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Protective Role Of Natural Products In Alloxan And Streptozotocin Induced Diabetic Nephropathy: A Concise Review

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ABSTRACT

Diabetic nephropathy is a common diabetic complication and a primary cause of end-stage renal failure in many parts of the world. Synthetic medications are excellent at lowering blood sugar levels, but they come with a slew of unpleasant drawbacks.To combat this, natural products that may be used as a dietary supplement to prevent diabetic nephropathy are needed. Most medicines that induce nephrotoxicity which exerts toxic effects by one or more common pathogenic mechanisms. Alloxan andStreptozotocin are the two most often used medicines among them. Alloxan and Streptozotocin-induced diabetic nephropathy in rats provide useful models for studying effect of natural product effect.Many researchers have utilised the model to investigate the effects of medications on diabetes. In traditional medicine, natural products such as crude herbals, extracts, polyherbal formulations, herbo-mineral formulations, and others have been used to treat diabetes.In this review, we compiled several natural herbs that are used in the management of Alloxan and Streptozotocin induced diabetic nephropathy with their parameters evaluated.

KEYWORDS: Alloxan,Streptozotocin,Diabetic nephropathy, Hyperglycemia, Diabetes

INTRODUCTION

Diabetes mellitus, or diabetes, is a group of metabolic disorders marked by a persistently high blood sugar level. Hyperglycemia is a symptom of diabetes mellitus, which is caused by difficulties with insulin production, insulin action, or both. Sustained hyperglycemia is also linked to long-term organ damage, malfunction, and failure, and is a key contributor to the development of numerous problems in diabetic patients.However, diabetes is the main cause of renal failure that requires dialysis or transplantation. Nephropathy is said to occur in 30-40% of diabetic patients and has become a major cause for end-stage renal disease (ESRD)(1).Diabetic nephropathy (DN) is the steady progression of renal insufficiency in the presence of persistent hyperglycemia. Early microalbuminuria, renal hyperfiltration, hyper-perfusion, enhanced capillary permeability to macromolecules, and proteinuria with or without chronic renal insufficiency that leads to ESRD are all symptoms of DN(2).In diabetes, the toxic concentration of blood glucose levels damages the renal

tissue, which leads to altered renal function, causing diabetic nephropathy. Elevated blood glucose and glycosylated protein levels, associated with increased oxidative stress produce hemodynamic changes within the renal tissue, thereby leading to altered kidney function in patients with diabetes mellitus(3). Approximately, 30% of all diabetic patients convert into diabetic nephropathy after 10-20 years of diabetes. The tubular cells of the kidney are one of the primary targets of hyperglycemia, and chronic exposure to high blood glucose levels causes early renal pathological changes such as tubulointerstitial changes, increased tubular basement membrane thickening, glomerular and tubular hypertrophy, protein matrix accumulation, and the development of renal hypertrophy(4). Elevated glucose and cholesterol levels, increased production of inflammatory cytokines are the predisposing factors for the progression of renal damage in diabetic nephropathy(5).Diabetic nephropathy is one of the most serious complications of both type 1 and type 2 diabetes, and its prevalence and mortality rates are rising in developed countries.Several medical herbs or natural medicines have recently been promoted as an alternative to the current DN treatment(6). In DN, when hyperglycemia is maintained for a long time, nephropathy occurs due to the multiple cellular mechanisms including, activation of protein kinase C (PKC) pathway, cytokines production, and enhanced polyol pathway, increased formation of advanced glycation end products, increased oxidative stress and hexosamine pathway. It can lead to high production of reactive oxygen species (ROS) and a simultaneous reduction of the antioxidant defense mechanisms, which can cause oxidative stress(7). Hyperglycemia in diabetes causes mitochondrial dysfunction and an increase in reactive free radicals, which leads to DNA damage and apoptosis. Hyperglycemia enhances glutathione oxidation and lipid peroxidation, as well as causing oxidative stress. Finally, hyperglycemia causes oxidative stress in diabetic nephrons, which activates a number of metabolic processes that result in renal cell death, increased albuminuria, and renal failure(8). In recent years, diabetic nephropathy has been defined as evidence of a renal abnormality characterised by proteinuria equivalent to or more than 300 mg/day in a diabetic patient. All of these new findings have resulted in the concept of diabetic nephropathy being renamed "diabetic kidney disease"(9). Because DN is the major cause of chronic kidney disease, which normally leads to ESRD or dialysis. The mortality of dialysis patients with DN is higher than that of non-diabetic patient(10). If glucose level in the blood remains high (hyperglycemia) over a long period, this can result in continuing damage to organs, such as the kidneys, liver, eyes, nerves, heart, and blood arteries. Other complications associated with damaged tissue in vital organs can lead to death in people with diabetes(11).Hyperglycemia has been linked to the progression of nephropathy in both experimental animals and diabetic patients in numerous studies(8). Diabetes without treatment causes significant tissue and vascular damage, which can lead to serious complications such retinopathy, neuropathy, nephropathy, cardiovascular complications, and ulceration(12).

Nephrotoxicity

The harmful impact of chemicals on renal function is known as nephrotoxicity(13). Nephrotoxicity is the term used to describe kidney impairment that occurs as a direct or indirect effect of medication exposure. It is common in elderly people with several chronic diseases, and drugs can cause nephrotoxicity through a variety of pathways, resulting in acute kidney damage and chronic kidney disease (14). Kidneys are the body's blood filtration system(15), and they are responsible for maintaining homeostasis, regulating the extracellular environment, and excreting harmful compounds and medications. Nephrotoxicity is caused by the poisonous effects of various

substances. Therefore, the kidney can be considered as a major target organ for exogenous toxicants. Nephrotoxicity is a kidney-specific feature in which excretion does not go smoothly owing to toxic chemicals or drugs(16). It is the cause of acute renal injuries in 60% of all clinical cases and is associated with several side effects and mortality and it can be diagnosed through simple blood tests(17). The presence of nephrotoxicity can be determined by the levels of blood urea nitrogen, the concentration of serum creatinine, glomerular filtration, and creatinine clearance. Drug-induced nephrotoxicity, which is the toxicity in the kidneys, it displays symptoms such as decreased urine output, fluid retention, fatigue, and nausea(15).

Chemical model to induced diabetic nephropathy

The chemical induction of diabetes appears to be the most commonly used method for inducing diabetes in experimental animals.Alloxan and streptozotocin are the two agents most widely used chemicals to induce experimental diabetes(18), and these models have been useful for the study of multiple aspects of the disease.The surgical and genetic approaches of inducing diabetes in animals are associated with a high rate of morbidity and mortality. As a result, the alloxan and streptozotocin induced diabetes model appears to be the most consistent and repeatable approach of inducing diabetes in experimental animals.

