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Review Article

A REVIEW ON MECHANISM AND PLANTS USED FOR DIABETIC NEPHROPATHY: A CURSE OF DIABETES

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ABSTRACT

Objective: Diabetes associates not only rise in blood glucose level but also several diseases. One of the basic diseases is diabetic nephropathy. This is also called end stage diabetes. **Method:** The various factors which are responsible for the disease are elevated metabolism, hypertension, and blockage of various molecular pathways such as AGE, RAAS, PKC, Hexsomamine and polylol. When we considered for its treatment, is associated with various multiple risk factor approach. Along with allopathic medicine herbal medicine had provided a sensible and better approach for the treatment of various kidney diseases. Effective approaches must be applied for the prevention of development Hyperlipidemia, decrease GFR and sustaining the progression to later stages of nephropathy may be beneficial. **Conclusion:** This review mainly explains the pathophysiology and all the basic causes of diabetic nephropathy along with the potential herbs which may be useful for the treatment of disease.

Keywords: Pathology, RASS, Hyperlipidemia, GFR.

INTRODUCTION

Diabetes Nephropathy is defined as partial loss of kidney function. Metabolic derangement, glomerular hypertension, advanced glycation end products, and oxidative stress is responsible for progression of diabetic nephropathy [1]. High sugar level leads to raise oxidative stress which is one of the important causative factors for diabetes nephropathy [2]. The early symptoms of diabetes nephropathy are related to increase blood sugar levels, and loss of glucose in the urine. High amounts of glucose in the urine are responsible for excretion of glucose and lead to dehydration. Dehydration symptoms mainly include increased thirst and water consumption. The inability of insulin to perform normally affects the metabolism of protein, fat and carbohydrate. Insulin is a metabolic hormone and allows the storage of fat and protein. A relative or absolute insulin deficiency ultimately leads to weight loss despite an increase in appetite [3]. Patients with diabetes also complain of fatigue, nausea and vomiting. Patients with diabetes are susceptible to developing infections of the bladder, skin, and vaginal areas. Changing in blood glucose levels can lead to blurred vision. Lethargy and coma is lead by exceptionally high glucose levels.

The main factor responsible for diabetic nephropathy mainly includes biochemical, hormonal, immunological and rheological.

1. Biochemical factors include long standing hyperglycemia and glycosylation process.
2. Various studies prove that growth hormone promotes the thickening of basement membrane in diabetes.
3. Both exogenous and endogenous insulin auto antibodies, IAA contributed in basement membrane thickening.
4. The red blood cell deformity due to glycosylation and fibrin down fall the results in altered permeability and hypercoagulability in diabetic patients [4].

Pathophysiology

Glomerular filtration barrier functions act as a complex biological sieve. The capillaries are able to filter very small molecules. Glomerular capillaries are highly permeable for water (hydraulic conductivity) and relatively impermeable to large molecules. The permeability is possible because of the unique three-layer (endothelial cells, Glomerular basement membrane and Podocytes) of glomerular filtration membrane. Glomerular filtration membrane consists of endothelial glycocalyx. The various pathological changes appear in the glomeruli of patients with long-duration diabetes mellitus, before developing the microalbuminuria, the severity of glomerular damage is proportional to glomerular filtration rate and duration of diabetes mellitus, and blood-glucose regulation [5]. Diabetic nephropathy is a clinically characterized by fall in Glomerular Filtration Rate (GFR), excessive deposition of extracellular matrix proteins (hypoprotenuria), peripheral glomerular basement membrane thickening, glomerular hypertrophy, tubular interstitial fibrosis, and lower albumin excretion and decreased in creatinine clearance [6].

