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DIABETIC NEPHROPATHY AND HERBAL MEDICINES

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ABSTRACT

Diabetic Nephropathy is defined as a persistent albuminuria and more commonly diagnosed by a urinary excretion of more than 300 mg/24 hour. It develops in around one third of patients with diabetes, with the Asia-Pacific region being the most severely affected. It is one of the causes of renal failure and end-stage renal disease. Factors like smoking and diastolic blood pressure have been found to be associated with microalbuminuria. Oxidative stress may play a key role in the pathogenesis of diabetic nephropathy. Role of traditional herbs and medicines in the treatment of diabetic nephropathy needs attention especially in India, where certain fruits and herbs are thought to have positive effects on health. Certain herbs such as *Anacardium occidentale*, *Benincasa cerifera*, *Brassica oleracea* and *Terminalia chebula* etc. have shown positive effects in diabetic nephropathy. The enormous cost of modern medicines indicate that alternative strategies are required for better management of diabetes. The study of herbal medicines might offer a natural key to unlock a diabetologists pharmacy for the future.

Key words: Diabetic nephropathy, Albuminuria, ACE inhibitor, Herbal Medicines.

INTRODUCTION

The kidneys play a critical role in maintaining overall health. These twin organs filter waste products and excess water from the blood and also produce hormones that are essential for the optimal maintenance of bodily functions. Diabetic nephropathy (nephropatia diabetica), also known as Kimmelstiel-Wilson syndrome, or nodular diabetic glomerulosclerosis (Kimmelstiel P, 1936) and intercapillary glomerulonephritis, is the condition that occurs when diabetes causes the kidneys to lose their ability to function properly. It is characterised by high levels of protein in the blood. High blood sugar caused by diabetes can cause problems in many parts of the body, including the kidneys. Kidneys contain many small blood vessels. With diabetes, these small blood vessels can be injured throughout the body, including the

kidneys. When diabetes damages the small blood vessels in the kidneys, this is called diabetic nephropathy. If this occurs, kidney cannot filter the blood properly and this causes the body to retain more water and salt than it should. Also, waste material accumulates in the body. Diabetes can also lead to nerve damage which can be another cause of diabetic nephropathy. It may be difficult to empty the bladder, which can back up and injure or infect the kidneys.

Diabetic nephropathy is an important cause of morbidity and mortality, and is now among the most common causes of end-stage renal failure (ESRF) in developed countries. Pathologically, the first changes seen at the time of microalbuminuria are thickening of the glomerular basement membrane and accumulation of matrix material in the mesangium. Subsequently, nodular deposits are characteristic, and glomerulosclerosis worsens (heavy proteinuria develops) until glomeruli are progressively lost and renal function deteriorates. Microalbuminuria is an important indicator of risk of developing diabetic nephropathy (Lee *et al.*, 2003). Progressively increasing albuminuria accompanied by hypertension, is much more likely to be due to early diabetic nephropathy.

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Signs and symptoms

Main symptoms of diabetic nephropathy include an increase in blood pressure (hypertension) and fluid retention in the body. Other complications include arteriosclerosis of the renal artery and proteinuria. Diabetic nephropathy has no symptoms throughout its early course. They develop in late stages and may be a result of excretion of high amounts of protein in the urine or due to renal failure:

- edema: swelling, usually around the eyes in the mornings; later, general body swelling may result, such as swelling of the legs
- foamy appearance or excessive frothing of the urine (caused by the proteinuria)
- unintentional weight gain (from fluid accumulation)
- anorexia (poor appetite)
- nausea and vomiting
- malaise (general ill feeling)
- fatigue
- headache
- frequent hiccups
- generalized itching

The first laboratory abnormality is a positive microalbuminuria test. The urine analysis may also show glucose in the urine, especially if blood glucose is poorly controlled. Serum and blood urea nitrogen may increase as kidney damage progresses. Kidney failure provoked by glomerulosclerosis leads to fluid filtration defects and other disorders of kidney function.

