Journal of Diabetes and Clinical Endocrinology

Review Article

The Role of Plant-Based Therapies in Diabetic Nephropathy

Thaifa M.S*, Manoj Kumar, Arya U.S, Aparna G. Babu

Department of Pharmaceutical Chemistry, The Dale View College of Pharmacy and Research Centre, Punalal, Poovachal, Trivandrum, Kerala, India

ABSTRACT

Diabetic nephropathy is a complication associated with diabetes mellitus. Diabetes mellitus is a chronic metabolic disorder caused by impaired metabolism of carbohydrate, fats, proteins resulting in hyperglycaemia leading to decreased utilization of carbohydrate, excessive glycogenolysis and gluconeogenesis from amino acids and fatty acids. Diabetic nephropathy is a kidney disease induced by diabetes and occurs due to high blood sugar in the kidney.

Keywords: Diabetic nephropathy; Polyol pathway; Hyperglycaemia

INTRODUCTION

Inside kidneys are millions of these tiny blood vessels that act as filters called glomeruli. Diabetes mellitus damages this important filtering system and causes them fail to function well. This review deals with the stages in diabetic nephropathy, mechanisms involved, treatment strategies that focus on plants used in diabetic nephropathy [1].

STAGES IN DIABETIC NEPHROPATHY

High blood sugar levels destroy glomeruli over time and account for progressive kidney diseases. Several mechanisms can induce the diabetic nephropathy including our varying life style. There are mainly five stages involved in the development of diabetic nephropathy. In stage 1; Kidneys increase in size accompanied by increased rate of filtration which gives over work to kidney [2]. It could be reversed as long as high level of sugar is controlled. In Stage 2; Renal structure changes in this stage, glomerular basilar membrane thickens and at the same time, proteinuria attacks after intensive exercises. It usually requires more than five years to progress to stage 2. The proteinuria means presence of an excess of serum protein in the urine, the excess of protein in the urine often causes the urine to become foamy, although foamy urine may also be caused by bilirubin in the urine [3]. In Stage 3; persistent albuminuria (albumin in urine) forms along with declined kidney function which occurs as diabetics suffer from the disease for 5-15 years. In stage 3, there still stands a chance to correct diabetic nephropathy if treated properly. In stage 4 also called clinical diabetic nephropathy. Massive loss of protein in urine (not less than 3.5 g/day), edema (fatigue) and high blood pressure are three most typical symptoms that are hard to reverse, when one's illness condition progress to the stage 4. In stage 5; Dialysis and kidney transplantation may be needed to sustain the patient's life. Stage 5 is the end of renal failure with uremia, due to diabetic nephropathy [4].

PATHOPHYSIOLOGY

Polyol path way is also called as the sorbitol-aldose reductase pathway, which is implicated in micro vascular damage to the kidney. Sorbitol cannot cross cell membranes and when it accumulates, it produces osmotic stress on cells by drawing water into insulin independent tissues. While most of the cells require the action of insulin for glucose to gain entry into the cells, the cells of kidney are insulin dependent, so glucose moves freely across the cell membrane, regardless of action of insulin. The cells will use glucose for energy as normal and any glucose not used for energy will enter the polyol pathway [5]. When blood glucose is normal, that is about 100 mg/dl or 5.5 mm/litre, this interchange causes no problems, as aldose reductase has a low affinity for glucose at normal concentrations. Aldose reductase is the enzyme, which is responsible for causing polyol path way. In a hyperglycemic state, affinity of aldose reductase for glucose rises, causing much sorbitol to accumulate and leaving less NADPH by using much more NADPH that is leaving less NADPH for other processes of cellular metabolisms. This change of affinity is what is meant by activation of polyol pathway. The amount of sorbitol, that accumulates however, may

Correspondence to: Thaifa MS, Department of Pharmaceutical Chemistry, The Dale View College of Pharmacy and Research Centre, Punalal, Poovachal, Trivandrum, Kerala, India, E-mail: thaisa101@gmail.com

Received: Apr 30 2024, **Accepted:** May 29 2024; **Published:** Jun 05, 2024, DOI: 10.59462/jdce.1.1.104

Citation: Thaifa MS, Kumar M, Arya US, Babu AG (2024) The Role of Plant-Based Therapies in Diabetic Nephropathy. Journal of Diabetes and Clinical Endocrinology, 1(1):104.

not be sufficient to cause osmotic influx of water. The NADPH acts to promote nitric oxide and glutathione production, and it's deficiency will cause glutathione deficiency as well. Aglutathione deficiency can lead to hemolysis caused by oxidative stress. Nitric acid is one of the vasodilators in the blood vessels. Therefore NADPH prevents reactive oxygen species from accumulating and damaging cells. Excessive activation of the polyol pathway increases intracellular and extracellular sorbitol concentration, there by increased concentration of reactive oxygen species and decreased concentration of nitric oxide and glutathione. Each of these imbalances can damage the cells [6].

