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RECENT UPDATE ON BOTANICALS FOR TREATMENT OF DIABETIC NEPHROPATHY

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ABSTRACT
Diabetic nephropathy is a major cause of end-stage renal disease, and there has been a continuous increase in its incidence worldwide in the past two decades. Diabetic nephropathy is characterized by microalbuminuria, renal and glomerular hypertrophy, mesangial expansion with glomerular basement membrane thickening, arteriolar hyalinosis, and global glomerular sclerosis, which ultimately cause the progression of proteinuria and renal failure. This article represents detail survey of the 20 plants and synthetic antioxidant used for Diabetic Nephropathy. The literature shows that there are more than 400 plant species showing anti-diabetic activity. In the indigenous Indian system of medicine, many plant species remain to be scientifically established especially those with reno-protective effects. It was found that all the plant parts or extracts used in Diabetic Nephropathy. The detailed study is needed to explore the ethno-botanical uses of medicinal plants and further clinical experimentation is also needed to scientifically evaluate these widely used herbal remedies for possible bioactive effects.

KEYWORDS: Traditional uses, Diabetic Nephropathy(DN) & Medicinal plants.

INTRODUCTION
An herbal drug constitutes a major part in all traditional systems of medicine. There are approximately 1250 Indian medicinal plants which are used in formulating therapeutic preparations according to Ayurvedic and other traditional systems of medicine. Plants provide varieties of resources that contribute to the fundamental need of food, clothing and shelter. Among plants of economical importance, Medicinal and Aromatic plants have played vital role in alleviating human sufferings. Plants are utilized as therapeutic agents as since times immemorial in both organized (Ayurveda and Unani) and unorganized (folk, tribal, native) forms. Pharmacological activity of medicinal plants is often known as a result of millennia of trial and error but they have to be carefully investigated if we wish to develop new drug that meet the criteria of modern treatment. Since time immemorial man has used various parts of plants in the treatment and prevention of many ailments. Historically all medicinal preparations were derived from plants, whether in the simple form of plant parts or in the more complex form of crude extracts, mixtures, etc. Today a substantial number of drugs are developed from plants which are active against a number of diseases. The majority of these involve the isolation of the active ingredient (chemical compound) found in a particular medicinal plant and its subsequent modification. In the developed countries 25 percent of the medical drugs are based on plants and their derivatives and the use of medicinal plants is well known among the indigenous people in rural areas of many developing countries[1]. Diabetic nephropathy (DN) refers to a characteristic set of structural and functional kidney abnormalities in patients with diabetes.[2] The structural abnormalities include hypertrophy of the kidney, increase in glomerular basement membrane thickness, nodular and diffuse glomerulosclerosis, tubular atrophy, and interstitial fibrosis.[3-4]

Diabetic nephropathy is also known as *Kimmelstiel Wilson Syndrome*. Other mechanisms, including glomerular hypertension with hyperfiltration, increased advanced glycation end products, sorbitol and protein kinase C (PKC) pathway activation, growth factors and cytokines such as transforming growth factor-β (TGF-β), and genetic susceptibility, have been identified as important deteriorating factors, but the precise mechanisms through which diabetic renal injury progresses remain to be resolved.[5]

Stages in DN
There are 5 stages in DN are-
Stage 1: Renal or kidney functions are changed in this stage. The kidney increases in size, and it is accompanied by high filtration and priming rate.
Stage 2: The structure of kidney is changed for worse and patients pass protein in their urine after intense physical activity.

Stage 3: This stage comes after patients have suffered from diabetes for 5 to 15 years and their renal functions begins to decline.
Stage 4: This stage is known as Clinical Diabetic Nephropathy whose characteristic is large amount of proteinuria, more than 3.5 grams daily, along with Edema and high blood pressure.
Stage 5: It is called uremia and patient's condition is critical. They need to undergo dialysis and kidney transplant to sustain their life. Other therapy are: dialysis, osmotherapy.[6]