Risk factors for developing diabetic nephropathy

Poor control of blood glucose

Long duration of diabetes

Presence of other microvascular complications

Pre-existing hypertension

Family history of diabetic nephropathy

Family history of hypertension (Ayodele *et al.*, 2004)

Treatment overview

Diabetic nephropathy is treated with medicines that lower blood pressure and protect the kidneys. These medicines may reverse kidney damage and are started as soon as any amount of protein is found in the urine. If there is high blood pressure, two or more medicines may be needed to lower blood pressure enough to protect the kidneys. If a person is taking other medicines, especially non-steroidal anti-inflammatory drugs (NSAIDs), the medicines that damage the kidneys, should be avoided. It is also important to keep the blood sugar as close to normal as possible. Limiting the amount of salt in diet can help keep high blood pressure from becoming worse. Proteins should also be restricted in diet (Samata *et al.*, 1991; Mani 1998). People with diabetes are 2 to 4 times more likely to die of heart and blood vessel diseases than people who don't have diabetes. Using low-dose aspirin

therapy and eating a low-fat diet can help prevent heart attack, stroke, and other large blood vessel diseases (Sundar *et al.*, 1991).

Conventional medicines that are used to treat diabetic nephropathy include:

Angiotensin Converting Enzyme Inhibitors, (ACEIs):

These include captopril, lisinopril, ramipril and enalapril. They have been shown to protect kidney function in people with Type I diabetes, even in those who do not have high blood pressure. They can lower the amount of protein being lost in the urine. Also, they may reduce risk of heart and blood vessel (cardiovascular) disease (Reboldi *et al.*, 2009).

Angiotensin II Receptor Blockers (ARBs):

They include candesartan, irbesartan, losartan, and telmisartan. The combination of these medicines may provide greater protection to kidneys than either medicine alone (Lewis *et al.*, 2001).

Calcium Channel Blockers (CCBs):

These lower blood pressure by making it easier for blood to flow through the vessels. Examples include diltiazem, verapamil, amlodipine and nifedipine (Tikkanen *et al.*, 1997).

Diuretics: Medicines such as chlorthalidone, hydrochlorothiazide or spironolactone help lower blood pressure by removing sodium and water from the body (Pahar *et al.*, 2000).

Beta-blockers: These lower blood pressure by slowing down heart beat and reducing the amount of blood pumped with each heart beat. Examples include atenolol, carvedilol and metoprolol (Strippoli *et al.*, 2006).

Herbal Medicines

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 (Grover *et al.*, 2001).

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

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

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 (Leonard *et al.*, 2006). Albino rats receiving graded doses of hexane extract of this plant by gavage (150 and 300mg/kg/day) and insulin (5 IU/kg) significantly reduced blood glucose level, total protein excreted, glycosuria and urea in diabetic rats. Histopathological study showed significant reduction in accumulation of mucopolysaccharides in the kidneys of diabetic animals. Phytochemical analysis has revealed the presence of alkaloids, polyphenols and saponins in the plant extract (Leonard *et al.*, 2006).

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

Chronic administration of *A. paniculata* to alloxan-induced diabetic rats for four weeks produced significant blood glucose reduction. Chloroform extract 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 (Rao, 2006).

Astragalus propinquus (Family: Fabaceae; Common name: Milk Vetch)

It improves the pathogenesis and development of diabetic nephropathy which is closely associated with the changes of plasma Endothelin I (ET-I) levels and platelet function (Liu ZQ *et al.*, 2001).

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

Fruits of *Benincasa cerifera* have free-radical scavenging property (Lim, 2007). They are widely used as a vegetable in India and other tropical countries. They are also used in urinary infections, epilepsy, peptic ulcer and haemorrhages from internal organs. *Benincasa cerifera* prevents lipid peroxidation and protects the kidneys from severe increase of reactive oxygen species and depletion of superoxide dismutase and reduced glutathione (Huang *et al.*, 2004).

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

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, reduces oxidative diabetic nephropathy

(Evans *et al.*, 2002). It contains anthocyanin pigments that are described as free radical scavenging and antioxidant agents. Its extract contains vitamins A, B and C all of which have protective roles against oxidative damage (Fowke *et al.*, 2003). It also contains substantial quantities of isothiocyanates some of which are very potent antioxidants. Daily ingestion of red cabbage polar extract (1gm/kg body weight) ameliorates oxidative stress and diabetic nephropathy (Jagdish *et al.*, 2006).

