.	All plant	Decoction	Forskolin E, F, G, H	Inhibition of hormone sensitive lipase
<i>Hyptis suaveolens</i> (L.) Poit.	Aerial part	Decoction	Diterpenes, Phenolic acids, triterpenes	Hypolipidemic Activity
<i>Lavandula dentata</i> L.	Leaves and steam	Decoction Infusion Raw powder	Phenolic compounds, terpenes, alkaloids	Hypoglycaemic activity

Lavandula multifida L.	Leaves and steam	Decoction	Luteolin-7-O-glycoside, isocutellarin-8-O-glycosides, hypolaetin-8-O-glycoside	Hypoglycaemic activity
Teucrium polium L.	Dried aerial parts	Decoction	Terpenoids, flavonoids, iridoids, sterols	Hypoglycaemic activity
Lavandula stoechas L.	Leaves	Decoction	Flavonoids, flavone glycosides, flavone 7-O-monoglycosides	Hypoglycaemic activity
Leonotis Leonurus(L) R.Br.	Leaves and stems	Decoction	Sterols, flavonoids, diterpenes, triterpenoid, tannins, carbohydrates,	Antihyperglycemic
Leonotis nepetifolia (L) R.Br.	Leaves	Decoction	Nepetaefolinol, leonotinin, labdane diterpenes	Anti nephropathy activity
Marrubium vulgare L.	Leaves	Decoction	Polysaccharides, amino acids, tannins, flavonoids, phenols, terpenes, alkaloids, steroids	Hypoglycaemic activity
Ocimum gratissimum L.	Leaves	Infusion, food vegetable	Flavonoids, polyphenols, quinones, coumarins, catechins	Hypoglycaemic activity
Ocimum sanctum L.	Leaves	Decoction	Rosarinic acid, apigenin, propanoic acid, isothymusin	Hypoglycaemic activity
Ocimum basilicum L.	Leaves	Decoction	Tannins, saponins, cardiac glycosides	Hypoglycaemic activity
Ocimum canum L.	Leaves	Decoction	Flavonoids, tannins	Alpha – glucosidase
Rosmarinus officinalis L.	Leaves	Decoction	Polyphenols, carnosol, rosmarinic acid	Hypoglycaemic activity
Salvia lavandulifolia Valh	Leaves	Decoction	Flavonoids, terpenoids	Hypoglycaemic activity
Salvia officinalis L.	Leaves	Decoction Infusion Tea	Fatty acids, carbohydrates, glycoside derivatives	Hypo lipidemic effect
Salvia fruticose Mill.	Aerial part	Decoction	Luteolin, apigenin, rutin	Hypoglycaemic activity
Teucrium cubense Jacq.	Dried aerial parts	Decoction	Terpenoids, flavonoids, iridoids, sterols	Hypoglycaemic activity

1. Ocimum sanctum L.



Figure 3: Ocimum sanctum L.

1.1. Traditional Uses

Ocimum sanctum is indigenous to India and is commonly found in Australia, Malaysia, In the Arab States and West Africa. *O. sanctum* is used worldwide to lower the risk factors of various disorders, such as hypoglycaemia.

1.2. Phytochemical Constituents

Rosmarinic acid, apigenin, propanoic acid, isothymusin, cirsimaritin, orientin, vicianin, and isothymonin have been found from the leaves.

1.3 Antidiabetic Activity

The aqueous suspension considerably decreases the blood glucose level ($P < 0.0001$) and oxidative stress with a significant increase in glycogen and protein in diabetic rats. A 70% ethanol extract of the leaves of *O. sanctum* has been reported to significantly decrease the blood glucose level in both normal and streptozotocin-induced diabetic rats [60]. In vivo studies of the ethanolic extract have also shown a decrease in the blood glucose level and an increase in the plasma insulin activity in type 2 diabetes mellitus. Another study revealed that significant decrease in diabetic symptoms (polyphagia, polydipsia, and tiredness) in type 2 diabetic patients who ate the leaf powders of *O. sanctum* [29]. Ethanol extract activates insulin production from the perfused pancreas, isolated islets, and clonal pancreatic cells. The extracts of the leaves of *O. sanctum* have been found to possess the following properties: anti-hyperglycaemic effects by increasing the insulin secretion from isolated islets, the perfused pancreas, and clonal pancreatic β -cells.

2. *Rosmarinus officinalis* L.



Figure 4: *Rosmarinus officinalis* L.