Prevalence

The prevalence of diabetes is increasing globally and the maximum increase is expected to be in developing countries like India. By the year 2010, it was estimated that nearly 220 million people worldwide were diabetic. India is facing a major health care burden due to the high prevalence of type 2 diabetes and there are indications that this would increase further in the next few decades. Nearly 30% of chronic renal failures in India are due to diabetic nephropathy.[7] Nephropathy due to diabetes can be diagnosed very easily and can be prevented. Increased prevalence of diabetic nephropathy in South Asians Racial differences in the prevalence of diabetic renal disease has been reported. Asian people have significantly ($p < 0.01$) higher prevalence (52.6%) of diabetic end stage renal disease (ESRD) when compared with the Caucasians (36.2%).[8] The prevalence of diabetic nephropathy in type 2 diabetic subjects is reported to be 5-9%.[9] The risk for cardiovascular disease (CVD) was 3 fold higher in South Indian NIDDM subjects with nephropathy when compared with their non-nephropathic counterparts.[10] Thus, in type 2 diabetes, many patients may not reach end stage renal disease due to premature death from CVD.

Etiology

The exact cause is unknown but some causes are poor control of blood sugar is thought to lead to kidney damage. If there is also having high blood pressure, kidney damage is even more likely; in some cases family history may also play a role. Not everyone with diabetes develops this kidney problem, People with diabetes who smoke, and those with type 1 diabetes also have higher risk for kidney problems.[11]

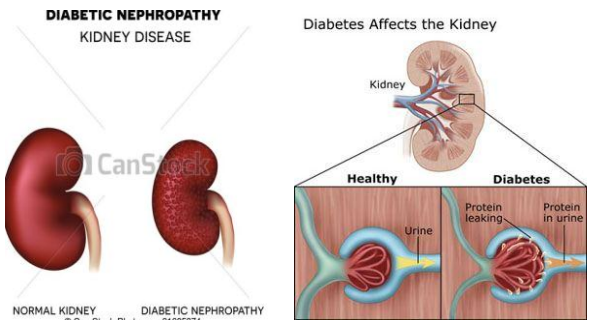


Fig. 1: Diabetic Nephropathy.

Signs and Symptoms

Often, there are no symptoms as the kidney damage starts and slowly gets worse. Kidney damage can begin 5 to 10 years before symptoms start. People who have more severe kidney disease may have, poor appetite, Polyuria, polydipsia, polyphagia, feel tired most of the time, general ill feeling, Headache, nausea and vomiting, swelling of the legs, and many other symptoms may also occur. About 30-35% of people with diabetes (both type 1 and 2) have albumin in urine (microalbuminuria and macroalbuminuria). Risk of kidney damage is increased in people with high blood pressure (risk increases progressively with the increase in blood pressure) and poor blood sugar control. Herbal medicines have gained significant importance in the last few decades and the demand to use natural products in the treatment of diabetes is increasing worldwide. Available literature shows that there are more than 400 plant species showing anti-diabetic activity. In the indigenous Indian system of medicine, many plant species remain to be scientifically established especially those with reno-protective effects.

Role of Botanicals in the treatment and management of diabetic induced neuropathy

Some of the herbs reported to be effective in diabetic nephropathy are:

Anacardium occidentale (Family: Anacardiaceae; Common name: Cashew)

Fig. 2: *Anacardium occidentale.*

It reduces diabetes induced functional and histological alterations in the kidneys. Hypoglycaemic action of this plant is seen in experimental type I diabetes. Streptozotocin induced diabetes in rats has been reported to be associated with functional and morphological changes in the kidney Histopathological study showed significant reduction in accumulation of mucopolysaccharides in the kidneys of diabetic animals.[13]

Andrographis Paniculata (Family: Acanthaceae; Common name: Kalmegh)

Fig. 3: ***Andrographis Paniculata.***

Chronic administration of *A. paniculata* to alloxan-induced diabetic rats for four weeks produced significant blood glucose reduction. Chloroform extract of this was found to be significantly inhibited the induction of albuminuria, proteinemia and uremia. The studies clearly indicated a significant anti-diabetic activity with the chloroform extract of A.paniculata roots and supports the traditional usage of the plant by Ayurvedic physicians for the control of diabetes. Also the extract is useful in preventing the incidence of long-term complication of diabetic nephropathy.[14]

Benincasa cerifera (Family: Cucurbitaceae; Common name: Kusmanda)

Fig. 4: ***Benincasa cerifera.***

Fruits of Benincasa cerifera have free-radical scavenging property. They are widely used as a vegetable in India and other tropical countries. Benincasa cerifera prevents lipid peroxidation and protects the kidneys from severe increase of reactive oxygen species and depletion of superoxide dismutase and reduced glutathione.[16]