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

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. After 12 weeks, the systolic blood pressure did not differ between treated and untreated nondiabetic or diabetic rats. However body weight was less and glycemia was greater in diabetic SHR rats than in no diabetic rats. Renal oxidative stress variables were greater in diabetic rats. 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 (Ribaldo *et al.*, 2009).

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

The ameliorative effect of the 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. The results indicated that the volatile oil from cinnamon contained more than 98% cinnamaldehyde and that it confers dose-dependent significant protection against alloxan induced renal damage. The maximum decrease in fasting blood glucose has been achieved at the dose of 20 mg/kg (Mishra *et al.*, 2010).

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

Chronic treatment with Curcumin obtained from *Curcuma longa* significantly attenuates both 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 (Sharma *et al.*, 2006).

Dietary fish oil

The effect of suppression of dienoic eicosanoid metabolism (arachidonic acid metabolism) on renal hypertrophy in diabetic rats was studied by feeding fish oil. Diabetic rats fed fish oil showed marked reduction in insulin requirements compared to control rats fed a beef fallow rich diet. The concentration of arachidonic acid metabolites were depressed in the renal cortex of diabetic fed fish oil. This alteration in eicosanoid metabolism was associated with a substantial enhancement of diabetic renal hypertrophy. Studies indicate that dietary fish oil has profound effects on renal eicosanoid metabolism in experimental diabetes and that these autocooids may participate in the biological events which regulate diabetic renal hypertrophy (Logan *et al.*, 1990).

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

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 (He *et al.*, 2006).

Ginkgo biloba (Family: Ginkgoaceae; Common name: Maidenhair Tree)

The effect of *Ginkgo biloba* leaf on renal lesions of early diabetic nephropathy was studied on sixty eight patients. The extract of *Ginkgo biloba* was orally given to patients. The therapeutic course was for three months. Indexes such as urinary micro-albumin, alpha 1 micro globulin, immunoglobulin, transferring, retinal binding protein protein and N-acetyl beta D glucosaminidase before and after treatment were compared. Compared with before treatment, the above levels decreased with significant difference in the treated group. However, there was no significant decrease in the above mentioned indexes in the control group (Zhu *et al.*, 2005).

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

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 docosaheptaenoic acid. Increased production of this complex lipid has been linked to benefit in a variety of inflammatory models and diseases including renal disease (Young *et al.*, 2008). 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. A soyabean diet improves serum glucose and insulin levels, as well as insulin sensitivity in diabetes. Although the exact mechanism has yet to be elucidated, it is possible that the soluble fiber component of soyabeans may be the most important factor (Anderson *et al.*, 1998). Approximately 15% of the soyabean is composed of insoluble carbohydrates and over 30% of the fiber in soyabeans is of the soluble variety. Moreover, soyabeans are slowly digested and have a low glycaemic index. They contain carbohydrates, fat, protein, vitamins, minerals like calcium, folic acid and iron (Lavigne *et al.*, 2000).

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

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 markers and increased antioxidant levels in diabetic kidney. The diabetic rats excreted large amount of proteins than untreated rats which was normalized during the treatment with the ethanol extract. 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 (Ram *et al.*, 2009).

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

The extract from leaves improved renal creatinine clearance and reduced renal total protein loss demonstrating nephroprotective properties. The organ to body weight ratio studies carried out showed pancreas and liver specific effects of *Indigofera tinctoria* leaves. These results were also supported by histo-pathological studies. It was concluded from the studies that alcoholic extract of leaves in long-term treatment may be beneficial in the management of type-1, type-2 diabetes (Bangar *et al.*, 2011).

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

Dietary protein substitution with flaxseed meal has been shown to reduce proteinuria and glomerular and tubulointerstitial lesions in obese spontaneous hypertensive rats. Flaxseed meal is more effective than soya proteins in reducing proteinuria and renal histologic abnormalities. The reduction in proteinuria and renal injury is independent on the amount of protein intake and glycaemic control (Velasquez *et al.*, 2003).

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

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 gain 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 of body weight per day for 20 days attenuated these diabetes-induced physiological abnormalities. Among the renal function parameters, the elevated urinary protein levels in diabetic control rats were significantly decreased by the American ginseng or heat processed American Ginseng administration, 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 (Kim *et al.*, 2007).