Role of different molecular pathway

Polyol pathway or Aldose Reductase pathway

The polyol pathway has a major role of two enzymes, first enzyme, aldose reductase (AR), which converts the glucose to Sorbitol with the aid of its co-factor NADPH, and the second enzyme, Sorbitol dehydrogenase (SDH), with its co-factor NAD+, which converts sorbitol to fructose, a process that increases the ratio of NADH/NAD and may leads to both oxidative stress and activation of protein kinase C [7]. Fructose and its metabolites fructose-3-phosphate and 3-deoxyglucose are more power full non- enzymatic glycation agents than glucose. Sorbitol may obstruct the uptake and metabolism of increasing. The physiological role of aldose reductase pathways is largely undetermined [8]. However, aldose reductase, Sorbitol and myo-inositol are thought to play an role in the osmoregulation of the kidney consumption of NADPH by aldose reductase results in the diminution of the levels of NADPH. This NADPH also acts as a co-factor for glutathione reductase, which reduces the oxidized glutathione into reduced glutathione. The excess Sorbitol is oxidized to fructose. The secretion of glucose by the polyol pathway may increase Advance Glycation End Products (AGE) formation. AGES, as well as binding of AGE to their receptors, are known to cause oxidative stress [9].

AGE Pathway

AGEs accumulate at site of microvascular injury in diabetes, including the kidney, the retina and within the vasculature their importance as downstream mediators of tissue injury in diabetic kidney disease is demonstrated by animal studies using inhibitors of advanced glycation to retard the development of nephropathy without directly influencing the glycemic control [10].

AGE receptors are present on various renal cell types2 including proximal tubular cells, mesangial cells, and podocytes AGE promote activation and expression of IL-6 and TGFβ1 via NF-kB dependent pathways. The proximal tubule is the main place for reabsorption of filtered AGEs. TGF-β1 expression is mainly linked to gathering of AGEs in the kidney. AGEs are lead via transcriptional up-regulation of TGF-β1[11]. It is possible by PKC or oxidative stress. In experimental diabetes, oxidative stress is increased relative to the accumulation of AGEs. AGEs can also enhance the formation of free radicals that act directly through catalytic sites in their molecular structure and via stimulation of membrane-bound NAD (P) H oxidase [12]. Through the RAGE receptor and diminution of cellular antioxidant systems, such as glutathione peroxidase, Mitochondrial dysfunction induced by AGEs and carbonyl intermediates may also contribute to the generation of superoxide AGE contribute to the release of proinflamatory cytokine and expression of growth factor and adhesion molecule such as VEGF and CTGF, PDGF, TGF-β1, IGF-1, TNF-α, IL-1β, and IL-6[13].

RAAS Pathway

There is very small information about the molecular mechanisms of renal injury in diabetic nephropathy, but inflammatory cells play an important role in progression of diabetes nephropathy. The renin-angiotensin aldosterone system (RAAS) is involved in destruction of kidney cell (Figure 4). The renal biopsies are helpful to investigate the expression of RAAS and their correlation with parolfactory parameters and injury [14].

Proteinkinase C pathway

PKC PKCs PKCs PKCs PKCs PKCs are activated by DAG, which is formed from excess Increased Increased glucose in in increase increase amount of DAG, which activates PKC. PKC activation leads to changes in renal blood flow, by decreasing production of NO, mesangial expansion, albuminuria and increases GFR, increases pro-inflammatory gene expression and vascular permeability in several models of experimental diabetes [15]. PKC activation may be responsible for the increased expression of ECM molecules both directly and through TGF- β1 over expression. The capacity of active PKC to induce the formation of the transcription factor AP-1 is believed to be the major underlying mechanism of this combined induction of TGF-β1 and ECM protein genes [16]. In the glomeruli, DAG levels are increased and PKC is downstream of DAG-sensitive isozyme's activated protein kinase (ERK) 1/2, which is essential for mesangial cell growth and enhanced gene expression, including growth factors and extracellular matrix proteins. ERK1/2 protein expression is unchanged, but its activity is significantly increased through dependent manner in mesangial cell and glomeruli. ET-1stimulated collagen IV expression is on the activation of ERK1/2 through PKC activation [17].