Brassica oleracea (Family: Brassicaceae; Common name: Red Cabbage)

Fig. 5: ***Benincasa oleracea.***

It is mainly used as a vegetable (Hazem et al., 2008). It has anti-oxidant and antihyperglycaemic activity. Main constituents are the isothiocyanates and anthocyanins play a important role in reduction of oxidative stress.[17] It contains anthocyanin pigments that are described as free radical scavenging and antioxidant agents.[18]

Camellia sinensis (Family: Theaceae; Common name: Green tea, Chaay)

Fig. 6: ***Camellia sinensis.***

Green tea prevents diabetes and hypertension-related renal oxidative stress, attenuating renal injury. Spontaneously hypertensive rats (SHR) with streptozotocin induced diabetes and nondiabetic SHR were treated daily with tap water or freshly prepared green tea. The oxidative stress parameters were significantly less in rats treated with green tea. These findings suggest that the consumption of green tea may reduce nephropathy in diabetic hypertensive patients.[19]

Cinnamomum zeylanicum (Family: Lauracaeae; Common name: Dalchini)

Fig. 6: ***Cinnamomum zeylanicum.***

Cinnamon oil upon early stage diabetic nephropathy due to its antioxidant and antidiabetic effect has been studied against alloxan (150 mg/kg i.p) induced diabetic nephropathy. Histological studies of the kidney revealed the protective effect of cinnamon oil by reducing the glomerular expansion, eradicating hyaline casts and decreasing the tubular dilatations.[20]

Curcuma longa (Family: Zingiberaceae; Common name: Turmeric)

Fig. 7: ***Curcuma longa.***

Chronic treatment with Curcumin obtained from Curcuma longa was shown to significantly attenuates renal dysfunction and oxidative stress in streptozotocin induced diabetic rats. The results confirmed evidence of oxidative stress in diabetic nephropathy and point towards the possible anti-oxidative mechanism being responsible for the nephroprotective action of curcumin.[21]

Ganoderma lucidum (Family: Ganodermataceae; Common name: Lingzhi Mushroom)

Fig. 8: ***Ganoderma lucidum.***

The effects of Ganoderma lucidum polysaccharide on renal complication in streptozotocin induced diabetic mice were studied. It was able to reduce the serum creatinine and blood urea nitrogen levels and urinary albumin excretion compared with diabetic model mice in a dose dependent manner. Increasing serum glucose and triglyceride levels in diabetic mice could also be lowered by Ganoderma lucidum polysaccharide. It has a capacity to improve the metabolic abnormalities of diabetic mice and prevent or delay the progression of diabetic renal complications.[22]

Glycine max (Family: Fabaceae; Common name: Soyabean)

Fig. 9: ***Glycine max.***

Soyabean decreases the progression of diabetic nephropathy (Irritani et al., 1997). It prevents morphological destruction of the kidney associated with diabetes mellitus. Soyabean feeding is known to enhance the conversion of polyunsaturated fatty acids to docosahexaenoic acid. Increased production of this complex lipid has been linked to benefit in a variety of inflammatory models and diseases including renal disease. Soyabeans have been shown to reduce urinary albumin excretion and total cholesterol in non-diabetic patients with nephritic syndrome. They may prevent the weight loss and morphological disruption of the kidney associated with diabetes mellitus.[23]

Gymnema montanum (Family: Asclepidaceae; Common name: Bidaria Tingens Deche)

Fig. 10: ***Gymnema montanum.***

It is an endemic plant species of India used traditionally for diabetes and its management. The ethanolic extract of Gymnema montanum at a dose of 200mg/kg body weight significantly normalized the elevated blood glucose, renal markers and lipid peroxidation in diabetic kidney. The ethanol extract has been found to be effective in reducing oxidative stress and ethnopharmacological use of Gymnema montanum in protecting diabetes and its complications.[24]

Indigofera tinctoria Leaves (Family: Fabaceae; Common name: True Indigo)

Fig. 11: *Indigofera tinctoria.*

The extract from leaves improved renal creatinine clearance and reduced renal total protein loss demonstrating nephroprotective properties.[25]

Linum usitatissimum (Family: Linaceae; Common name: Common Flax or Linseed)