Polygonatum odoratum (Family: Asparagaceae; Common name: Scented Solomons Seal)

The ethanolic extract and soluble fractions of this plant were evaluated using an *in vivo* model of renal advanced glycation end-product (AGE) accumulation in streptozotocin-induced diabetic rats and an *in vitro* bovine serum albumin-glucose assay. It was found that isolates inhibited AGE formation more effectively than the positive control, aminoguanidine. The results indicate that this plant could be used as novel natural product drug for mitigating diabetic complications (Dong *et al.*, 2010).

Propolis

It is a resinous hive product collected by honeybees from many plant sources (Tawaza *et al.*, 1999). It is a traditional medicine used as early as 300 BC and has been reported to exert a broad spectrum of biological functions including anti-oxidant activity. The major components of propolis are flavonoids, phenolic acid esters, terpenoids and prenylated derivatives of coumaric acids (Shinohara *et al.*, 2002). 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. Renal glutathione, superoxide dismutase and catalase levels were significantly increased while malonaldehyde was markedly reduced (Burdock *et al.*, 1998). Propolis can control the blood glucose, modulate the metabolism of lipids leading to decreased output of lipid peroxidation and scavenge the free radicals in rats with diabetes (Fuliang *et al.*, 2005). Propolis has been reported to save vitamin C, maintain cellular glutathione, conserve the integrity of biomembranes and reduce leakage of cytosolic lactate dehydrogenase in the liver. Moreover, it may diminish primary DNA damage of the cells (Luan *et al.*, 2000).

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

Pterocarpus santalinus treatment caused significant lowering of blood sugar and improvement in glucose tolerance tests. A decrease was observed in HbA1c on regular long term control over blood glucose levels. The antioxidant effect of the red sandal wood extract was also evident, as it caused a reduction in malondialdehyde (MDA) in the brain, liver and muscle tissues. 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 showed decreased levels after treatment and returned to control values. The kidneys were examined histologically for Diabetic Nephropathy and showed regression following treatment. Sixteen weeks combination therapy also resulted in decreases in LDL-C/HDL-C, TC, TG and an increase in HDL-C of treated diabetic rats. The use of the aqueous extract of *P. santalinus* caused improvements in glycemia, lipid peroxidation and brain, liver and heart masses (Halim *et al.*, 2011).

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

Rhubarb extract was given orally to rats with diabetic nephropathy induced by subtotal nephrectomy and injection of streptozotocin. As a result, high blood and urinary glucose levels, which were conspicuous in similarly treated rats that were not given rhubarb extract, were ameliorated. 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 (Yokozawa *et al.*, 1997).

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

It has been reported to protect rats from diabetic nephropathy, against streptozotocin induced diabetes, 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 (Liu *et al.*, 2005).

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

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 (Vessal *et al.*, 2010).

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

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 % change in body weight when compared with diabetic control. Diabetic groups treated with TG showed absence of the sclerotic lesions produced by diabetic condition thereby, indicated that TG has the potential to treat diabetes mellitus and prevent the associated renal damage (Varma and Jaybhaye, 2010).

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

It has anti-oxidant and free radical scavenging properties (Nalamolu *et al.*, 2006) and mainly used in Ayurveda in the treatment of diabetes, asthma, sorethroat, vomiting, hiccough, diarrhoea, bleeding, piles, gout, heart and bladder diseases. 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. The seed extract has indicated a potent action in short

term study and a prolonged duration of anti-diabetic action in long term study and this could be due to multiple sites of action possessed by the active principle. Chloroform extract has shown significant anti-diabetic and reno-protective effects (Cheng *et al.*, 2003).

Vitis vinifera (Family: Vitaceae; Common name: Grape Vine)

STZ injected rats showed significant increases in blood glucose, polyuria, proteinuria and a decrease in body weight compared with age-matched control rats. After 6 weeks, diabetic rats exhibited renal dysfunction, as evidenced by reduced creatinine and urea clearance, and proteinuria along with a marked increase on oxidative stress, such as determined by lipid peroxidation and activities of key antioxidant enzymes. Treatment with resveratrol significantly attenuated renal dysfunction and oxidative stress in diabetic rats. The studies reinforce the important role of oxidative stress in diabetic kidney and points towards the possible anti-oxidative mechanism being responsible for the reno-protective action of resveratrol (Sharma *et al.*, 2006).