2.1. Traditional Uses

Rosmarinus officinalis is a native of the Mediterranean region and one of the most common culinary herbs that are grown throughout the world, including South America, as evergreen plants [28]. Rosemary has been used traditionally since ancient times to relieve renal colic, analgesic, rheumatic, carminative, diuretic, expectorant, dysmenorrhea, asthma, colds, bronchitis, flu, digestive, palpitation, anaemia, dizziness, pain, anxiety soothing hearth, hypertension, insomnia, sluggishness memory, labyrinthitis, vitiligo, tachycardia, and diabetes [28].

2.2. Phytochemical Constituents

Rosemary has been reported to contain various classes of polyphenols, such as Flavonoids, phenolic acids and phenolic terpenes. Carnosol, carnosic, and rosmarinic acids have been reported to be the most abundant constituents. Several compounds have been isolated, such as flavonoids (diosmetin, diosmin, genkwanin, hispidulin, luteolin, rutin, genkwanin, kaempferol-3-O-rutinoside, kaempferol, naringenin-C-hexoside, hesperetin, apigenin-7-O-glucoside, quercetin, and phenols (rosmarinic, caffeic, and chlorogenic acids); flavonoids (quercetin, luteolin, lutein, zeaxanthin, and isothiocyanate); and other compounds (including caffeic acid, chlorogenic acid, and isothiocyanate). Polyphenols (caffeic, chlorogenic, rosmaridiphenol, rosmadial, methoxycarnosate); and flavonoids (quercetin, lutein, zeaxanthin, and isothiocyanate). labiatic, neochlorogenic, rosmarinic acids; coumaric acid; m-hydroxybenzoic acid; Vanillic acid; coumaroylquinic acid; ferulic acid; syringic acid; protocatechuic acid, dicaffeoylquinic acid; and hydroxyphenylacetic acids: homovanillic acid and p-hydroxybenzoic acid).

2.3. Antidiabetic Activity

Rosemary extract and its polyphenols (carnosic and rosmarinic acids) have been reported to possess significant antidiabetic effects in different in vivo models of type 2 diabetes and insulin-like effects in insulin target cells in in vitro models. The aqueous extract has been reported to have potential to reduce the oxidative stress. When tested for alpha-glucosidase inhibitory activity, Rosemary was found to show significant activity (60% decreases) induced by streptozotocin and blood glucose levels.

3. *Salvia officinalis* L



Figure 5: *Salvia officinalis* L.

3.1. Traditional Uses

Salvia officinalis is native to the Southern Europe and Mediterranean areas; it is a perennial round shrub widely naturalized throughout the world. *S. officinalis* is used against diabetes mellitus in many countries. *S. officinalis* is used in Asia and Latin America's folk medicine to treat different kinds of diseases, such as seizure, gout, ulcers, rheumatism, dizziness, inflammation, tremor, diarrhoea, paralysis, obesity, and diabetes.

3.2. Phytochemical Constituents

The main phytochemicals of *S. officinalis* flowers, leaves and stems are fatty acids, carbohydrates, glycosidic derivatives (flavonoid glycosides, cardiac glycosides,), phenolic compounds (coumarins, tannins, flavonoids), polyacetylenes, steroids, terpenoids Monoterpenoids, diterpenoids, triterpenoids, sesquiterpenoids and waxes. Chlorogenic and ellagic acids, epigallocatechin gallate, epicatechin, rutin, luteolin-7-glucoside, quercetin, and rosmarinic acid are the most predominant compounds.

3.3 Antidiabetic Activity

S. officinalis has been reported to have a wide range of pharmaceutical applications, including hypoglycaemic and hypolipidemic effects. Additionally, *S. officinalis* has been reported to have a hypoglycaemic effect on diabetic animals and be beneficial for type 2 diabetes. It has been shown to lower liver glucose production in 2 diabetic patients. Methanolic extracts of *S. officinalis* have considerably decreased serum glucose levels in type 1 diabetic rats. The aqueous extract of *S. officinalis* has been shown to have insulinlike effects. Infusions (tea) of *S. officinalis* have been reported to reduce liver glucose production and increase insulin action. *S. officinalis* has been shown to be as effective as Metformin is a commonly used oral antidiabetic agent used to treat type 2 diabetes [28].

4. *Salvia fruticosa* Mill.



Figure 6: *Salvia fruticosa* Mill.

4.1. Traditional Uses

Salvia fruticosa is native to the Eastern Mediterranean area and Jordan [30]. *S. fruticosa* has also been utilized for improving memory and as a hypoglycaemic agent [74].