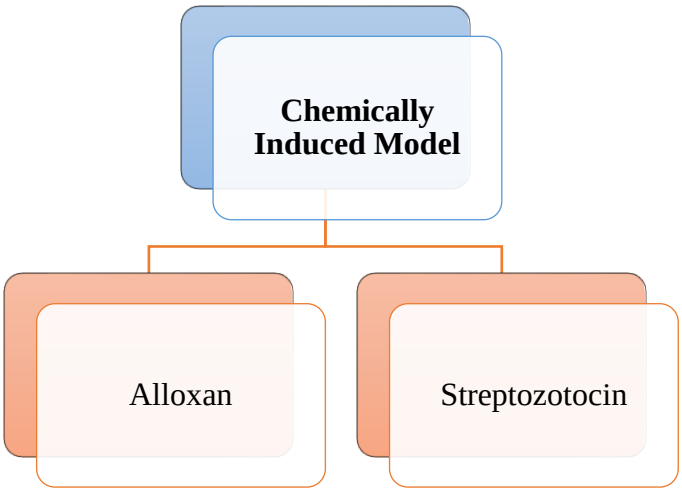

Fig.1 Most frequently diabetogenic chemical model to induced diabetic nephropathy

The dose of these agents required for inducing diabetes depends on the animal species, route of administration, and nutritional status(19). Drug-induced nephrotoxicity is an extremely common condition and is responsible for a variety of pathological effects on the kidneys(20). Most drugs found to cause nephrotoxicity to exert toxic effects by one or more common pathogenic mechanisms. These include altered intraglomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, and thrombotic microangiopathy(20).Nephrotoxic drugs (ND) as therapeutic agents that have the potential to cause adverse effects on renal function as a result of direct toxicity or compromised renal perfusion, ND include acute tubular necrosis, glomerular and tubulointerstitial injury, hemodynamically mediated damage and obstructive nephropathy(21). Recognition of drug-induced nephrotoxicity as a significant contributor to kidney disease including acute kidney injury and chronic kidney disease has gained increasing momentum in recent times.

Consequences of drug toxicity might include both glomerular and tubular injuries leading to acute or chronic functional changes(22). STZ and Alloxan inhibit many cellular functions includes its selective uptake by pancreatic β cells and its toxic effector mechanism in the animal body to create a diabetic model(23)(24).

Alloxan Induced Diabetic Nephropathy

Alloxan is also called as mesoxalylurea, mesoxalylcarbamide 2, 4, 5, 6-tetraoxohexa hydropyrimidine or pyimidinetetrone. The name Alloxan emerged from the merging of two words, i.e., Allantoin and Oxaluric acid(24). The compound has the molecular formula, $C_4H_2N_2O_4$, and a relative molecular mass of 142.06. Alloxan was first isolated by Brugnatelli in 1818 and initially described by Frederick Wohler and Justin Liebig in 1838(25).It is a urea derivative and is highly unstable in the water at neutral pH, but reasonably stable at pH 3(26). Alloxan is important for diabetogenic drugs to create animal models of diabetes mellitus(23). It has been widely used to produce experimental diabetes in animals such as rabbits, rats, mice, and dogs with different grades of disease severity by varying the dose of alloxan used, hence it is used to induce diabetes in laboratory animals(24). Induction of diabetes mellitus by giving subcutaneous freshly prepared alloxan solution 120 mg/ kg dissolved in 0.5 ml acetate buffer (pH 5.5) to overnight fasting animals. After 48 hours of alloxan injection, rats were fasted overnight (8-10hrs) and administered glucose (3gm/kg body weight) by gastric intubation(27). After 72h of alloxan, 18 h fasting blood sugar was estimated by glucose oxidase method(28). Diabetogenic effects of alloxan differ in various animal species and are also influenced by the nutritional state of experimental animals. Fasted animals are more susceptible to ALX(29). The drug has been its diabetogenic action when administered parenterally, i.e., intravenously, intraperitoneally, or subcutaneously. The dose of alloxan required for inducing diabetes depends on the animal species and route of administration(30).

Mechanism of Alloxan induced diabetic nephropathy

Alloxan exerts its diabetogenic action when it is administered parenterally: intravenously, intraperitoneally, or subcutaneously(31). Alloxan-induced destruction of the pancreatic islet beta-cell produces permanent diabetes mellitus in a wide range of species and, in the appropriate dose, it is selective to islet beta cell, producing minimal effects on other structures.(18) Diabetes mellitus was experimentally induced in New Zealand white male rabbits by intraperitoneal administration of four doses of alloxan as 80 mg/kg body weight at weekly intervals following 12hr fasting. Histomorphological alterations were recorded for the pancreas, kidneys, lungs, heart, and brain in diabetic rabbits(26).Alloxan causes diabetes by a mechanism that involves partial degradation of the beta (b) cells of pancreatic islets and subsequent compromise in the quality and quantity of insulin produced by these cells(25).Alloxan has two distinct pathological effects: it selectively inhibits glucose-induced insulin secretion through specific inhibition of glucokinase, the glucose sensor of the beta cell, and it causes a state of insulin-dependent diabetes through its ability to induce ROS formation, resulting in the selective necrosis of beta cells(32). After entering the β-cells, ALX participates in several processes that can cause damage to β-cells leading to their necrosis(29).Alloxan reacts with two -SH groups in the sugar-binding site of glucokinase and results in the inactivation of the enzyme(30).Alloxan can generate reactive oxygen species (ROS) in a cyclic reaction with its reduction product, dialuric acid, as depicted in the text box 'Chemical redox cycling reactions between alloxan and dialuric acid, and protective actions of cytoprotective enzymes'. In

the beta-cells, the toxic action of alloxan is initiated by free radicals formed in this redox reaction(32).

Streptozotocin-Induced Diabetic Nephropathy

Streptozotocin (STZ) is a naturally occurring nitrosourea with a molecular weight of 265 and empirical formula of C14 H27 N5 O12. It is widely used to induce insulin-dependent diabetes mellitus in experimental animals because of its toxic effects on islet beta cells(33).Streptozocin (STZ) is a glucosamine-nitrosourea compound that has been in the clinical trial since 1967(26). STZ has four important biological properties as evidenced by its antibiotic, β-cell cytotoxic, oncolytic, as well as oncogenic effects. STZ is an antibiotic and antitumor agent, which induces diabetes mellitus via the reduction of nicotinamide adenine dinucleotide in pancreatic β-cells in vivo(23). Diabetes can be induced by STZ either by a single injection or by multiple low dose injection of STZ. It is the most commonly used drug for the induction of diabetes in rats(26). Diabetes was induced in male Wistar albino rats aged 2–3 months (180–200 g/body weight) by intraperitoneal administration of STZ dissolved in freshly prepared 0.01 M citrate buffer, pH 4.5. After 72 h, rats with marked hyperglycemia (fasting blood glucose≥250mg/dl) were selected and used for the study(34). Further, the administration of a 5% glucose solution during the first 24 h following STZ injection prevented early mortalities(35). The fasting serum glucose level was measured by the glucose oxidase-peroxidase method using a glucose test kit. Only rats with fasting blood glucose level of 250 mg/dl and above were considered as diabetic and those with blood sugar level 130 mg/dl and below were considered as non-diabetic(36). The main characteristic symptoms in STZ-induced diabetic rats showed a significant increase in blood glucose (hyperglycemia), water intake (polydipsia), food intake (hyperphagia), which accompanied with severe loss of body weight. Increased water and food consumption result in a direct accumulation of glucose in the blood and an increase in the urinary excretion of glucose(37). STZ-induced diabetic rats, severe hyperglycemia were developed, with a marked increase in proteinuria and albuminuria(36).