CONCLUSION

Diabetes mellitus is world's largest growing metabolic disorder. Tight control of blood glucose can reduce clinical complications in diabetic patients, however alternative treatment strategies are needed to prevent oxidative stress complications and to optimize recovery. It is well documented that modulation of oxidative stress through treatment with antioxidants can effectively reduce diabetic snag. Oxidative stress induced by hyperglycaemia in diabetes is a major cause for development and progression of diabetic micro vascular complications such as nephropathy. In India, diabetes has been calculated to drain 5-25 % of the average Indian families income. Onset of diabetic kidney disease is associated with a 10-30% increase in treatment costs. The cost of dialysis and cost of renal transplant is an amount unaffordable to majority of the patients. In India alone, approximately 850,000 individuals are affected by diabetic nephropathy, placing a huge economic burden on society also. Enormous cost of modern medicines indicate alternative strategies are required for better management. With the result, interest in the search of new drugs from natural sources is gaining global attention. These may play a vital role in future in the treatment of diabetes and studies may be carried for determining their mechanism of action and also in the isolation and identification of main principles useful for treating diabetes induced nephropathy.

REFERENCES

- Abo-Salem OM, El-Edel RH, Harisa GE, El-Halawany N, Ghonaim MM. Experimental diabetic nephropathy can be prevented by propolis: Effect on metabolic disturbances and renal oxidative parameters. *Pak J Pharm Sci*, 22(2), 2009, 205-210.
- Anderson JW, Blake JE, Turner J, Smith BM. Effects of soy protein on renal function and proteinuria in patients with type 2 diabetes. *Am J Clin Nutr*, 68(6), 1998, 1347S-1353S.
- Ayodele OE, Alebiosu CO, Salako BL. Diabetic nephropathy--a review of the natural history, burden, risk factors and treatment. *J Natl Med Assoc*, 96(11), 2004, 1445-54.
- Bangar AV, Saralay MG. Anti-hyperglycaemic activity of ethanol extract and chloroform extract of *Indigofera tinctoria* leaves in streptozotocin induced diabetic mice (Family-Papilionaceae). *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, 2(1), 2011, 444-455.
- Burdock GA. Review of the biological properties and toxicity of bee propolis (propolis). *Food Chem Toxicol*, 36(4), 1998, 347-63.
- Cheng HY, Lin TC, Yu KH, Yang CM, Lin CC. Antioxidant and free radical scavenging activities of *Terminalia chebula*. *Biol Pharm Bull*, 26(9), 2003, 1331-5.
- Choi YE, Ahn SK, Lee WT, Lee JE, Park SH, Yoon BB, Park KA. Soybeans ameliorate diabetic nephropathy in rats. *Evid Based Complement Alternat Med*, 7(4), 2010, 433-40.
- Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. *Endocr Rev*, 23(5), 2002, 599-622.