Hexosamine Pathway

The hexokinase converts fructose-6-phosphate into glucosamine-6-phosphate. Fructose-6-Phosphate amidotransferase (GFAT) is the rate-limiting enzyme of this pathway. Both high glucose and angiotensin II activate the GFAT promoter in mesangial cells, and this is a further mechanism that may enhance flux through the hexokinase [18]. Over expression of GFAT in MC leads to enhance both TGF- β and fibronectin expression. Furthermore, high glucose induced TGF- β1 and ECM production appear, at least in part, mediated by the hexokinase because they are significantly reduced by the GFAT inhibitor azaserine [19].

The mechanism by which flux increases through the HBSP induced gene transcription is uncertain, but it has been proposed that N-acetyl glucosamine may covalently modify transcription factors and signaling molecules, thus altering their activity. An increased flux through this path-way is associated with PKC activation, increased TGF-β expression and ECM production. They all are associated to. They all are associated with the development of DN. In addition, TGF-β closely interacts with the RAS and PKC activity and their interplay could be central in the development of DN [20].

JAK/STAT pathway

The Janus kinase/signal transducers and activator of a transcription (JAK/STAT) pathway are an essential intracellular mechanism of cytokines and other stimuli that regulates gene expression and cellular activation, proliferation, and differentiation (Figure 5). Members of the JAK/STAT pathway have been claimed as new molecular targets of anti-inflammatory treatment in acute and chronic inflammatory diseases, and their activation is involved throughout the development of the diabetes complications [21-22].

Drug from natural sources

Plants have played a major role in maintaining human health and improving the quality to life. Plant served humans well as valuable components of medicines, seasonings, beverages, cosmetics and dyes for thousands of the years. Herbal medicine is based on the premise that plants contain natural substances that can promote health and alleviate illness [23].

In India, around 20,000 medicinal plant species have been recorded but more than 500 traditional plant communities use about 800 plant species for curing different diseases [24]. In the developing countries 80% of the people rely on these various medicinal systems for their health care needs [25]. The treatments of diabetes include diet, exercise, and use of oral hypoglycaemic agents as primary forms of treatment for diabetes [Table 1]. Currently available synthetic anti diabetic agents are expensive and produce serious side effects [26].

Table 1: Medicinal Plant used and their mechanism for treatment of Diabetic nephropathy

S. N	Plant Name/Family	Local Name	Parts Used	Chemical Constituent	Mechanism of action	Reference
1	*Curcuma Longa (Zingiberaceae)*	Haldi	Rhizomes	Curcumin	Showed hypoglycemic, hypolipidemic & antioxidant activity	[14]
2	*Abies Pindrow Royle (Pinaceae)*	Morinda / Rodha	Entire Plant	Volatile Oil	Insulin secretagogue activity	[22]
3	*Abroma Augusta Linn (Sterculiaceae)*	Devil's Cotton	Roots & Leaves	Fixed Oil, Alkaloid	Lowering blood sugar	[23]
4	*Mangifera Indica Linn. (Anacardiaceae)*	Mango	Leaves	Mangiferin	Reduction of intestinal absorption of glucose	[24]
5	*Vinca Rosea (Apocynaceae)*	Periwinkl, Sadabahar	Leaves	Vincristine , Vinblastine	Beta cell rejuvenation, regeneration and stimulation	[22-24]
6	*Pterocarpus Mrsopium (Leguminocae)*		Stem Bark	Kinotannic Acid Kino-Red & (-) 25Epicatechin	Enhancing insulin release	[24-25]
7	*Cuminum Cyminum (Ambelliferae)*		Cumin Seed	Pinene, A-Terpinol	Show reduction in renal oxidative stress and AGE	[25]