Mechanism of Streptozotocin-induced diabetic nephropathy

Streptozotocin is a naturally occurring chemical; accustomed to produce Type1 diabetes within animal design and Type2 diabetes along with multiple low doses.Streptozotocin prevents insulin release and causes a situation of insulin-dependent diabetes mellitus. Streptozotocin is less lipophilic as well as selectively gathered in pancreatic beta tissue via the actual low-affinity GLUT2 sugar transporter within the plasma membrane(38). Thus, insulin-producing cells that do not express this glucose transporter are resistant to streptozotocin(32).The streptozotocin enters the pancreatic cell via a glucose transporter-GLUT2 (Glucose transporter 2) and causes alkylation of DNA. Further STZ induces activation of poly adenosine diphosphate ribosylation and nitric oxide release, as a result of STZ action, pancreatic -cells are destroyed by necrosis and finally induced insulin-dependent diabetes(30).Streptozotocin is also selective for the pancreatic islet beta-cell and can also produce permanent diabetes in mice, rats, dogs, and other species although the rabbit is relatively resistant(18). Intravenous injection of 60mg/kg dose of streptozotocin in adult Wistar rats causes swelling of pancreas followed by degeneration of Langerhans islet beta cells and induces experimental diabetes mellitus in the 2-4 days. Three days after the degeneration of beta cells, diabetes was induced in all animals(26).Streptozocin is a natural diabetogenic agent that induces permanent diabetes in animal models by damaging pancreatic β-cells that stops insulin production.

Its β-cell toxicity is reasoned through the Carbamoylation of proteins, alkylation of DNA, the release of free radicals (ROS and RNS), and inhibition of O-GlcNAcse(38).The biochemical Streptozotocin enters the pancreatic cell via a glucose transporter-GLUT2 and causes alkylation acid (DNA)(39).Streptozotocin prevents Cellular reproduction with a much smaller dose than the dose needed for inhibiting the substrate connected to the DNA or inhibiting many of the enzymes involved in DNA synthesis(33).

Natural productsproducts used in ALX and STZ induced diabetic nephropathy

Natural products are easily available medication for targeting several human disorders(40)(41).Natural medicinal plants are the gift of nature to have disease free healthy life to humans(42). Natural productsextends its protective effect through a variety of mechanisms. Most natural products, such as crude herbals, extracts, polyherbal formulations, andherbo-mineral formulationshave been employed in the therapy of Alloxan and Streptozotocin caused diabetic nephropathy. Several natural herbs that are used in the management of Alloxan and Streptozotocin induced diabetic nephropathy with their parameters protected are listed in Table 1 & 2.

Table 1. Plant and plant products used in ALX induced diabetic nephropathy

Sr. No.	Natural Products	Parameters Protected
1	Aloe VeraGel	Fasting Blood Glucose, Urea, Uric Acid, Albumin, Protein and Creatinine, Lipid Peroxidation, Histological Analysis(43)
2	Phaleria macrocarpaBoerl	Histological Analysis(44)
3	Mucuna Pruriens Root	Glucose Tolerance Test, Estimation of Fasting Blood Glucose (FBG), Urea, Serum Total Protein, Serum Albumin, Serum Concentration of Sodium Ion, Potassium, Bicarbonate Ion, Cholesterol, HDL-Cholesterol, Triglyceride. Hematological Analysis- RBC, WBC, Hb, HCT, MCH, Corpuscular Volume, MCHC, MCV, Differential White Blood Cell Counts(45)
4	Cardamom Leaves	Blood Glucose Level, Total Cholesterol Level, Body Weight(46)
5	Lyciumbarbarum	Body weight and fasting blood glucose, Urinary Protein, Serum Creatinine, Urea Nitrogen. Enzyme-linked immunosorbent assay (ELISA), Immunohistochemical staining, Western Blot Analysis(47)
6	BalanitesaEgyptiaca Seeds	Serum Insulin Level, Serum Glucose, Serum Urea and Creatinine, Serum Total Protein and Albumin, Serum Total Lipid, Triglycerides, Cholesterol, HDL-Cholesterol, and VLDL-Cholesterol, Hematological Parameters: RBCs Count and Hct, WBCs, Histological Analysis(44)

7	Tectona grandis linn.	Blood Glucose Level(28)
8	Extract of phlogacanthusthyrsiflorusnees	Phytochemical screening, Antihyperglycemic study, Antioxidant enzyme assays- SOD, CAT, and GR, Kidney histopathological studies(48)
9	Allium ampeloprasum extract	Blood biochemical tests-HbA1C, MDA level, liver, and kidney catalase level(49)
10	Polygala Javana	Serum Glucose, Insulin level, Urea, Serum Creatinine, HBA1C, Protein, Albumin, Globulin, SGPT, SGOT, ALP, Total Cholesterol, Total triglycerides, LDL-C, VLDL-C, HDL-C, and Phospholipids(50)
11	Inula japonica	Plasma Glucose Levels, water Intake and food consumption, organ weight, Plasma Cholesterol, Triglyceride, Glycosylated Albumin and Insulin Levels, Oral Glucose Tolerance Test (OGTT)(51)
12	Lepidium sativum L. Seed	Fasting blood glucose and hemoglobin A1c,Immunoglobulins (IgG, IgA, and IgM),Liver enzymes, Kidney functions parameters- urea, creatinine and uric acid,Antioxidants and lipid peroxide-catalase, superoxide dismutase, glutathione reductase and glutathione reduced,serum triglycerides, total cholesterol, LDL cholesterol, VLDL cholesterol, HDL cholesterol, Histopathological examination of pancreas(52)
13	Fenugreek Extract	Blood Glucose Levels, Cholesterol, Triglycerides, HDL-C, Total Protein, Bilirubin, ALT, AST, ALP, Creatinine, and Urea. Histopathological Examination(46)
14	Ficus Glomerata Linn	Fasting Blood Glucose, Body Weight, Serum Urea, Serum Creatinine, and Serum Cholesterol Levels(53)
15	Aegle Marmelos	fasting plasma glucose levels, glucose, urea and GST levels, GSH and MDA levels(54)
16	ArjunaStem Bark	Levels of Glucose in Serum, Liver Kidney and Pancreas Histopathology(55)
17	Vernonia Amygdalina	Serum Chemistry Profile: Creatinine, Blood Urea Nitrogen Renal Antioxidant Studies: SOD, GSH, Hydrogen Peroxide, Total Protein, Histopathology(56)
18	Allium Sativum	Histopathological Analysis, Gross Morphometrical analysis, Photomicrography(57)