- Fowke JH, Chung FL, Jin F, Qi D, Cai Q, Conaway C et al. Urinary isothiocyanate levels, brassica, and human breast cancer. *Cancer Res*, 63(14), 2003, 3980-6.
- Fuliang HU, Hepburn HR, Xuan H, Chen M, Daya S, Radloff SE. Effects of propolis on blood glucose, blood lipid and free radicals in rats with diabetes mellitus. *Pharmacol Res*, 51(2), 2005, 147-52.
- Grover JK, Vats V, Rath SS, Dawar R. Traditional Indian anti-diabetic plants attenuate progression of renal damage in streptozotocin induced diabetic mice. *J Ethnopharmacol*, 76(3), 2001, 233-8.
- Halim ME, Misra A. The effects of the aqueous extract of *Pterocarpus santalinus* heartwood and vitamin E supplementation in streptozotocin-induced diabetic rats. *Journal of Medicinal Plants Research*, 5(3), 2011, 398-409.
- He CY, Li WO, Guo SX et al. Effect of polysaccharides from *Ganoderma lucidum* on STZ induced diabetic nephropathy in mice. *J Asian Nat Prod Res*, 8(8), 2006, 705-11.
- Huang HY, Huang JJ, Tso TK, Tsai YC, Chang CK. Antioxidant and angiotension-converting enzyme inhibition capacities of various parts of *Benincasa hispida* (wax gourd). *Nahrung*, 48(3), 2004, 230-3.
- Iritani N, Sugimoto T, Fukuda H, Komiya M, Ikeda H. Dietary soybean protein increases insulin receptor gene expression in Wistar fatty rats when dietary polyunsaturated fatty acid level is low. *J Nutr*, 127(6), 1997, 1077-83.
- Ivorra MD, Payá M, Villar A. A review of natural products and plants as potential antidiabetic drugs. *J Ethnopharmacol*, 27(3), 1989, 243-75.
- John L, Rao PS, Kanagasabapathy AS. Prevalence of diabetic nephropathy in non-insulin dependent diabetics. *Indian J Med Res*, 94, 1991, 24-9.
- Kataya HA, Hamza AA. Red Cabbage (*Brassica oleracea*) Ameliorates Diabetic Nephropathy in Rats. *Evid Based Complement Alternat Med*, 5(3), 2008, 281-7.
- Kim HY, Kang KS, Yamabe N, Nagai R, Yokozawa T. Protective effect of heat-processed American ginseng against diabetic renal damage in rats. *J Agric Food Chem*, 55(21), 2007, 8491-7.
- Kirtikar KR, Basu BD: *Terminalia chebula*, In Indian Medicinal Plants. Vol 1; 2nd edition 1935, 1020-1023.
- Lavigne C, Marette A, Jacques H. Cod and soy proteins compared with casein improve glucose tolerance and insulin sensitivity in rats. *Am J Physiol Endocrinol Metab*, 278(3), 2000, E491-500.
- Lee G. End-stage renal disease in the Asian-Pacific region. *Semin Nephrol*, 23(1), 2003, 107-14.
- Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*, 345(12), 2001, 851-60.
- Lim SJ. Effects of fractions of *Benincasa hispida* on antioxidative status in Streptozotocin induced diabetic rats. *Korean J Nutr*, 40(4), 2007, 295-302.
- Liu G, Guan GJ, Qi TG, Fu YQ, Li XG, Sun Y, Wu T, Wen RZ. Protective effects of *Salvia miltiorrhiza* on rats with streptozotocin diabetes and its mechanism. *Zhong Xi Yi Jie He Xue Bao*, 3(6), 2005, 459-62.