8	*Catharanthus Roseus (Apocynaceae)*	Sadabahar	Leaves, Twig & Flower	Indole Alkaloid, Vincristine Vinblastin	Enhance secretion of insulin from the beta- cells of Langerhans	[25]
9	*Ocimum Sanctum Linn. (Labiatae)*	Tulsi	Leaves	V.Oil, Phenol, Aldehyde, Fixed Oil, Alkaloid, Tannin, Ascorbic Acid	Decrease in the plasma glucose level	[25]
10	*Aconitum Carmichaelic (Ranunculaceae)*		Root	Diterpenoid, Alkaloids	Improve peripheral glucose uptake	[26]
11	*Adiantum Capillus-Veneris (Polypodiaceae)*		Adiantum Plant	Triterpenes	Inhibit insulin resistance and inhibit intestinal glucose absorption	[27]
12	*Aegle marmelos (Rutaceae)*		Fruit	Omethylhalfordinol & Isopentylhalfordinol	Stimulating glucose uptake or enhancing insulin secretion	[28]
13	*Allium Sativum (Liliaceae)*	Lehsun	Roots	V.Oil, Allin, Allicin Protein, Carbohydrate, Vit.	Act on the pancreas and stimulate the production of insulin so as to control the sugar levels	[29-30]
14	*Allium Cepa (Liliaceae)*	Pyaz	Bulb	A,B,C, Allyl Propyldisulphide	Stimulate insulin release from pancreas and normalizing the effects of glucose metabolizing enzyme	[29-30]
15	*Galega Officinalis (Leguminoceae)*	French Lilac	Goat's Rue Seed	Berberin	Inhibit insulin resistance and inhibit intestinal glucose absorption	[24-30]
16	*Embellica Officinalis Gaertn (Euphorbiaceae)*	Amla	Fruits	Vit.C, Tannin	Act as α-amylase and α glucosidase inhibitor. Significant antiglycation activity	[25-30]
17	*Opuntia Ficusindica (Cactaceae)*		Stems	3-Methoxytyramine, Candicine, Hordinine, Nmethyltyramine, Tyramine	Inhibit insulin resistance and inhibit intestinal glucose absorption	[30]
18	*Pandanus Odorus Linn. (Pandanaceae)*	Kevra	Root	Essential Oil	Decrease plasma glucose level	[30]
19	*Rubus Fruticosus (Rosaceae)*		Edible Fruit	Casuarictin, Pendunculagin, Sanguin H- And Lambertianin	Inhibits the activity of hepatic GIucose-6-phosphatase	[30]
20	*Taraxacum Officinale (Asteraceae)*	Dandalion	Laves	Taraxinic Acid Taraxacin), Tetrahydroridentin B, Taraxasterol, Taraxerol, Cycloartenol, Beta-Sitosterol	Stimulate insulin secretion from beta cells	[30]
21	*Tinospora Cardifolia Willd. (Menispermaceae)*	Giloe	Root	Berberine, Starch	It act on regeneration of beta cells of islets of langerhans	[26-30]
22	*Trigonella Foenum Graceum (Leguminosae) Papillionaceae: Flabaceae)*	Methi	Seed	Protein, Fat, V.Oil, Fixed Oil, Carbohydrate	Reduces hepatic and renal glucose-6-phosphalase and fructose -1, 6-biphosphatase activity	[24-25]
23	*Zingiber Officinale Roscoe (Zingiberaceae)*	Adrak	Rhizome	Sesquiterpene	Enhance cell-mediated glucose uptake via increasing insulin-sensitivity	[29-30]
24	*Aloe Vera (Liliaceae)*	Gheequar	Entire Plant	Aloin Glycoside	Increase insulin secretion	
25	*Aloe Barbadensis (Liliaceae)*	Gheequar	Leaves	Barbaloin, Isobarbaloin, Resin	Increases production and release of insulin	[26-31]
26	*Anacardium Occidentale (Anacardiaceae)*	Kaju	Entire Plant	Flavonols, Terpenoid, Caumarin, Phenolic Compound,Essential Oil	Stimulate insulin secretion from beta cells	[25-32]
27	*Andrographis Paniculata Nees (Acanthaceae)*	Kalmegh	Entire Plant	Diterpenoid Lactone Andrographoloid	Improve glucose metabolism	[33]
28	*Annona Squamosa (Annonaceae)*	Sharifa	Leaves	Acetogenins-Squamosin B, Squamosamide,Reticulatain-2,Isosquamosin, Juercetin-3-O-glucoside	Inhibits the activity of hepatic GIucose-6-phosphatase	[25-34]
29	*Azadirachta Indica (Meliaceae)*	Neem	Leaves	Nimbidin, Nimbin, Nimbidol, Nimbosterol	Increase the peripheral glucose uptake by inhibiting the action of epinephrine on glucose metabolism	[25-35]