4.2. Phytochemical Constituents

Three flavonoids (luteolin, apigenin, rutin) and three phenolics were identified. The aerial parts yielded acids, namely ferulic, gallic and rosmarinic acids. Moreover, dehydro-abietic acid and carnosol were isolated from the root [74].

4.3. Antidiabetic Activity

S. fruticosa has been reported to have hypoglycaemic activity, which is the ability to lower the blood glucose level. Glucose absorption in the intestine [75]. This plant is well known for its antidiabetic activities. In Jordan. The oral administration of a 10% leaf infusion of 0.25 g/kg BW caused a significant effect on blood glucose in normal rabbits. Alloxanized rabbits showed significant decrease in blood glucose without any effect in normal rabbits. effect on normal ones.

5. *Lavandula angustifolia* Mill.



Figure 7: *Lavandula angustifolia* Mill.

5.1. Traditional Uses

Lavandula angustifolia is endemic to the northern part of Jordan and the Mediterranean. region (France, Spain, and Italy). *L. angustifolia* has been used in Jordanian folk medicine since ancient times in the management of diabetes.

5.2. Phytochemical Constituents

L. angustifolia is a rich source of phenolic derivatives, especially rosmarinic and gallic acids [44]. Other phenolic compounds, such as lavandufurandiol, lavandunat, lavandupyrone A and B, lavandufluoren, lavandudiphenyls A and B, ethyl 3-phenylpropionate, 4-(1-hydroxy-1-methylethyl) benzoic acid, methyl 3-(3,4-dihydroxyphenyl) propanoate, and isosalvianolic acid, were isolated from the ethyl acetate extract of *L. angustifolia*.

5.3. Antidiabetic Activity

A bio-evaluation of the methanolic extract of *L. angustifolia* regarding the management of diabetes mellitus was conducted. Bio-evaluation of methanolic extract of *L. angustifolia* for diabetes mellitus management was done. The inhibitory effect of *L. angustifolia* on HSL and PL activities was shown in diabetic dyslipidaemia. The IC₅₀ values were 175.5 and 56.5 µg/mL, respectively, in a dose-dependent manner. The inhibitory activity of *L. angustifolia* may be due to the presence of rosmarinic acid, which has IC₅₀ values of 125.2 and 51.5 µg/mL for PL and HSL, respectively, gallic acid has IC₅₀ values of 10.1 and 14.5 µg/mL for PL and HSL, respectively, and are the major compounds of *L. angustifolia* [28]

6. *Ocimum basilicum* L.



Figure 8: *Ocimum basilicum* L.

6.1. Traditional Uses

Ocimum basilicum is indigenous to Africa and Asia. Basil is good for digestion and can be used to cure epistaxis when combined with camphor. The infusion of *O. basilicum* is useful in cephalagia, fever, coughs, gouty joints, Internally used for otitis, snake bites, stomach ailments and gout, nephritis, and internal piles. The infusion of basil seed is used to treat gonorrhoea, chronic Dysentery, diarrhoea and diabetes mellitus.

6.2. Phytochemical Constituents

The phytochemical analysis of the aqueous extract of *O. basilicum* showed the presence Contains tannins, saponins and cardiac glycosides. Phenolic acids, caffeic acid derivatives, The major constituents of *O. basilicum* are and flavonol-glycosides.

6.3. Antidiabetic Activity

The aqueous extract was found to significantly reduce plasma triglycerides (TG) and cholesterol in acute hyperlipidaemia induced by Triton WR-1339 in rats. The aqueous extract of the whole plant exhibited a hypoglycaemic effect in normal and streptozotocin diabetic rats. In addition, the methanol-dichloromethane extract of the leaves has The extracts have been reported to have different anti-hyperglycaemic effects. Pharmacological effects such as blood glucose-lowering and hepatoprotective effects. The aerial parts extract showed antidiabetic activity, possibly by inhibiting carbohydrate metabolizing enzymes and increasing the mobilization of glucose from the liver. The extract exhibited strong dose-dependent inhibitory activity on rat intestinal sucrose, maltose and porcine pancreatic alpha-amylase. The ethanolic extract All the leaves showed hepatoprotective activity against H₂O₂ and CCl₄ induced liver damage.

7. *Marrubium vulgare* L.



Figure 9: *Marrubium vulgare* L.

7.1. Traditional Uses

Marrubium vulgare is indigenous to the Mediterranean Sea region and is widespread in In many temperate parts of North Africa, Asia and Europe. In Morocco, *M. vulgare* is used for diabetes, in Mexico and Algeria for diabetes. mellitus.