TREATMENT

The various treatments associated with the diabetic nephropathy include; by using herbal plants, through supplements, traditional Chinese medicine, immune therapy, blood purification, dialysis, yoga as meditation therapy, hormonotherapy. Among all the treatment strategies, plants play a major role in the management of diabetic nephropathy *via* aldose reductase inhibition, and by other complementary mechanisms. Even though a large variety of compounds have been synthesized with aldose reductase inhibitory activity, very few compounds are clinically available because of undesirable side effects and poor pharmacokinetics. The active constituent isolated from polygonum multiforum, the 2,3,5,4'-tetrahydroxy stilbene exhibit anti-oxidant and anti-inflammatory effects. Oxidative stress caused by hyperglycemia is believed to be the major molecular mechanism, underlying diabetic nephropathy. So this Tetra Hydroxyl Stilbene (THS) can be used against the diabetic nephropathy. *Andrographis paniculata* nees are used for various ethno medical conditions including hyperglycemia and hypertension complications. The extracts of these plants have been reported to possess anti-diabetic activity [7]. It's mechanism of action is suggested *via* by activating α'-angiotensin receptors to enhance the secretion of B-endorphin, which can stimulate the opioid micro receptors to reduce hepatic gluconeogenesis and to enhance the glucose up take in the muscle. The active constituents present in *Andrographis paniculata*, responsible for the activity is andrographolide and 14-deoxy-11,12-dehydro andrographolide. *Silybum marianum* belongs to the asteraceae family. The alloxan induces the diabetes mellitus in laboratory animals. Silymarin protect against oxidative peroxidation in experimental animals and increases the levels of reduced glutathione (GSH). It could protect pancreatic tissue by preventing the rise in both plasma glucose and pancreatic lipid peroxidation [8]. Also silymarin restored endocrine pancreatic function by improving insulin and glucagon expression to achieve normoglycaemia (that is normal glucose level). Also other studies shows that, components of silymarin, could stimulate proliferation as well as protein and DNA synthesis in kidney cells, which also restore renal morphology.

Hence can be used against diabetic nephropathy. *Syzigium cumini* skeels, novel therapeutic agent for diabetes have a folk medicinal value. The various parts of this plant have a major role in the regulation of diabetic nephropathy. Diabetic nephropathy is one of the important microvascular complications of diabetes mellitus; this is single largest cause of end stage renal disease requiring chronic dialysis. Recent studies have shown that reactive oxygen species play a major role in the development of diabetic nephropathy. High glucose directly increases hydrogen peroxide production by mesangial cell. So by administering, we can reduce the Reactive Oxygen Species (ROS), hence reducing the diabetic nephropathy. The rhizomes of *Anemarrhena asphodeloides* belongs to the family Lilliaceae, possess lowering blood glucose level capacity after oral administration. The active constituents were conformed to be the mangiferine, and its glucoside exerts an antidiabetic property and activity against diabetic nephropathy by increasing insulin sensitivity [9].

The *Terminalia arjuna* consists of chief constituent arjunolic acid, they will act on non-protein sulfhydryl groups in the kidney, which have diabetic nephropathy. This causes a free radical scavenging ability, hence causes anti-oxidantactivity, hence give action against diabetic nephropathy. *Apocynum venetum* is a traditionally used drug. They act by promoting diuresis. They are also capable of scavenging oxygen free radicals there by inhibiting the production of free radicals, thereby causing anti-oxidant effect and resulting in reduction of oxygen stress or oxidative stress, finally they will show activity against diabetic nephropathy. *Ginkgo biloba* leaf has protective action on early diabetic nephropathy through significantly decreased urinary micro albumin. *Ginkgo biloba* extract injection has also be shown to be effective in diabetic nephropathy through decreasing urinary albumin excretion rate, regulating blood lipids, improving renal function and hemo rheology. The active constituents present in the *Origanum vulgare* are rosmarinic acid, carvacrol and thymol. These compounds exhibit higher anti-oxidant activity. The rosmarinic acid isolated from *Origanum vulgare* shows potent aldose reductase inhibitory activity, there by resist polyol path way, resulting in reduced diabetic nephropathy. *Rosmarinus officinalis* brings about a significant decrease in the level of total protein and albumin in blood. It also restores level of elevated liver function enzymes to normal. From this it is clear that *Rosmarinus officinalis* have a role in beta cell protection, there by reduces the diabetic nephropathy. Also the nepetrin and nepetin isolated from *Rosmarinus officinalis*, were found to have potent aldose reductase inhibitory activity. Rosmarinic acid alone was reported to inhibit glomerular hypertrophy and glomerulosclerosis [10].