19	Potentilla Fulgens	Lipid Peroxidation Assay, Assays for Antioxidant Enzymes: Catalase Activity, Superoxide Dismutase, Glutathione Peroxidase, Reduced Glutathione(58)
20	Extract of Melastomamalabathricum Linn. leaf	Acute toxicity test, Bodyweight and fasting blood glucose, levels of blood glucose, serum insulin, urea, creatinine and glycosylated hemoglobin,serum protein, albumin, globulin, SGPT, SGOT, ALP level, TC, TG, HDL, LDL-C, V-LDL, Phospholipid(59)
21	Pongamia pinnata Linn.	Oral Glucose Tolerance Test, Normoglycemic Studies, TC, TG, LDL, HDL, SGOT, SGPT, ALP, Urea, Creatinine, Protein and Albumin, Hb, Hba1c, Lipid Peroxidase, Superoxide Dismutase, Catalase(60)
22	Coriandrum Sativum	Serum Glucose Level, Level of Serum Albumin, Creatinine, Protein, Urea and Uric Acid, Level of Serum Insulin, Lipase, A-Amylase, LDH, Histopathology Study(61)
23	SidaCordata	Glucose Tolerance Test, Hypoglycemic Activity, Chronic Multiple Study, Analysis of Blood Parameters-ALP, ALT, aspartate AST, LDH, bilirubin, and glutamyl transferase, Assessment of Tissue Antioxidant Enzymes,CAT activity,POD Activity, SOD activity,GST,GSR, Glutathione Peroxidase Assay,GSH,Estimation of Lipid Peroxidation,Nitrate Assay, H_2O_2Assay, Tissue Protein Estimation, Histopathological Determination(62)
24	Artemisia campestris leaf	Serum glucose, creatinine, urea and uric acid levels, lipid peroxidation, Advanced oxidation protein products levels, Reduced glutathione levels, Superoxide dismutase, Glutathione peroxidase, kidney protein content, Histopathological study(63)
25	GirardiniaHeterophylla	Oral Glucose Tolerance Test, Serum Creatinine, Fasting Plasma Insulin, Uric Acid, Urea, BUN, SGPT, SGOT, Total Bilirubin, MDA, SOD, CAT, GSH, Histopathology(11)
26	Portulaca Grandiflora	Serum Glucose, Creatinine, Uric Acid, and Urea Levels, Histopathology(64)
27	Cinnamomum zeylanicum	fasting blood glucose, total cholesterol, high density lipid, urea and urinary protein, lipid peroxidation, reduced glutathione, catalase(65)
28	Syrian Capparis Spinosa	Blood Glucose Level, Body Weight, SGPT, Creatinine, Total

	Leaves	Cholesterol(12)
29	Eleusine coracana	Blood Glucose Levels, Body Weights, TG, TC, HDL, LDL(66)
30	Momordica grosvenori	Serum glucose, triacylglycerols, and total cholesterol, urea nitrogen and creatinine, Lipid peroxidation, glutathione, superoxide dismutase, renal microsomal HO-1 activity, Protein estimation, Histopathological examination(67)

Table 2. Plant and plant products used in STZ induced diabetic nephropathy

Sr. No.	Natural Products	Parameters Protected
1	Asparagus Racemosus (Shatavari)	Body Weight, Kidney Weight, Blood Glucose Levels, Glycosylated Haemoglobin Level, Blood Uric Acid Level, Blood Urea Nitrogen Level, Blood Creatinine Level, Volume of Urine, Urine Microalbumin Level, Histopathological Studies(68)
2	Stereospermumsuavelolens(Patala)	Serum and Urine Renal Parameters Such as Creatinine, Urea, Uric Acid, Total Proteins,Albumin. Antioxidant Enzyme Assays Such as Lipid Peroxidation, Reduced Glutathione Content, Superoxide Dismutase, Catalase, Histopathological Study of Kidney(69)
3	GymnemaSylvestreLeaves	Blood Glucose Level, Triglyceride and Cholesterol Level, HDL Cholesterol, CPK-MB, and SGPT Level, Albumin Level(70)
4	N-Butanol Toona sinensisSeed	Body Weight, KW/BW Ratio (%), Serum Glucose, Hbalc (%), Urine Volume, Urine Protein, Ucr, Scr, BUN, T-AOC, SOD, MDA, GSH-Px, CAT, Histopathology of Kidney(71)
5	Nelumbo nucifera leaves	Renal morphology assessment and IHC analysis, glucose, creatinine and blood urea nitrogen, Lipid peroxidation and antioxidant enzymes assays, Western blot analysis, Detection of intracellular reactive oxygen species(72)
6	Morus nigra L.	Kidney Function Tests: FBS, Creatinine, Urea, Uric Acid, Albumin, CBC: WBC Levels, Hemoglobin Level, Histopathology of Kidney(73)
7	Morus alba Aqueous Leaf	Blood Glucose, Serum A-Amylase Levels, Serum TC, HDL Levels, Serum Level of TAC, Serum Creatinine, Urea, and Histopathological Study(74)
8	Momordica Dioica	Serum Glucose, Kidney Weight, Protein, Lipid Peroxidation, Ascorbic Acid, Superoxide Dismutase, Catalase, Reduced

		Glutathione, Glutathione Peroxidase, and Glutathione-S-Transferase and Histopathology(75)
9	Nigella Sativa Seed	Histopathology of Kidney(76)
10	Aesculus hippocastanum Seeds	Histopathological examination of renal tissue Kidneys,Immunoexpression of fibronectin, Biochemical assay-Measurement of plasma cytokine levels,MDA, Determination of blood glucose, urea nitrogen and serum creatinine, Urine analysis for proteinuria(77)
11	Medicago Sativa	Body Weight, Volume of Kidney, Volume of Cortex and Medulla, Total Volume of Glomeruli, Stereological Study(78)
12	PhellodendriCortex extract	Serum glucose level, Serum insulin level, Serum BUN level, Serum creatinine level, urinary total protein, Urine creatinine, superoxide dismutase, catalase, glutathione S-transferase, and xanthine oxidase, Histological analysis(79)
13	Extract of Cassiae Semen	fasting blood glucose levels, HbA1c, total cholesterol, and triglyceride levels, proteinuria and creatinine clearance, COX-2 mRNA or protein levels, renal histopathologic changes(80)
14	Cassia Auriculata Linn.	Hba1c (%), Serum Total Protein, Serum Albumin, Serum Creatinine, BUN, Urinary Total Protein, Urinary Albumin, Urinary Creatinine Clearance, KW:BW, Urine Volume, SOD, Catalase, GSH, MDA, Body Weight, Food Intake and Water Intake, Histopathology of Kidney(81)
15	Acacia Nilotica Pods Extract	serum levels of glucose, creatinine, and urea,LPO, MDA, GSH, NO, SOD, Histopathological and histochemical studies(82)
16	Extract of Zingiber Zerumbet	Body-weight, Plasma glucose, HbAlc, Analysis of Urine Parameters,Renal Histological Analysis,Western Blot Analysis(83)
17	Extract of Adenantherapavonina L. seed	blood glucose estimation, HbA1c, serum lipids, serum cholesterol, serum triglycerides, HDL cholesterol, VLDL cholesterol, serum LDL cholesterol, albumin, creatinine, urea, and total protein, urine collections, and urinary protein, albumin, and glucose excretion levels, histopathological examination(34)
18	Punica granatum Linn	Preliminary phytochemical screening,Bodyweight, Kidney