7.2. Phytochemical Constituents

Marrubium vulgare is a rich source of polysaccharides, amino acids, tannins, flavonoids, phenols, terpenes, alkaloids, and sterols. Numerous phytochemicals such as flavonoids Diterpenes (luteolin, ladanein, apigenin, quercetin, chrysoeriol, isoquercitrin, and vitexin), Phenylpropanoid esters (acteoside (or verbascoside), forsythoside B, ballotetriside, arenarioside, marruboside, alyssonoside, and marruboside), and flavonoids (isoflavones, luteolin, luteoside, luteoforide, and luteolin-7-glucoside). Tannins (catechin, epicatechin, proanthocyanidins, condensed tannins), and sterols *M. vulgare* has been isolated from these. Several flavonoid glycosides and labdane diterpenoids have been isolated from the same source. The phytochemical investigation of *M. vulgare* yielded a labdane diterpenoid, a glycosidic peregrinol and a flavonoid derivative. and 4',5,7- trihydroxyflavone.

7.3. Antidiabetic Activity

The hypoglycaemic effect of *M. vulgare* has been shown in vivo in scientific studies. *M. vulgare* has been reported to have hypoglycaemic and antioxidant properties. activities. The 80% ethanolic extract of *M. vulgare* showed a moderate alpha-glucosidase It has an IC₅₀ of 12.66 µg/mL for inhibitory activity. The methanolic extract exhibited a considerable decrease in blood glucose and a significant increase in plasma insulin and tissue glycogen contents. Treatment with infusion from the aerial parts The blood glucose level was significantly reduced in a dose-dependent manner by of *M. vulgare*. In alloxan diabetic rats. The ethanolic extract from the root considerably suppressed the increase in the plasma glucose level in healthy rats. Moreover, *M. vulgare* shows an antidiabetic effect by suppressing the carbohydrate absorption from the intestine and thereby reducing the postprandial increase in the blood glucose level. The aqueous extract was administered orally and caused significant antidiabetic and antihyperlipidemic effects. dose-dependent effects in treated animals. *M. vulgare* greatly reduces the blood glucose level, pancreatic levels of interferon-gamma and nitric oxide, total cholesterol, low-density lipoprotein (LDL), very LDL cholesterol and triglycerides compared with diabetic mice. The methanolic extract was found to have PPAR γ agonist activity in a luciferase reporter assay. PPAR γ adjusts the glucose and lipid metabolism and its synthetic agonists such as pioglitazone ameliorate insulin resistance, thus it is clinically employed for diabetes therapy [29].

8. *Teucrium polium* L.



Figure 10: *Teucrium polium* L.

8.1. Traditional Uses

Teucrium polium is a native of Southwest Asia and the Mediterranean region. It widely spread throughout almost all the Mediterranean countries, Europe, south-western Asia, North Africa. Traditionally, *T. polium* is used for the treatment of various types of pathological conditions including diabetes, inflammations, gastrointestinal disorders and rheumatism. It is also used by Iranians for its anti-inflammatory, antipyretic, diuretic, diaphoretic, tonic, Antispasmodic, antihypertensive, analgesic, antibacterial and antidiabetic properties. In In many type 2 diabetic patients in southern Iran, the aqueous extract of the dried leaves of this plant is used. aerial parts of *T. polium* as an antidiabetic drug.

8.2. Phytochemical Constituents

The phytochemical studies of *T. polium* have shown the presence of different classes of compounds in the aerial part including terpenoids, flavonoids, iridoids and sterols. root. The roots and aerial parts have been reported to

contain numerous flavonoids including salvigenin, luteolin, apigenin, cirsiolol, rutin, cirsimaritin and eupatorin. Additionally, two A hydrophilic extract of the plant has been found to contain iridoid glycosides, teuhircoside and teucardoside. fraction. A number of steroidal compounds, including stigmasterol, β -sitosterol, campesterol, The same source has yielded the isolation of two other steroids, namely, closterol and brassicasterol.

8.3. Antidiabetic Activity

T. polium and its isolates have been reported to possess wide range of pharmacological activities such as hypoglycaemic and hypolipidemic activity. T. polium enhanced The plant extract increased insulin secretion by almost 135% after one dose. At a high glucose concentration, 0.1 mg plant leaf powder/mL of the culture medium) (16 mmol/L). The aqueous extract (50 mg/kg) significantly (p 0.05) reduced the serum glucose level of diabetic Sprague–Dawley male rats from 283.622.1 to 96.211.9 mg/dL. T. polium extract has been reported to reverse the symptoms of streptozotocin-induced By regulating the expression of the pancreatic transcription factor pancreas/duodenum homeobox gene-1 (Pdx1) and forkhead transcription factor (FoxO1), these genes can regulate diabetes in rats [29]. T. polium showed a considerable decrease in the blood glucose level of STZ-diabetic rats and showed protective effects on pancreatic tissue in STZ-induced oxidative It is based on its high oxidative capacity. In addition, T. polium exhibited low alpha amylase inhibitory activity (5%) [29].