Fig. 12: *Linum usitatissimum.*

Dietary protein substitution with flaxseed meal has been shown to reduce proteinuria and glomerular and tubulointerstitial lesions in obese spontaneous hypertensive rats.[26]

Panax quinquefolius (Family: Araliaceae; Common name: American Ginseng)

Fig. 13: *Panax quinquefolius.*

The effects of American ginseng and heat- processed American ginseng on diabetic renal damage using streptozotocin (STZ) induced diabetes has been studied. The diabetic rats have shown a loss of body weight and increase in kidney weight, food intake, and urine volume, whereas the oral administration of heat processed American ginseng at a dose of 100mg/kg shows improvement. Among the renal function parameters, the elevated urinary protein levels in diabetic control rats were significantly decreased by the American ginsing and the decreased creatinine clearance level was significantly increased in rats administered with heat processed American ginseng. These findings indicate that heat processed American ginseng may have beneficial effect on pathological conditions associated with diabetic nephropathy.[27]

Propolis

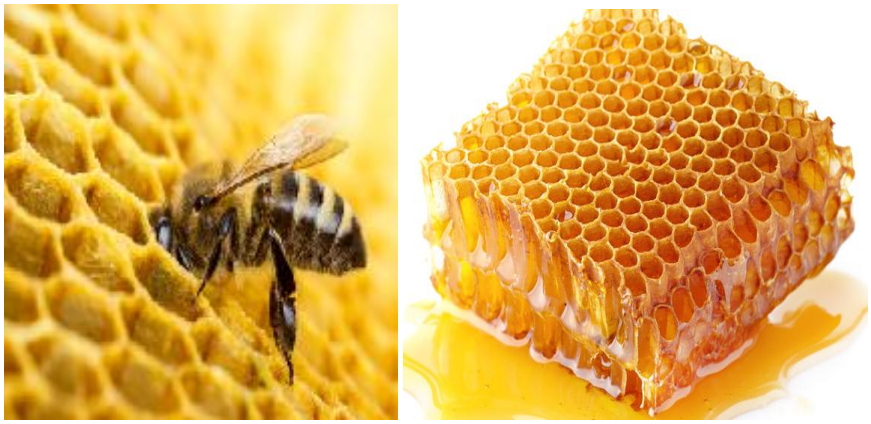


Fig. 14: Propolis.

It is a resinous hive product collected by honeybees from many plant sources (Tawaza et al., 1999). It has shown a protective effect in diabetic associated metabolic disturbances, renal function and oxidative stress in streptozotocin induced diabetic rats. Oxidative stress may play a key role in the pathogenesis of diabetic

nephropathy (Osama et al., 2009). Propolis and its extract have anti-oxidant properties. Oral administration of propolis extract in doses of 100, 200 & 300 mgs/kg body weight improved the body and kidney weights, serum glucose, lipid profile, malonaldehyde and renal function tests.[28]

Pterocarpus santalinus (Family: Fabaceae; Common Name: Red Sandal Wood)

Fig. 15: *Pterocarpus santalinus.*

Pterocarpus santalinus treatment caused significant lowering of blood sugar and improvement in glucose tolerance tests. The extract also caused a decrease in the formation of lipid peroxidase, estimated by thiobarbituric acid reactive substance (TBARS) and increased antioxidants. Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase and glutathione transfers in erythrocytes. Serum creatinine and urine albumin were found to be decreased levels after treatment and returned to control values.[29]

Rheum officinale (Family: Polygonaceae; Common name: Rhubarb)

Fig. 16: *Rheum officinale.*

Rhubarb extract showed an improvement of hyperlipidaemia, and accelerated excretion of urinary urea nitrogen and creatinine was observed. The results indicated that rhubarb extract has potential as a new therapeutic agent for inhibiting the progression of diabetic nephropathy.[30]

Salvia miltiorrhiza (Family: Lamiaceae; Common name: Red Sage)

Fig. 17: *Salvia miltiorrhiza.*

It has been reported that plant was shown to reduce diabetic nehropath by suppressing the over-expression of transforming growth factor- beta (TGF-beta 1), connective tissue growth factor (CTGF), fibronectin (FN) and plasminogen activator inhibitor 1 (PAI-1) in renal cortex.[31]