- Liu YN, Shen XN, Tao GY. Effects of grape seed proanthocyanidin extract on experimental diabetic nephropathy in rats. *Wei Sheng Yan Jui*, 35(6), 2006, 703-5.
- Logan JL, Benson B, Lee SM. Dietary fish oil enhances renal hypertrophy in experimental diabetes. *Diabetes Res Clin Pract*, 10(2), 1990, 137-45.
- Luan J, Wang N, Tian L. Study on the pharmacologic effect of propolis. *Zhong Yao Cai*, 23(6), 2000, 346-8.
- Mani MK. Patterns of renal disease in indigenous populations in India. *Nephrology*, 4, 1998, S4-S7.
- Mishra A, Bhatti R, Singh A et al. Ameliorative effect of the cinnamon oil from *cinnamon zeylanicum* upon early stage diabetic nephropathy. *Planta Med*, 76(5), 2010, 412-17.
- Pahor M, Psaty BM, Alderman MH, Applegate WB, Williamson JD, Furberg CD. Therapeutic benefits of ACE inhibitors and other antihypertensive drugs in patients with type 2 diabetes. *Diabetes Care*, 23(7), 2000, 888-92.
- Ramkumar KM, Ponmanickam P, Velayuthaprabhu S, Archunan G, Rajaguru P. Protective effect of *Gymnema montanum* against renal damage in experimental diabetic rats. *Food Chem Toxicol*, 47(10), 2009, 2516-21.
- Rao NK, Nammi S. Antidiabetic and renoprotective effects of the chloroform extract of *Terminalia chebula* Retz. Seeds in streptozotocin-induced diabetic rats. *BMC Complement Altern Med*, 6, 2006, 17.
- Rao NK. Anti-Hyperglycemic and Renal Protective Activities of *Andrographis paniculata* Roots Chloroform Extract. *Iranian Journal of Pharmacology and Therapeutics*, 5(1) 2006 47-50.
- Reboldi G, Gentile G, Angeli F, Verdecchia P. Choice of ACE inhibitor combinations in hypertensive patients with type 2 diabetes: update after recent clinical trials. *Vasc Health Risk Manag*, 5(1), 2009, 411-27.
- Ribaldo PD, Souza DS, Biswas SK, Block K, et al. Green tea (*Camella sinensis*) attenuates nephropathy by down regulating NOX4 NADPH oxidase in diabetic spontaneously hypertensive rats. *J Nutr*, 139(1), 2009, 96-100.
- Samanta A, Burden AC, Jagger C. A comparison of the clinical features and vascular complications of diabetes between migrant Asians and Caucasians in Leicester, U.K. *Diabetes Res Clin Pract*, 14(3), 1991, 205-13.
- Sharma S, Anjaneyulu M, Kulkarni SK, Chopra K. Resveratrol, a Polyphenolic Phytoalexin, is also found to attenuate Diabetic Nephropathy in Rats. *Pharmacology*, 76(2), 2006, 69-75.
- Sharma S, Kulkarni SK, Chopra K. Curcumin, the active principle of turmeric (*Curcuma longa*), ameliorates diabetic nephropathy in rats. *Clin Exp Pharmacol Physiol*, 33(10), 2006, 940-5.
- Shinohara R, Ohta Y, Hayashi T, Ikeno T. Evaluation of antilipid peroxidative action of propolis ethanol extract. *Phytother Res*, 16(4), 2002, 340-7.
- Singh J, Upadhyay AK, Bahadur A, Singh B, et al. Anti-oxidant phytochemicals in cabbage (*Brassica oleracea* L. var. capitata). *Scientia Horticulturae*, 108(3), 2006, 233-7.
- Strippoli GF, Craig MC, Schena FP, Craig JC. Role of blood pressure targets and specific antihypertensive agents used to prevent diabetic nephropathy and delay its progression. *J Am Soc Nephrol*, 17(4), 2006, S153-5.
- Tazawa S, Warashina T, Noro T. Studies on the Constituents of Brazilian Propolis. Part 2. *Chem Pharm Bull*, 31(13), 2000, 1388-1392.
- Tedong L, Dimo T, Dzeufiet PDD, Asongalem AE, Sokeng DS, Callard P, et al. Antihyperglycemic and renal protective activities of *anacardium occidentale* (anacardiaceae) leaves in streptozotocin induced diabetic rats. *Afr J Trad CAM*, 3(1), 2006 23-35.
- Tikkanen I, Johnston CI. Comparison of renin-angiotensin to calcium channel blockade in renal disease. *Kidney Int Suppl*, 63, 1997, S19-22.
- Varma SB, Jaybhaye DL. Antidiabetic and Nephroprotective effect of *Tectona grandis* linn. In Alloxan induced Diabetes. *Int J Ayurveda Res*, 1(3), 2010, 163-6.
- Velasquez MT, Bhathena SJ, Ranich T, Schwartz AM, Kardon DE, Ali AA, et al. Dietary flaxseed meal reduces proteinuria and ameliorates nephropathy in an animal model of type II diabetes mellitus. *Kidney Int*, 64(6) 2003, 2100-7.
- Vessal G, Akmal M, Najafi P, Moein MR, Sagheb MM. Silymarin and milk thistle extract may prevent the progression of diabetic nephropathy in streptozotocin-induced diabetic rats. *Ren Fail*, 32(6), 2010, 733-9.
- Yokozawa T, He LQ, Muto Y, Nagasaki R, Hattori M, Oura H. Effects of rhubarb extract in rats with diabetic nephropathy. *Phytotherapy Research*, 11(1), 1997, 73-75.
- Zhu HW, Shi ZF, Chen YY. Effect of extract of *Ginkgo biloba* leaf on early diabetic nephropathy. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 25(10), 2005, 889-91.