30	*Bambusa Arundinacea (Gramineae)*		Leaves &Stem	Dimethoxybenzoquinone	Stimulate insulin secretion from beta cells	[26-36]
31	*Boerhaavia Diffusa (Nyctaginaceae)*	Punarnava	Leaves & Entire Plant	Alkaloid Punarnavaine, Punarnavoside	Increase plasma insulin levels and improve glucose tolerance	[37]
32	*Brassica Juncea (Brassicaceae)*	Mustard, Sarsu	Leaves & Seed	Isothiocyanate Glycoside Singrin, Protein, Fixed Oil	Food adjuvants for diabetic patients	[22-38]
33	*Camellia Sinensis (Theaceae)*	Green Tea (Chai)	Leaves	Catechins	Inhibit insulin resistance and inhibit intestinal glucose absorption	[39]
34	*Capsicum Annum Linn (Solanaceae)*	Mirch	Entire Plant	Capsaicin,Pritein	Anti inflammatory effects of capsaicin results due to binding of capsaicin to the VR1 receptors which activates pancreatic macrophages	[26-40]
35	*Carum Carvi (Umbelliferae)*	Shia Jira	Fruits	V.Oil, Resin, Carvone, Fixed Oil	Stimulate insulin secretion from beta cells	[26-41]
36	*Cinnamomum Zeylanicum Nees (Lauraceae)*	Dalchini	Bark	V.Oil, Tannin, Mannitol, Ca.Oxalate,	Show potential antidiabetic effect through its up regulation of uncoupling protein-1 (UCP1) and enhancing the translocation of GLUT4 in the muscle and adipose tissues	[42]
37	*Coccinia Indica (Cucurbitaceae)*		Coccinia Root/ Lvy Gourd	Cucurbitacins (Triterpenoid), A-Elaterin	Hypoglycemic effect is also due to insulin secretagogue activity	[29-43]
38	*Eucalyptus Globulus labill (Myrtaceae)*	Eucalyptus	Leaves	Essential Oil , Cineol	Increase insulin secretion from clonal pancreatic beta line	[26-44]
39	*Eugenia Jambolana (Myrtaceae*		Fruit		Potent hypoglycemic and hypolipidaemic	[22-44]
40	*Ficus Religiosa Linn. (Moraceae)*	Peepal	Entire Plant	Tannin	Initiating release of insulin	[29-44]
41	*Ficus Bengalensis Linn. (Moraceae)*	Bargad	Bark	Tannin	Reduce glucose-6-phosphatase activity	[22-44]
42	*Gymnema Sylvestre (Asclepiadaceae)*	Gudmar	Leaves	Gymnemic Acid, Quercital	Regeneration of γ-cells of the islets of Langerhans	[25]
43	*Helicteres Isora Linn. (Sterculiaceae)*	Indian Screw Tree	Root	Saponin ,Tannin, Lignin	Insulin-sensitizing and hypolipidemic activity	[29]
44	*Hibiscus Rosa Sinensis Linn (Malvaceae)*	Gudhal (China Rose)	Entire Plant	Vit.B,C, Fat,	Stimulate insulin secretion from beta cells	[44]
45	*Lepidium Sativum (Leguminocae)*		Whole Plant	Berberine	Inhibition of renal glucose reabsorption which in turn to reduce blood sugar	[30]
46	*Lupinus Albus Linn. (Fabaceae)*	Turmas	Seed	Alkaloid , Fatty Oil, Asparagines	Lower serum glucose level	[44]
47	*Ricinus Communis (Euphorbiaceae)*		Caster Bean Root	Anathraquinone, Triterpenoid , Alkaloids	Reduce oxidative stress	[25-45]
48	*Vassinium Myrtillus (Ericaceae)*		Bilberry Leaves	Phenolic Glycosides &Triterpenoids	controlling or lowering blood sugar levels	[46]
50	*Coriandrum Sativum (Umbelliferae)*	Dhania	Seed	V.Oil, Fixed Oil, Protein	Insulin releasing and insulin like activity	[47]
51	*Coscinium Fenestratum Calebr (Menispermaceae)*	Jharhaldi	Stem	Barberine ,Glycoside,Saponin	Increase enzymatic antioxidants	[48]
52	*Croton Cajucara Benth (Euphorbiaceae)*	Jamalgota	Bark	Fixed Oil	Reduce oxidative stress	[49]
53	*Dipteracanthus Prosratus (Acanthaceae)*		Whole Plant	Alkaloid ,Tannin, Diterpenoid, Saponins	Stimulate insulin secretion from beta cells	[50]
54	*Eclipta Alba (Compositae)*	Bhringraj	Leaves	Ecliptin Alkaloid	Decrease the activities of glucose-6-phosphatase and fructose-1,6-bisphosphatase	[51]
55	*Enicostemma Littorale Blume (Gentianaceae)*	Chhota Chirayata	Entire Plant	Swertiamarine Glycoside	Decreases the activities of glucose-6-phosphatase and increase in serum insulin levels	[52]