Silybum adans (Family: Asteraceae; Common name: Milk Thistle)

Fig. 18: *Silybum adans.*

Milk thistle extract attenuates diabetic nephropathy in streptozotocin induced diabetic rats. The effect was possibly by increasing kidney catalase (CAT) and glutathione peroxidase (GPx) activity and decreasing lipid peroxidation in renal tissue.[32]

Tectona grandis (Family; Lamiaceae, Common name: Teak Wood)

Fig. 19: *Tectona grandis.*

Diabetic animals treated with Tectonia grandis (TG), have shown significant reduction in the elevated level of plasma glucose when compared with diabetic control. While considering renal parameters, diabetic animals treated with TG revealed significant decrease in serum creatinine, urine albumin and urine total protein levels and significant increase in serum albumin, total protein and percentage change in body weight when compared with diabetic control.[33]

Terminalia chebula (Family: Combretaceae; Common name: Black Myroblans)

Fig. 20: ***Terminalia chebula.***

It has anti-oxidant and free radical scavenging properties (Nalamolu et al., 2006) Triphala is a popular traditional medicine containing Terminalia chebula. It has renoprotective effects (Kirtikar et al., 1935). Terminalia chebula is widely used as a traditional medicine by diabetic patients in India. Although the fruits are known for their anti-diabetic properties, the whole powder of dried fruits is also being widely used for the control of diabetes. Chloroform extract has been shown to produce significant anti-diabetic and reno-protective property. Terminalia chebula is widely used as a traditional medicine by diabetic patients in India. Although the fruits are known for their anti-diabetic properties, the whole powder of dried fruits is also being widely used for the control of diabetes.[34-35]

Synthetic antioxidant

Antioxidant are mainly of three types i.e antioxidant enzyme, molecular antioxidant, synthetic antioxidant. Examples of antioxidant enzymes are superoxide dismutase(SOD), catalase, glutathione peroxidase. Example of molecular antioxidant are vitamine C, vitamine E, carotenoids and flavonoids. Example of synthetic antioxidant are tempol, lutein, resveratrol, tanshinone II A etc. SOD contain highly reactive form of oxygen which convert reactive free radical superoxide into peroxide with zinc and manganese acting as cofactor.[36] In catalase peroxide is less reactive then superoxide but still somewhat unstable and able to cause formation of SOD[37] as well as other superoxide to oxygen and water and glutathione peroxidase that contribute to formation of free radical. glutathione peroxidases convert highly reactive molecule like lipid peroxides into less reactive molecule.[38]

Antioxidant plants

Ocimum sanctum, cubeba Linn., Allium sativum Linn., Terminalia bellerica, Camellia sinensis Linn. Zingiber officinale Roscoe, Trigonella foenumgraecum Linn., Eugenia caryophyllus. several Indian and Chinese plants. The majority of the antioxidant activity is due to the flavones, isoflavones, flavonoids, anthocyanin, coumarin lignans, catechins and isocatechins.[39]

Green tea and black tea leaves are obtained from dried leaves of Camellia sinensis Linn., belonging to the family Theaceae. Its chemical composition is similar to that of fresh tea leaves. Green tea contains polyphenols, which include flavonols, flavandiols, flavonoid and phenolic acids. Piper species, commonly used in diet and traditional medicine, were assessed for their antioxidant potential. Black pepper (P. nigrum Linn.) was richest in glutathione peroxidase and glucose-6-phosphate dehydrogenase, green pepper was richest in peroxidase and vitamin C, while vitamin E was greater in P. longum Linn. and P. nigrum Linn. Cardamom spice consists of whole or ground dried fruit of Elettaria cardamomum (Linn.) Maton, a herbaceous perennial of the ginger family (Zingiberaceae) containing essential oil.[40]

Experimental Models Practices for DN studies

The animal models for nephropathy share many features which are common to human nephropathy and have been delineated by targeting proteinuria, glomerulosclerosis, glomerulonephritis, glomerular hypertrophy, tubulointerstitial nephritis. Therefore, suitable animal models help us to identify the mechanisms involved in human nephropathy and to develop potential drugs for the treatment of renal complications.

Chemical agents that develops diabetes and later on diabetic nephropathy are

STZ(streptozotocin), Alloxan, Anthracycline, Aminoglycoside, Cadmium, Carbon tetrachloride and Cisplatin, Maleic acid.