		weight and kidney hypertrophy, Blood glucose level, Serum and urine parameters, antioxidant parameters-SOD, CAT and GSH,Histopathological evaluation(1).
19	Croton hookeri	Blood glucose level, urinary micro albumin, urinary creatinine,urinary total protein, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, serum creatinine, Total cholesterol, High-density lipoprotein cholesterol, triglycerides, glutathione, oxidized GSH, Intercellular reactive oxygen species, Superoxide dismutase, catalase peroxidation assay, Assessment of inflammatory cytokines, Western blot analyses, Histological evaluation, Immunohistochemistry analyses(79)
20	Skimmin (coumarin)	Blood glucose concentration, blood urine nitrogen, Serum Creatinine, and Urin Albumin, Creatinine clearance ratio, Histological examination, ELISA and Western blot analysis Plasma(84)
21	Kombucha	Fasting Blood Glucose, Total Protein, Albumin, Urea, Creatinine and Uric Acid, Histological Study(85)
22	Terminalia chebula	estimation of blood glucose, estimation of albumin, creatinine, total protein, and lipid profile, Body Cholesterol, LDL, HDL, VLDL, Triglycerides(36)
23	Allium Sativum	Serum Glucose Levels, Serum Cholesterol Levels, Serum Triglyceride Levels, Urinary Protein Levels(86)
24	Moringa OleiferaLeaves	Body Weight and Blood Glucose, Oral Glucose Tolerance Test, Glycosylated Hemoglobin, Hemoglobin and Insulin, Total Protein, Lipid Peroxidation Assay, Superoxide Dismutase Activity, Catalase Activity, Glutathione, Ascorbic acid Levels, Histopathological Study(87)
25	PicrorrhizaRhizoma Extracts	Body-weight, Detection of blood glucose level, Changes in kidney weight, Detection of serum BUN and creatinine levels, Histology and histomorphometry(88)
26	Extract of Terminalia Chebula Retz. Seeds	blood glucose level, urinary protein, albumin and creatinine levels, Short term studies, Long term studies(89)
27	Ganoderma lucidum	blood glucose levels, TG, UAE, serum creatinine, BUN, glomerular area and mesangial matrix index, malondialdehyde levels, and superoxide dismutase activity(90)

28	Lespedeza cuneata	Serum total protein, blood urea nitrogen, advanced glycation end products (AGEs), Malondialdehyde(91)
29	Zea Mays L.	Plasma glucose, HbA1c, fructosamine, creatinine, urinary creatinine, urinary albumin excretion, Creatinine clearance(92)
30	Moutan Cortex	Blood glucose, serum creatinine, urine protein, Cell proliferation assay, Immunohistochemical assay, Determination of IL-6 and MCP-1 by ELISA kits, Western blot analysis(79)

CONCLUSION

According to the findings of the aforementioned investigations, each particular natural substance extends its protective effect through a variety of mechanisms. Most natural products, such as crude herbals, extracts, polyherbal formulations, andherbo-mineral formulationshave been employed in the therapy of Alloxan and Streptozotocin caused diabetic nephropathy, as shown in the above contents. The parameters evaluated provide an understanding of natural products that might be used in further research.

ABBREVIATIONS

DM- diabetes mellitus, DN- diabetic nephropathy, STZ- streptozotocin, ALX- alloxan, ESRD- end stage renal disease, PKC- protein kinase C, AGE -glycation end products, ROS- reactive oxygen species, GSH- glutathione, DKD- diabetic kidney disease, CKD- chronic kidney disease, AKI- acute kidney injury, CKD- chronic kidney disease, DIN- drug induced nephrotoxicity, ND- nephrotoxic drugs, BGL-blood glucose level, URP- urine renal parameters, SRP- serum renal parameters, SOD- superoxide dismutase, CAT- catalase, TC- total cholesterol, LDL-low density lipoprotein, VLDL- very low density lipoprotein, HDL- high density lipoproteins, SGPT- serum glutamate pyruvate transaminase, SGOT-serum glutamate oxaloacetate transaminase, HbA1c- hemoglobin A1c, GSH- glutathione, MDA-malondialdehyde, POD- peroxidase, KW:BW- kidney weight : body weight, UAE-urine albumin excretion, BUN-blood urea nitrogen, LPO- lipid peroxidase, TAC- total antioxidant capacity, ALP-alkaline phosphatase, AST- aspartate transaminase, CPK- creatine phosphokinase, NO- nitric oxide, FBS- fasting blood sugar, CBC- complete blood count, MCV- mean corpuscular volume, MCHC- mean corpuscular hemoglobin concentration GST-glutathione-s-transferase, GSR-glutathione reductase,AOPP- Advanced oxidation protein products, OGTT- Oral Glucose Tolerance Test, Cr-urinary creatinine, ALT- alanine aminotransferase, AST- aspartate aminotransferase

REFERENCES

1. Mestry SN, Dhodi JB, Kumbhar SB, Juvekar AR. Attenuation of diabetic nephropathy in streptozotocin-induced diabetic rats by Punica granatum Linn. leaves extract. J Tradit Complement Med [Internet]. 2017;7(3):273–80. Available from: http://dx.doi.org/10.1016/j.jtcme.2016.06.008
2. Vishwanath M, Razdan R. Ellagic Acid Ameliorates the Progression of Nephropathy in