The Polygonum hydropiper contains the constituent's isoquercetin and other flavonoids. They when isolated were found to possess potent aldose reductase inhibitory activity. Hence the plant is used in the treatment of diabetic nephropathy. The chief constituent of *Englhardtia chrysolepis* is a stilbin which shows aldose reductase inhibitory activity and also active constituent taxifolin dihydro flavonols also shows aldose reductase inhibitory activity. The chief constituent obtained from *Chrysanthemum indicum* is luteloin which will causes heme oxygenase-1 expression, there by resulting in reduction in oxidative stress, causing potent aldose reductase inhibitory activity. Hence used in the treatment of diabetic nephropathy. The various phyto constituents from green tea was found to show aldose reductase inhibitory activity. It was found to show preventive effect in diabetic nephropathy by exhibiting its anti-oxidant activity; hence it will reduce the oxidative stress associated with the diabetic nephropathy. The major constituent

present in the *Salacia chinensis* is mangiferine, which will prevent the expression of beta cell there by advanced glycation end products will be reduced and also it will prevent extra cellular matrix accumulation, thereby causing inactivation of polyol pathway and reactive oxygen species regeneration, hence prevents diabetic nephropathy. The recent studies also show that *salacia chinensis* is a nephroprotective drug. This mangiferine will lower blood glucose level. In addition to that, they will alter the level of bio active parameters including urea, uric acid and creatinine.

Similarly the levels of red blood, white blood cells and their functional composition or indices were significantly improved through the administration of mangiferin. So the mangiferin can be administered for preventing diabetic nephropathy. The *Belamcanda chinensis* consists of chief constituent flavonoid apocynin, which may cause a decrease in protein kinase C and thereby decrease the oxidative stress and also result in aldose reductase inhibitory activity; there by used in treatment of diabetic nephropathy. This *Belamcanda chinensis* belonging to the family Iridaceae is reported to have a pharmacological activity of hypoglycemic effect by bringing about an increase in serum insulin concentration. Also this *Belamcanda chinensis* shows significant lowering effect of fasting blood glucose level, due to the presence of isoflavone glycoside also shows anti-oxidant and anti-inflammatory activity. It also reduces oxidative stress there by showing activity against diabetic nephropathy.

CONCLUSION

Diabetes is a disease, which has a assumed vital public health importance because of the complications associated with it. Among that complication most important one is the diabetic nephropathy. Various mechanisms including polyol pathway along with a complex integrating paradigm have been implicated in glucose mediated complications. Also some researchers focus on the key enzyme, aldose reductase, which cause or generate the polyol pathway. Various complementary therapies like ayurveda, Chinese traditional medicine, homeopathy, hormone therapy are also performed against diabetic nephropathy. But each treatment may have its own merits and de-merits. Some of these medicinal plant extracts are a potential source of anti-diabetic drugs because of their therapeutic efficacy and anti-diabetic mechanisms reported in experimental animals. However at present, the cellular or molecular mechanism of action of these plants extracts remains to be established.

Future research directed at the identification of active components is the only viable option for supporting the efficacy claims for all herbs. Even though various compounds with aldose reductase inhibitory activity have been synthesized, a very few compounds are under clinical use. But there are many plants, whose mechanism of action is not elucidated completely and research funding to investigate the potential beneficial effects of medicinal plants is critically important for optimal patient care and safety.

REFERENCES

1. Jefferson JA, Shankland SJ, Pichler RH. Proteinuria in diabetic kidney disease: A mechanistic viewpoint. Kidney Int. 2008;74(1):22-36.
2. Gabbay KH. Hyperglycemia, polyol metabolism and complications of diabetes mellitus. Annu Rev Med. 1975;26:521-536.
3. Dodda D, Ciddi V. Plants used in the management of diabetic complication. Indian J Pharm Sci. 2014;76(2):97-106.
4. Dunlop M. Aldose reductases and the role of polyol pathway in diabetic neuropathy. Kidney Int. 2000;58:S3-S12.
5. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414(6865):813-820.
6. Lee MJ, Rao YK, Chen K, Lee YC, Chung YS, Tzeng YM, et al. Andrographodile and 14-deoxy-11,12-dehydroandrographodile from *andrographis paniculata* attenuates high glucose induced fibrosis and the apoptois in murine renal mesangial cell lines. J Ethnopharmacol. 2009;132(2):497-505.
7. Soto C, Pezer J, Garcia V, Uria E, Vadillo M, Raya L, et al. Effect of silymarin on kidneys of rats suffering from alloxan induced diabetes mellitus. Phytomedicine. 2010;17(14):1090-1094.
8. Xie W, Du L. Diabetes is an anti-inflammatory disease: Evidence from traditional chinese medicine. Diabetes Obes Metab. 2011;13(4): 289-301.
9. Miller PL, Scholey JW, Rennke HG, Meyer TW. Glomerular hypertrophy aggravates epithelial cell injury in nephritic rats. J Clin Invest. 1990;85(4):1119-1126.
10. Gugliucci A. Glycation as the glucose link to diabetic complications. J Am Osteopath Assoc. 2000;100(10):621-634.