9. Hyptis suaveolens (L.) Poit



Figure 11: Hyptis suaveolens (L.) Poit

9.1. Traditional Uses

Hyptis suaveolens is a native of tropical America. It is widely distributed in the Northern Territory and Queensland of Australia, China, Indonesia, French Polynesia, the Federated States of Micronesia, Niue Islands, Guam, Hawaiian Islands of the USA, and West and Central Africa. H. suaveolens is traditionally used to treat diabetes mellitus, eczema, fever, cancer, and headache.

9.2. Phytochemical Constituents

Diterpenes (suaveolic acid, suaveolol, and methyl suaveolate), phenolic acids (rosmarinic acid and methyl rosmarinate), and triterpenes (oleanolic and ursolic acids) were isolated from H. suaveolens.

9.3. Antidiabetic Activity

The 50% aqueous ethanolic extract of H. suaveolens has been reported to have significant antihyperglycemic activity in streptozotocin-induced diabetic rats and decrease In a significant way, the cholesterol and triglyceride levels were affected [29]. The aerial part of H. suaveolens has been reported to have antidiabetic and antioxidant properties.

10. Leonotis leonurus (L.) R. Br



Figure 12: Leonotis leonurus (L.) R. Br

10.1. Traditional Uses

Leonotis leonurus is indigenous to Southern Africa. It is widely distributed in the Eastern and the provinces of Western Cape, Kwazulu-Natal and Mpumalanga. L. leonurus (leaves and stems) is traditionally used in South Africa to treat diabetes, Coughs and colds, flu, chest infections, high blood pressure, eczema, epilepsy, menstruation delayed, intestinal worms, and constipation. The tea prepared from the whole plant is used for piles, arthritis, bladder and kidney diseases, cancer, obesity, rheumatism.

10.2. Phytochemical Constituents

The phytochemical investigation of L. leonurus showed the presence of sterols, flavonoids, diterpenes, triterpenoid, tannins, carbohydrates, quinines and alkaloids. Flavonoids such as apigenin 8-C-glucoside, apigenin 6-C-arabinoside-8-C-glucoside, apigenin 7-O-glucoside, The luteolin 7-O-glucoside-3-methyl ether, luteolin 7-O-glucoside, apigenin 7-O-(6- O-p-coumaroyl)-glucoside luteolin 3-methyl ether, 6-methoxyluteolin-4-methyl ether, apigenin were isolated [49]. Diterpenoids include marrubin and leoleorin K, L, M, and N. The leaves have been reported to have.

10.3. Antidiabetic Activity

L. leonurus has been reported to lower the blood glucose level in streptozotocin induced diabetic rats. Additionally, L. leonurus' aqueous extract has antihyperglycemic and antilipidemic activities. The aqueous leaf extract caused a significant (p 0.05–0.001) hypoglycaemic effect in rats, which was ascribed to different diterpenoids, polyphenolics, The plant extract contains flavonoids and other phytochemicals [29].

Common Invitro Studies Used in Diabetic Nephropathy:

- High glucose -induced mesangial cell injury model
- Podocyte apoptosis assay
- ROS estimation using DCFH-DA standing
- MTT cell viability assay
- Western blot for TGF-B1, Fibronecti, collagen IV
- RT-PCR for inflammatory and fibrosis markers
- AMPK/ NF- KB pathway analysis
- Flow cytometry for apoptosis
- Immunofluorescence staining for nephrin / podocin

Diabetic nephropathy research are the two most important and widely used in vitro studies in:

1. High Glucose–Induced Mesangial Cell Injury Model [30, 31]

This is one of the most frequently used experimental models to study diabetic nephropathy, as the expansion of mesangial cells and the accumulation of extracellular matrix are important pathological characteristics of diabetic nephropathy.

Principle

Diabetic conditions are simulated by culturing mesangial cells in a high glucose medium (25–30 mM glucose). High glucose induces oxidative stress, inflammation and fibrosis, which results in increased production of extracellular matrix proteins including fibronectin, collagen IV and TGF- β 1.