Streptozotocin Induced Diabetic Rats. Int Res J Pharm. 2017;8(1):55–60.
3. Madhan Kumar SJ, Malarvani T, Sathiyanarayamurthy S. Nephroprotective effects of Cynodon dactylon aqueous extract in STZ induced diabetic male rats – histological study. Int J Pharmacogn Phytochem Res. 2016;8(11):1812–7.
4. Gupta P, Sharma P, Shanno K, Jain V, Pareek A, Agarwal P, et al. Nephroprotective role of alcoholic extract of Pterocarpus marsupium heartwood against experimentally induced diabetic nephropathy. J Pharm Pharmacogn Res. 2016;4(5):174–86.
5. Almalki WH, Arafa E-SA, Abdallah AY, Mahfoz AM, Osman AO, Abd El-Latif HA, et al. Zinc Chloride Protects against Streptozotocin-Induced Diabetic Nephropathy in Rats. Pharmacol & Pharm. 2016;07(08):331–42.
6. Chaudhari HS, Bhandari U, Khanna G. Embelia ribes extract reduces high fat diet and low dose streptozotocin-induced diabetic nephrotoxicity in rats. Excli J. 2013;12:858–71.
7. Ashrafi M, Nazifi S, Namazi F, Kazemipour N, Karimi B, Goudarzi T, et al. Renal Protective Effect of Saffron Aqueous Extract in Streptozotocin Induced Diabetic Rats. Int J Med Res Heal Sci. 2017;6(9):151–61.
8. Jamshidi HR, Zeinabady Z, Zamani E, Shokrzadeh M. Attenuation of Diabetic Nephropathy by Carvacrol through Anti-oxidative Effects in Alloxan-Induced Diabetic Rats. Res J Pharmacogn. 2018;5(2):57–64.
9. Martínez-Castelao A. Diabetic Kidney Disease: A New Concept for an Old Problem. Open Access J Urol Nephrol. 2017;2(3):1–7.
10. Zhang G, Zhou L, Xu Z, Pronyuk K, Chen X, Wang H, et al. Diabetic Nephropathy: Causative and Protective Factors. Glob J Med Res. 2015;15(2):1–11.
11. Gusain SS, Upadhyaya K. Anti-Diabetic potential of Girardinia heterophylla in alloxan induced rat model. Int J Pharm Med Res. 2016;4(2):310–6.
12. Hussain J, Sarhan H, Bassal M. Effect of Syrian Capparis Spinosa Leave Extract on Alloxan-Induced Diabetes in Rats. Int J Pharm Phytopharm Res. 2017;7(6):31–43.
13. Barnett LMA, Cummings BS. Nephrotoxicity and Renal Pathophysiology : A Contemporary Perspective. Toxicol Sci. 2018;164(2):379–90.
14. Fusco S, Garasto S, Corsonello A, Vena S, Mari V, Gareri P. Medication-Induced Nephrotoxicity in Older Patients. Curr Drug Metab. 2016;17(6):1–18.
15. Prakash R, Pavithra D, Praveen D, Chowdary PR, Aanandhi MV. Review Article A review on drug-induced nephrotoxicity. 2018;10(2):9–11.
16. Kim SY, Moon A. Drug-induced nephrotoxicity and its biomarkers. Biomol Ther. 2012;20(3):268–72.
17. Heidari-soreshjani S, Asadi-samani M, Yang Q, Saeedi-boroujeni A. Phytotherapy of nephrotoxicity-induced by cancer drugs : an updated review. J Nephropathol. 2017;6(3):254–63.
18. Feeney WP. The Chinese or Striped-Back Hamster. Lab Rabbit Guinea Pig, Hamster, Other Rodents,. 2012;907–12.
19. Kumar S, Singh R, Vasudeva N, Sharma S. Acute and chronic animal models for the evaluation of anti-diabetic agents. Cardiovasc Diabetol [Internet]. 2012;11(1):1–13. Available from: http://www.cardiab.com/content/11/1/9
20. Naughton CA. Drug-induced nephrotoxicity. 2016;(October 2008).
21. Bicalho MD, Soares DB, Botoni FA. Drug-Induced Nephrotoxicity and Dose Adjustment

Recommendations : Agreement Among Four Drug Information Sources. Int J Environ Res Public Health. 2015;(12):11227–40.

22. Aiswarya N, R RR, J SP, Chandran V, Teerthanath S, B PS, et al. Nephroprotective Effect of Aqueous Extract of Pimpinella anisum in Gentamicin Induced Nephrotoxicity in Wistar Rats. 2018;10(3):403–7.
23. Busineni Jayasimha Goud, Dwarakanath.V BKC swamy. Streptozotocin - A Diabetogenic Agent in Animal Models. Int J Pharm Pharm Sci. 2015;3(1):253–69.
24. Rohilla A, Ali S. Alloxan Induced Diabetes : Mechanisms and Effects. 1943;3(2):819–23.
25. Macdonald O, Mohammed A. ScienceDirect Alloxan-induced diabetes , a common model for evaluating the glycemic-control potential of therapeutic compounds and plants extracts in experimental studies. Medicina (B Aires) [Internet]. 2018;53(6):365–74. Available from: https://doi.org/10.1016/j.medici.2018.02.001
26. Singh MP, Pathak K. Animal models for biological screening of anti-diabetic drugs: An overview. Eur J Exp Biol. 2015;5(5):37–48.
27. Helal EGE, Abd SM, El EH. Antidiabetic and Antihyperlipidemic Effect of Balanites aegyptiaca Seeds (Aqueous Extract) on Diabetic Rats. Egypt J Hosp Med. 2013;52(7):725–39.
28. Sharma V, Samanta KC. Hypoglycemic activity of methanolic extract of Tectona grandis linn . Root in alloxan induced diabetic rats. J Appl Pharm Sci. 2011;01(04):106–9.
29. Herichova I. On the Mechanisms of Diabetogenic Effects of Alloxan and Streptozotocin. Diabetologie. 2014;14(8):130–98.
30. Tripathi V, Verma J. Different Models Used to Induce Diabetes: A Comprehensive Review. Int J Pharm Pharm Sci ISSN-. 2014;6(6):29–32.
31. Szkudelski T. The mechanism of alloxan and streptozotocin action in B cells of the rat pancreas. Physiol Res. 2001;50(6):537–46.
32. Lenzen S. The mechanisms of alloxan- and streptozotocin-induced diabetes. Diabetologia. 2008;51(2):216–26.
33. Nagarchi K, Ahmed S, Sabus A, Saheb SH. Effect of Streptozotocin on Glucose levels in Albino Wister Rats. J Pharm Sci Res. 2015;7(2):67–9.
34. Pandhare R. Extract of Adenanthera pavonina L . seed reduces development of diabetic nephropathy in streptozotocin-induced diabetic rats. Avicenna J Phytomedicine. 2012;2(4):233–42.
35. Haroon HB, Murali A. Antihyperglycemic and neuroprotective effects of Wattakaka volubilis (L.f.) Stapf root against streptozotocin induced diabetes. Brazilian J Pharm Sci. 2016;52(3):413–23.
36. Singh A, Srivastav R, Pandey AK. Effect of the seeds of Terminalia chebula on blood serum, lipid profile and urine parameters in STZ induced Diabetic rats. J Pharmacogn Phytochem. 2018;7(2):1–5.
37. Emam A, Baragob A, Hassan W, Malki A, Elsiddig H, Farag H, et al. Investigate Evaluation of Oxidative Stress and Lipid Profile in STZ-Induced Rats Treated with Antioxidant Vitamin. Pharmacol Pharm. 2014;5:272–9.
38. Islam M, Rupeshkumar M, Reddy KB. Streptozotocin is more convenient than Alloxan for the induction of Type 2 diabetes. Int J Pharmacol Res. 2017;07(01):6–11.
39. Sharma R, Dave V, Sharma S, Jain P, Yadav S. Experimental Models on Diabetes : A Comprehensive Review. Int J Adv Pharm Sci. 2013;4:1–8.