Harmone develop diabetes is Dexamethasone and *Viral agents develop* diabetes are: RNA Picornoviruses, Mengo-2T, Reovirus.

Surgical model also develop diabetes is Pancreatectomy.

Steptozotocin induced diabetes

Steptozotocin or streptozocin or Izostazin or Zanosar(STZ, 2-deoxy-2-(3-methyl-3- nitrosoureido)-D-glucopyranose) was discovered in a strain of the soil microbe Streptomyces achromogenes. It was classified as an alkylating agent in the nitrosourea class of anti-cancer drugs and was used to treat cancer of Islets of Langerhans in the pancreas but it is toxic to the insulin producing beta cells of the Islets of Langerhans in the pancreas, and thus it is widely employed to induce diabetes in animals. Administration of a single dose of STZ (40 mg/kg, 50 mg/kg, 55 mg/kg, 60 mg/kg and 65 mg/kg i.p. or i.v.) in rats results in hyperglycaemia

within 72 hours.[41] Nephropathy was noted in rats between 4–8 weeks after the administration of STZ (50 mg/kg, 55 mg/kg, 60 mg/kg i.p., once) result in increase in proteinuria, serum creatinine, blood urea nitrogen (BUN), extracellular matrix deposition and thickening of glomerular basement membrane[42] and triggers multiple pathways, including activation of protein kinase-C, poly (ADP-ribose) polymerase and NADPH oxidase, decrease the bioavailabilty of NO, generation of ROS and advanced glycation end products resulting in renal damage and nephropathy.[43] It is toxic to cells by causing damage to the DNA, though other mechanisms may also contribute. DNA damage induces activation of poly ADP-ribosylation, which is likely more important for diabetes induction than DNA damage itself.[44] Streptozotocin is similar enough to glucose to be transported into the cell by the glucose transport protein GLUT2, but is not recognized by the other glucose transporters. This explains its relative toxicity to beta cells, since these cells have relatively high levels of GLUT2.[45-46] Multiple low dose of STZ induce diabetes by causing immune mediated pancreatic insulititis in rats at a dose of 50mg/kg, i.p. STZ in combination with cyclosporine A enhance diabetogenic efficacy. STZ combined with freund adjuvant(mycobacterium butyricum, listeria monocytogenes) administer 24 hr prior to STZ(25mg/kg) and then repeated in 3 subsequents weeks produce hyperglycemia. Advantages of using STZ are: greater selectivity towards β cells, lower mortality rate and longer or irreversible diabetes induction.[47]

Alloxan induced diabetes

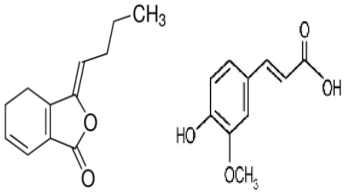
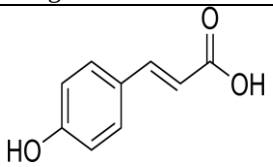
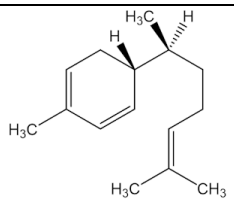
Alloxan (2,4,5,6-tetraoxypyrimidine; 2,4,5,6-pyrimidinetetrone) is an oxygenated pyrimidine derivative which is present as alloxan hydrate in aqueous solution. Alloxan has been used to induce experimental diabetes due to the selective destruction of the insulin-producing pancreatic beta-islets.[48] Alloxan induces a multiphasic blood glucose response when injected into to an experimental animal, which is accompanied by corresponding inverse changes in the plasma insulin concentration followed by sequential ultrastructural beta cell. The mechanism of alloxan action through several experimental studies have demonstrated that alloxan evokes a sudden rise in insulin secretion in the presence or absence of glucose which appeared just after alloxan treatment.[49] This particular alloxan-induced insulin release occurs for short duration followed by the complete suppression of the islet response to glucose even when high concentrations of glucose were used. Another mechanism is the effect of ROS on the DNA of pancreatic islets. The fragmentation of DNA takes place in the beta cells exposed to alloxan that causes DNA damage, which stimulates poly ADP-ribosylation, a process participating in DNA repair. Drawback of using alloxan are: high mortality in rats, cause ketosis in animal and diabetes induced is reversible.