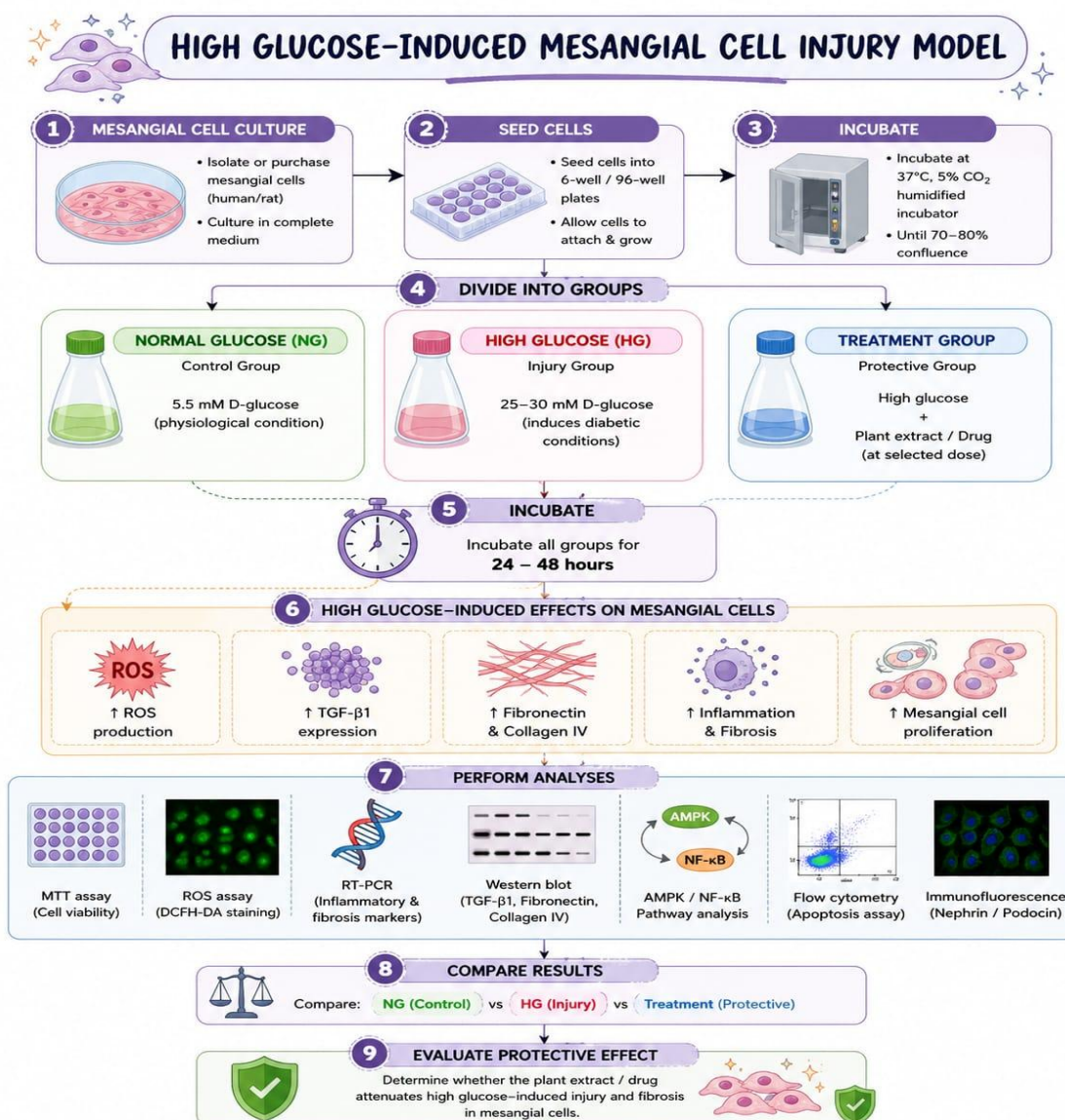


Figure 13: High glucose-induced mesangial cell injury model

2. Podocyte Apoptosis Assay [32,33]

Podocyte injury and apoptosis play a significant role in the development of proteinuria and diabetic nephropathy. Thus, podocyte apoptosis assays are regarded as very significant in DN studies.

Principle:

Podocytes are specialized cells of the kidney that make up the glomerular filtration barrier. In diabetic conditions, high glucose and oxidative stress cause podocyte apoptosis.