56	*Glycerrhiza Glabra Leguminosae)*	Mulethi	Root	Triterpenoid,Saponin, Glycerrhizin	Stimulate insulin secretion from pancreatic beta cell	[53]
57	*Hydrastis Canadensis (Berberidaceae)*		Goldenseal Root	Hydrastine, Berberine & Canadine, Terpenoids	Reduce oxidative stress	[54]
58	*Hygrophila Auriculata (Acanthaceae*		Barleria Plant Rootm, Seed	Semi-Drying Oil	Increases insulin release from the pancreatic islets	[55]
59	*Inula Helenium (Compositae)*		Elecampane Root	Inulin	lowers plasma insulin and glucose levels	[56]
60	*Ipomoea Aquatica Forsk. (Convolvulaceae)*	Kalmisag	Leaves	Carotene	Increases insulin release from the pancreatic islets	[57]
61	*Lagerstroemia Speciosa (Lythraceae)*		Lagerstoemi a Leaves, Fruits	Napthoquinone Lawsone, Alkaloids	Inhibition of blood glucose level	[58]
62	*Lathyrus Japonica (Papilionaceae)*		Whole Plant	Berberine, Kaempferol, Quercetin	Stimulate insulin secretion	[59]
63	*Luffa Aegyptiaca Mill. (Cucurbitaceae)*	Ghiatori	Seed	Fatty Oil	Lactigogue activity	[60]
64	*Lyceum Barbarum (Solanaceae)*		Box Thorn Leaves	Withanolide, Indole, Isoquinoline Alkaloids	Increases insulin release from the pancreatic islets	[61]
65	*Momordica Charantia Linn. (Cucurbitaceae)*	Karela	Fruit	Momordicine Alkaloid, Ascorbic Acid	Inhibition of α-glucosidase activity	[62]
66	*Nelumbo Nucifera Gaertn (Nymphaeaceae)*	Lotus	Rhizome	Nuciferin, Nornuciferin	Reduce blood sugar level	[63]
67	*Panax Ginseng Mey (Araliaceae)*	Pannag	Root & Entire Plant	Glycans, Panaxans I,J,K & L	Improves insulin sensitivity	[64]
68	*Piper Nigrum (Piperaceae)*	Black Paper	Fruit	Piperine	Increases insulin release from the pancreatic islets	[65]
69	*Punica Granatum Linn (Punicaceae)*	Anar	Seed	Vit.C, Protein, Tannin, Gallic Acid, Pelletierine	Reduction in blood sugar level	[66]
70	*Phyllanthus Amarus (Euphorbiaceae)*	Bhui Amla	Entire Plant	Alkaloids	Anti-oxidant activity as it could inhibit lipid- peroxidation, reduce blood sugar level	[25]
71	*Rauwlfia Serpentine (Apocynaceae)*		Roots	Ajmalicin (Indole Alkaloid)	Free radical scavenging activity; Strong antioxidant activities	[61]
72	*Salacia Oblonga (Hippocrateaceae)*	Saptrangi	Stem, Root & Leaves	Salasol A & B, Salasones A-E, Salaquinones A & B	α-glycosidase inhibitors	[44]
73	*Strycnus Nux Vomica (Loganiaceae)*	Snake Wood	Seeds	Strychnine ,Brucine, And Strychnicine, Loganin, Caffeotannic Acid	Increases insulin release from the pancreatic islets	[62]
74	*Swertia Chirayata Roxb (Gentianaceae)*	Chirayata	Entire Plant	Zanthone Mangiferin, Gentianine, Swerchirin	Stimulates insulin release from islets of pancreatic beta cell	[63]
75	*Syzigium cumini (Myrtaceae)*	Clove, Laung	Seed	Alkaloids, Amino Acids, Flavonoids, Glycosides, Phytosterols, Saponins, Steroids, Tannins And Triterpenoids	Decreases free radical formation which clearly shows the antioxidant property, and show hypoglycemic effect	[25]
76	*Withania Somnifera (Solanaceae)*	Ashwagand ha	Root	Withanine, Somnine, Withaferine, Withanolides	Hypoglycemic, antioxidant, diuretic and hypocholesterolemic	[64]
77	*Terminalia Belerica (Combretaceae)*	Bahera	Fruit	Gallic Acid, Ellagic Acid, Chebulagic Acid, Chebulaginic,	Stimulates insulin secretion. Enhances insulin action andinhibits both protein glycation and starch digestion	[65]
78	*Terminaslia Chebula (Combretaceae)*	Haritaki, Black Myrobalan		Chebulinic Acid, Ellagic Acid, Punicalagin,	Increases insulin release from the pancreatic islets	[66]
79	*Tribulus Terrestris (Zygophyllaceae)*	Gokhru	Saponin	Harmine	Significantly decreases fasting glucose level in diabetic	[43]