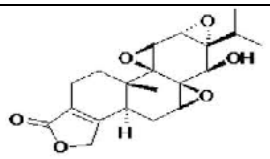
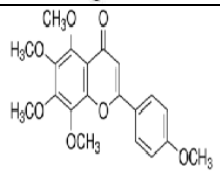
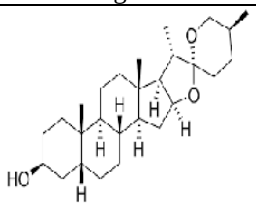
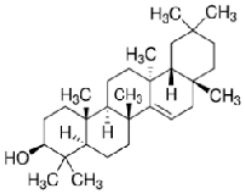
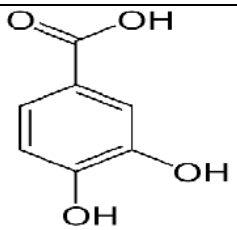
Anthracycline-induced diabetes

Adriamycin (doxorubicin) is classified as an anthracycline class of antibiotic and it is an effective antitumour drug used to treat cancer of various organs such as bladder, breast, stomach and thyroid. Administration of adriamycin (2 mg/kg i.v., twice at 20-day intervals) for 20 weeks in rats, results in significant increase in proteinuria, serum creatinine, BUN, and progression of glomerulosclerosis.[50]

Other accepted models - virus, hormone and surgical model.

Some example of Plants and their Predominant bioactive constituent used for DN.

Plants	Predominant bioactive		Reference
Rhizome of Ligusticum chuanxiong Hort.	Z-ligustilide (LGT), ferulic acid (FA), and tetramethylpyrazine (TMP)	 Z-ligustilide ferulic acid	[51]
Morus alba leaves	coumaric acid	 coumaric acid	[52]
ginger (Zingiber officinale) rhizome extract	Zingiberene, followed by AR-curcumene, α-Bergamotene Gingerol, Zingerone, β-esquiphellandrene, (Z)-β-Farnesene, Caryophyllene and ç-Elemene	 Zingiberene	[53]

mulberry leaf	polysaccharide		[54]
Tripterygium wilfordii, or *léi gōng téng* (Mandarin)	Tripterygium Glycosides	 Triptolide	[55]
Citrus plants	Tangeretin (5, 6, 7, 8, 4'-pentamethoxyflavone),	 Tangeretin	[56]
Rhizome of Anemarrhena asphodeloides Bunge (AA, family Liliaceae)	Steroidal saponins (sarsasapogenin)	 sarsasapogenin	[57]
Abroma augusta leaf	Taraxerol, a pentacyclic triterpenoid	 Taraxerol	[58]
Sansevieria roxburghiana Leaves	Protocatechuic Acid(Phenolic)	 Protocatechuic Acid	[59]

CONCLUSION

Diabetes mellitus is metabolic disorder related with structural and functional alterations of various organs system & diabetic complications are associated with macrovascular and microvascular damage to the major organs of the body. Universally the role of herbals for complications of nervous system with or without diabetes is accepted. The study of ethno-medical system and herbal medicines as therapeutic agents of a paramount importance in addressing health problems of traditional communities and third world countries as well as industrialized societies.[60] Scientific indication on herbals & other phytoconstituents showed positive results for the treatment and management of neuropathy and neurodegeneration in diabetes. Based on this scientific proofs in future these herbal & phytoconstituents based approach will prove beneficial for betterment of the life of people who are suffering from diabetic neuropathy and neurodegeneration. Antioxidants have a diversity of biochemical actions such as inhibition of reactive oxygen species production, scavenging of free radicals. The presence of alkaloids, benzoquinones, catechols, carotenoids, flavonoids, glycosides, flavonol glycosides, steroid glycosides, glycoalkaloids, terpenoids, monoterpenoids, diterpenoids, triterpene saponins, sterols and polyphenols in medicinal plant showed nephroprotective activity.[61] So, the present review works update the herbals plants/extract active against DN. The utilization of these natural sources of antioxidants may be useful for human exposure to nephrotoxic agents and patients who suffer from renal diseases. Further studies are needed to elucidate exact mechanism of action of these bioactive principles for protection against DN and potential worth of these natural against Diabetic nephropathy.

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