40. Sonawane GB, Mishra A, Rawat S, Rawat S, Pathak S, Singh SK, et al. Incipient Need of Medicinal Plants in Targeting Chronic Obstructive Pulmonary Disease. In: Dua K, Nammi S, Chang D, Chellappan DK, Gupta G, Collet T, editors. Medicinal Plants for Lung Diseases: A Pharmacological and Immunological Perspective [Internet]. Singapore: Springer Singapore; 2021. p. 151–68. Available from: https://doi.org/10.1007/978-981-33-6850-7_6
41. Mahajan L, N KS, Sonawane G, Barde S, Sakhare R, Moon R, et al. The Highlights On Herbs Acts As An Anti-Cancer Property – A Systematic Review. Nat Volatiles Essent Oils. 2021;8(4):15692–704.
42. Sonawane G, Mishra A, Chawra H, Singh SK, Pansare K. Okra Mucilage : Potential Role in Drug Delivery. SGVU J Pharm Res Educ. 2021;6(2):649–61.
43. Siddiqui BS and MS. Protective Effect of Aqueous Suspension of Aloe Vera Gel Against Oxidative Stress and Renal Damage in Alloxan Induced Diabetic Mice. Suresh Gyan Vihar Univ Int J Environ Sci Technol. 2015;1(1):1–10.
44. Evy Sulistyoningrum S and FRI, Faculty. Phaleria macrocarpa (Scheff.) Boerl improved renal histological changes in alloxan-induced diabetic rats. Int J Med Plants Altern Med. 2013;1(5):87–92.
45. Obasi AA, Ene CU. Antidiabetic Properties of Ethanolic Root Extract of Mucuna Pruriens on Alloxan Induced Diabetic Rats. Int J Res Pharm Biosci. 2017;4(5):17–29.
46. Winarsi, H., Sasongko, N. D., Purwanto, A. and Nuraeni I. Effect of cardamom leaves extract as antidiabetic , weight lost and hypocholesterolemic to alloxan-induced Sprague Dawley diabetic rats. Int Food Res J. 2014;21(6):2253–61.
47. Zhao Q, Li J, Yan J, Liu S, Guo Y, Chen D, et al. Lycium barbarum polysaccharides ameliorates renal injury and inflammatory reaction in alloxan-induced diabetic nephropathy rabbits. Life Sci. 2016 Jul;157:82–90.
48. Bora J, Syiem D, Bhan S. Methanolic Flower Extract of Phlogacanthus Thyrsiflorus Nees. Attenuates Diabetic Nephropathy in Alloxan-Induced Diabetic Mice. Asian J Pharm Clin Res. 2018;11(7):113–6.
49. Rahimi-madiseh M, Heidarian E, Kheiri S. Effect of hydroalcoholic Allium ampeloprasum extract on oxidative stress, diabetes mellitus and dyslipidemia in alloxan-induced diabetic rats. Biomed Pharmacother. 2017;86:363–7.
50. Nadu T, Unit E, Nadu T. Antidiabetic and Antihyperlipidaemic Effect of Polygala Javana Dc on Alloxan Induced Induced Diabetic Rats. Int Res J Pharm. 2012;3(9):231–4.
51. Han JS, Ang MY, En JR. Anti-diabetic and Hypolipidemic Effects of Aqueous-Extract from the Flower of Inula japonica in Alloxan-Induced Diabetic Mice. Biol Pharm Bull. 2006;29(3):455–9.
52. Attia ES, Amer AH, Hasanein MA. The hypoglycemic and antioxidant activities of garden cress (Lepidium sativum L .) seed on alloxan-induced diabetic male rats. Nat Prod Res [Internet]. 2017;6419(December):1–5. Available from: http://doi.org/10.1080/14786419.2017.1413564
53. Babu R. Antidiabetic and Histopathological Analysis of Fenugreek Extract on Alloxan Induced Diabetic Rats. Int J Drug Dev Res. 2010;(2):356–64.
54. Upadhya S, Upadhya S. A study of hypoglycemic and antioxidant activity of Aegle marmelos in alloxan induced diabetic rats. Indian J Physiol Pharmacol. 2004;448(4):476–80.
55. Krishnakumari S. Effect of T . Arjuna Stem Bark Extract on Histopathology of Liver , Kidney and Pancreas of Alloxan-Induced Diabetic Rats. African J Biomed Res. 2006;9(September):189–97.
56. Adeoye AT, Oyagbemi AA, Omobowale TO, Adedapo AD, Ayodele AE, Yakubu MA, et al.

Nephroprotective Effects of Vernonia amygdalina in Alloxan-induced Diabetes in Rats. Int J Biochem Res Rev. 2018;21(1):1–15.

57. Bassey E, Oyebadejo S, Ikanna A, Oyebadejo S, Ibom A-. Histopathological Assessment of the Kidney of Alloxan Induced Diabetic Rat Treated with Macerated Allium Sativum (garlic). Asian J Biomed Pharm Sci. 2014;04(35):13–7.
58. Valrielyn Saio DS and RSD. Effect of Potentilla fulgens on lipid peroxidation and antioxidant status in alloxan-induced diabetic mice. J Basic Clin Pharm. 2012;3(2):249–54.
59. Gyeom S, Yu K, Oh N, Kee J. Clinical implications of aminotransferase elevation in hospitalised infants aged 8-90 days with respiratory virus detection. 2020;(February):1–7.
60. Biswal B, Karna N, Patel R. Okra mucilage act as a potential binder for the preparation of tablet formulation. Der Pharm Lett. 2014;6(3):31–9.
61. Sharma B, Sharma G, Joshi SC, Singh SK, Sharma B, Chand S. To Evaluate the Antidiabetic and Rejuvenating Capability of Tissues on Alloxan Induced Diabetic Rats under the Effect of Ethanolic Leaf Extract of Coriandrum sativum : A Histopathological Study. Pharmacogn J. 2017;9(6):792–8.
62. Shah NA, Khan MR. Antidiabetic Effect of Sida cordata in Alloxan Induced Diabetic Rats. Biomed Res Int. 2014;1–15.
63. Sefi M, Fetoui H, Soudani N, Chtourou Y, Makni M, Zeghal N. Pathology – Research and Practice Artemisia campestris leaf extract alleviates early diabetic nephropathy in rats by inhibiting protein oxidation and nitric oxide end products. Pathol -- Res Pract [Internet]. 2012;208(3):157–62. Available from: http://dx.doi.org/10.1016/j.prp.2012.01.002
64. Kumar CP, Rani GS. Journal of Natural Products and Resources Evaluation of Diabetic Nephropathy using Endogenous Plant Portulaca grandiflora Extract in Alloxan Induced Diabetic Rats. J Nat Prod Resour Visit. 2019;5(2):227–9.
65. Awanish Mishra, Rajbir Bhatti, Amarjit Singh MPSI. Ameliorative Effect of the Cinnamon Oil from Cinnamomum zeylanicum upon Early Stage Diabetic Nephropathy. Planta Med. 2010;76:412–7.
66. Yaro AH, Aliyu M, Borodo SB, Nazifi AB. Antihyperglycaemic and Antihyperlipidaemic Activities of Ethanol Leaf Extract of Eleusine coracana (Linn.) Gaertn. in Alloxan-Induced Hyperglycaemic Rats. J Appl Pharm Sci. 2018;8(07):28–32.
67. Song F, Chen W, Nussler AK. Effect of Momordica grosvenori on oxidative stress pathways in renal mitochondria of normal and alloxan-induced diabetic mice. Eur J Nutr. 2007;46(2):61–9.
68. Godwin SE, Jose MA. Effect of Asparagus Racemosus Against Streptozotocin- Nicotinamide Induced Type-2 Diabetes Mellitus With Special Reference To Diabetic Nephropathy in Rats. Int J Pharm Chem Sci. 2014;3(2):367–75.
69. Pharmacol CE, Balasubramanian T, Gp S, Karthikeyan M, Chatterjee TK. Therapeutic Effect of Stereospermum suavelolens on Diabetic Nephropathy. J Clin Exp Pharmacol. 2014;4(5):1–7.
70. Suman RK, Borde MK, Mohanty IR, Deshmukh YA. Antidiabetic Activity of Gymnema Sylvestre Leaves Extract on Streptozotocin Induced Diabetic Rats. Indo Am J Pharm Res. 2015;5(05):2054–60.
71. Li WZ, Wang XH, Zhang HX, Mao SM, Zhao CZ. Protective effect of the n-butanol Toona sinensis seed extract on diabetic nephropathy rat kidneys. Genet Mol Res. 2016;15(1):1–9.
72. Chen H, Yang M, Hung T. Nelumbo nucifera leaves extract attenuate the pathological progression of diabetic nephropathy in high-fat diet-fed and streptozotocin-induced diabetic