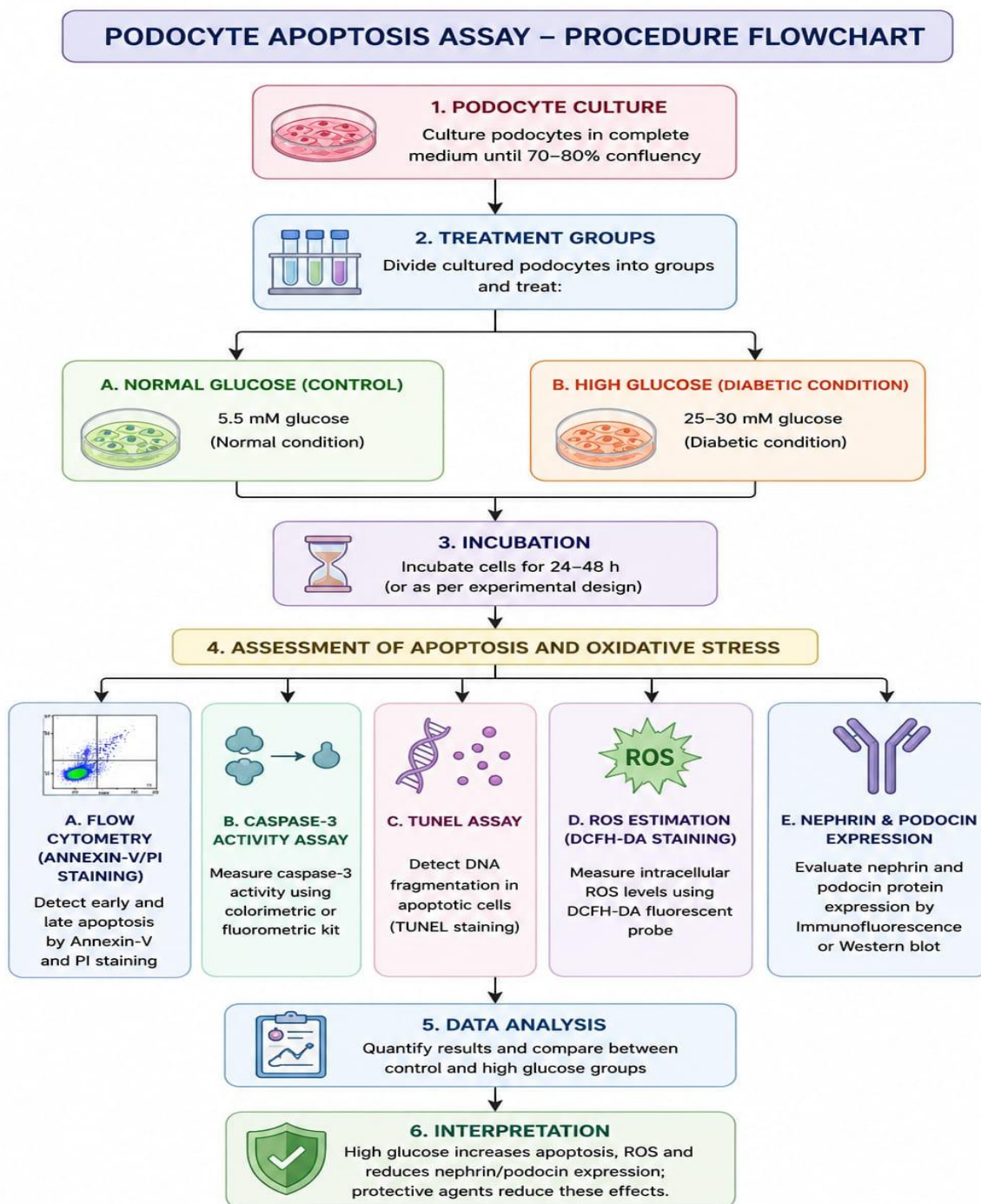


Figure 14: Podocyte Apoptosis Assay Flow Diagram

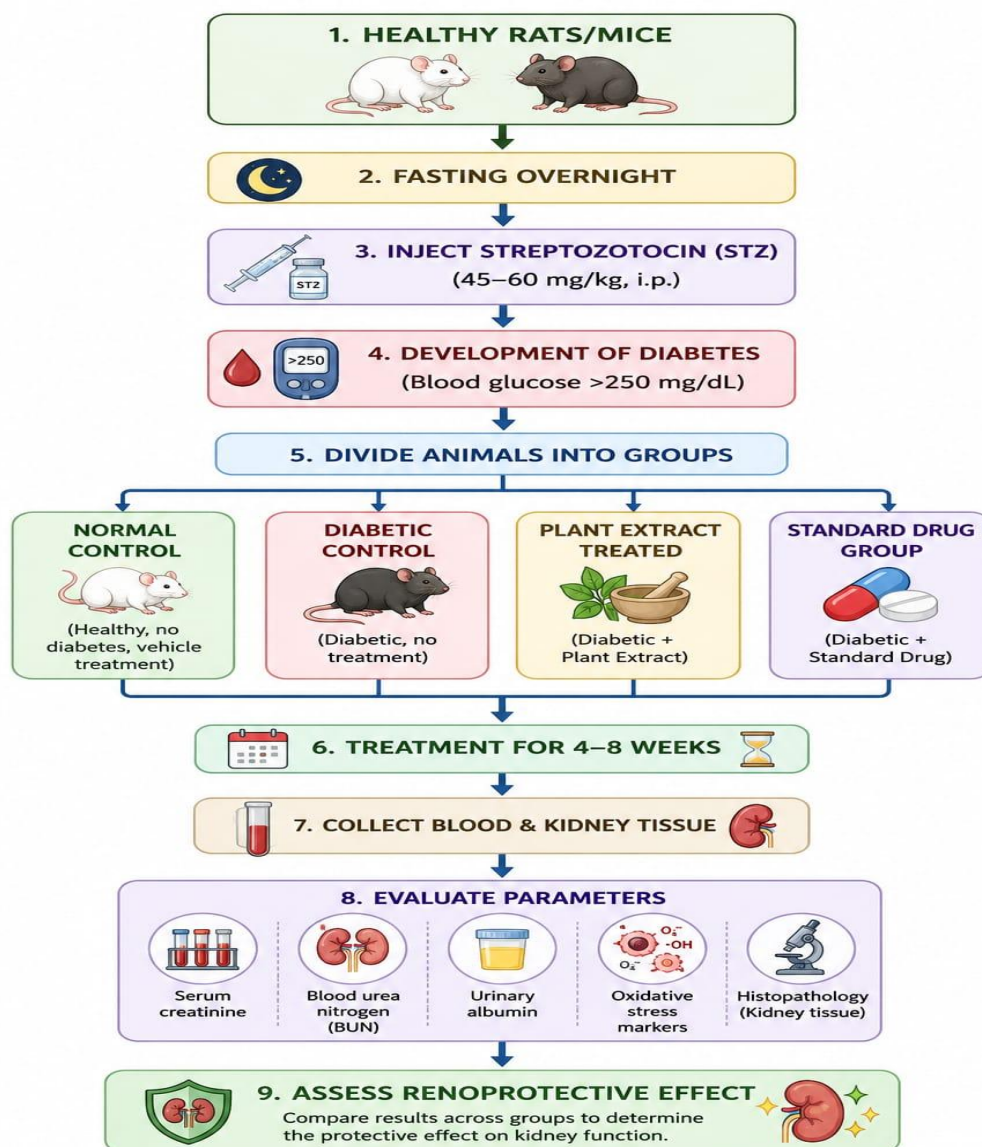
Common In-Vivo Studies Ford Diabetic Nephropathy Using Lamiaceae Family Species:

The renoprotective effects of Lamiaceae plants against diabetic nephropathy have been mainly assessed in vivo using streptozotocin (STZ)-induced diabetic rats or mice.

Stz-Induced Diabetic Nephropathy Model [34,35]**Principle**

Streptozotocin (STZ) is a chemical that selectively destroys the pancreatic β -cells, resulting in insulin deficiency and chronic hyperglycemia. High blood glucose for a long time leads to kidney damage, which is similar to diabetic nephropathy in humans, such as:

- ❖ Glomerular injury
- ❖ Albuminuria
- ❖ Oxidative stress
- ❖ Renal fibrosis

**Figure 15****Conclusion:**

Finally, diabetic nephropathy is one of the most serious complications of diabetes mellitus and a leading cause of chronic kidney disease and end-stage renal failure in the world. Hyperglycaemia, oxidative stress, inflammation and fibrosis are all important factors in the progression of renal damage. While traditional treatments like ACE inhibitors, ARBs, SGLT2 inhibitors, and lifestyle changes can help slow the progression of the disease, there is still a need for safer and more effective treatments. The Lamiaceae

family plants are rich in phytochemicals and have been found to have potent antidiabetic, antioxidant, anti-inflammatory, and Reno protective properties. Several species such as *Ocimum sanctum*, *Rosmarinus officinalis* and *Salvia officinalis* have been shown to have promising nephroprotective effects in experimental in vitro and in vivo studies. Hence, the medicinal plants of Lamiaceae family can be used as potential complementary therapeutic agents in the treatment of diabetic nephropathy.

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