rats. J Food Drug Anal [Internet]. 2019;1–13. Available from: https://doi.org/10.1016/j.jfda.2018.12.009

73. Hassanalilou T, Payahoo L, Shahabi P, Abbasi MM, Asghari M. The protective effects of Morus nigra L . leaves on the kidney function tests and kidney and liver histological structures in streptozotocin-induced diabetic rats . Biomed Res. 2017;28(14):6113–8.
74. Salama AAA, Ibrahim BMM, Yassin NA, Mahmoud SS, Amina A, El-din G, et al. Regulatory Effects of Morus alba Aqueous Leaf Extract in Streptozotocin-Induced Diabetic Nephropathy. Der Pharma Chem. 2017;9(1):46–52.
75. Gupta R, Katariya P, Mathur M, Bajaj VK, Yadav S, Kamal R, et al. Antidiabetic and Renoprotective Activity of Momordica Dioica in Diabetic Rats. Diabetol Croat. 2011;40(3):81–8.
76. Saheb SH, Desai SD, Das KK, Haseena S. Effect of Nigella Sativa Seed on Streptozotocin Induced Diabetic Reno Toxicity : Histological Observations. Int J Anat Res. 2016;4(3):2566–70.
77. Elmas O, Erbas O, Yigitturk G. The efficacy of Aesculus hippocastanum seeds on diabetic nephropathy in a streptozotocin-induced diabetic rat model. Biomed Pharmacother [Internet]. 2016;83:392–6. Available from: http://dx.doi.org/10.1016/j.biopha.2016.06.055
78. Med I, Medica EE, Abstracts IP, Abstracts C. Effects of Medicago sativa on Nephropathy in Diabetic Rats. Indian J Pharm Sci. 2007;69(December):1–6.
79. Kim H, Kong M, Kim Y. Beneficial effects of Phellodendri Cortex extract on hyperglycemia and diabetic nephropathy in streptozotocin-induced diabetic rats. BMB Rep. 2008;710–5.
80. Kim YS, Jung DH, Sohn E, Lee YM, Kim C, Kim JS. Extract of Cassiae semen attenuates diabetic nephropathy via inhibition of advanced glycation end products accumulation in streptozotocin-induced diabetic rats. Phytomedicine [Internet]. 2013;1–6. Available from: http://dx.doi.org/10.1016/j.phymed.2013.11.002
81. Mhetre NK, Patel AN. Renoprotective Effect of Hydroalcoholic Extract of Aerial Parts of Cassia. Int J Pharm Pharm Sci. 2013;5(4):270–9.
82. Omara EA, Nada SA, Razik A, Farrag H, Sharaf WM, El-toumy SA. Phytomedicine Therapeutic effect of Acacia nilotica pods extract on streptozotocin induced diabetic nephropathy in rat. Eur J Integr Med [Internet]. 2012;19(12):1059–67. Available from: http://dx.doi.org/10.1016/j.phymed.2012.07.006
83. Tzeng T, Liou S, Chang CJ, Liu I. The Ethanol Extract of Zingiber zerumbet Attenuates Streptozotocin-Induced Diabetic Nephropathy in Rats. Hindawi Publ Corp. 2013;1–9.
84. Zhang S, Yang J, Li H, Li Y, Liu Y, Zhang D, et al. Skimmin, a coumarin, suppresses the streptozotocin-induced diabetic nephropathy in wistar rats. Eur J Pharmacol [Internet]. 2012;692(1–3):78–83. Available from: http://dx.doi.org/10.1016/j.ejphar.2012.05.017
85. Dias FO, K CS. Protective Effect of Kombucha on Diabetic Nephropathy in Streptozotocin - Induced Diabetic Rats. Int J Sci Res. 2016;5(3):2014–7.
86. Thomson M, Al-amin ZM, Al-qattan KK, Shaban LH, Ali M. Anti-diabetic and hypolipidaemic properties of garlic (Allium sativum) in streptozotocin-induced diabetic rats. Int J Diabetes Metab. 2007;15:108–15.
87. Ram Niwas Jangir GCJ. Antidiabetic and Antioxidant Potential of Hydroalcoholic Extract of Moringa Oleifera Leaves in Streptozotocin-Induced Diabetic Rats. Eur J Pharm Med Res. 2016;3(9):438–50.
88. Lee H, Ku S. Effect of Picrorrhiza Rhizoma Extracts on Early Diabetic Nephropathy in

Streptozotocin-Induced Diabetic Rats. J Med Food. 2008;11(2):294–301.

89. Rao NK, Nammi S. Antidiabetic and renoprotective effects of the chloroform extract of Terminalia chebula Retz. seeds in streptozotocin-induced diabetic rats. Biomed Cent. 2006;6:1–6.
90. C.-Y. HE, W.-D. LI, S.-X. GUO, S.-Q. LIN Z-BL. Effect of polysaccharides from Ganoderma lucidum on streptozotocin-induced diabetic nephropathy in mice. J Asian Nat Prod Res. 2006;8(8):705–11.
91. Kim MS, Sharma BR, Rhyu DY. Beneficial effect of lespedeza cuneata (G. don) water extract on streptozotocin-induced type 1 diabetes and cytokine-induced beta-cell damage. Nat Prod Sci. 2016;22(3):175–9.
92. Uzuki RS, Kada YO, Kuyama TO. The Favorable Effect of Style of Zea mays L . on Streptozotocin Induced Diabetic Nephropathy. Biol Pharm Bull. 2005;28(May):919–20.