80	*Urtifca Dioica Linn. (Urticaceae)*	Bichhu Booti	Leaves	Fatty Oil	Increase insulin secretion	[67]
81	*Zea Mays (Gramineae)*	Maize, Makkai	Corn Silk	Flavonoids, Terpenoids Glucurono-Xyloolgosaccharides	Increasing insulin level as well as recovering the injured beta cells.	[68]

Plant materials which are used as conventional medicine for the management of diabetes are considered one of the good sources for the progress of new drug. Plant extract or different plant preparations being prescribed by the traditional practitioners and also accepted by the users for diabetes in many countries [27]. The World Health Organization (WHO) has listed 21,000 plants which are used for medicinal purposes around the world. The tribal's constitute about 7.5 percent of India's population [28]. Traditional healers use 2500 plant species out of which 100 species of plants are acting as a regular source of medicine. In the developed countries, 25 per cent of the medical drugs are based on plants and their derivatives [29].

Traditional plant treatments have been used throughout the world for the therapy of diabetes mellitus[19]. At presents time the international diabetes federation estimates that 194 million people suffer from diabetes worldwide and this number is estimated at 333 million people in 2025. It is also estimated that 33 million adult with diabetes in India This figure is likely to more 57.2 in 2025 [30].

Medicinal Plants for treatment of diabetes nephropathy in India

India has an officially record of 45,000 plant species out of which 7500 species are of medicinal importance. India has a rich history of using potent herbs and herbal components for treating diabetes. Many Indian plants have been investigated for their beneficial use in different types of diabetes [Table 1] [31]. The active principles present in medicinal plants have been reported to possess pancreatic beta cells regenerating; insulin releasing and fighting the problem of insulin resistance [32].

The antidiabetic activity of herbal plant depends upon variety of mechanisms such as Inhibition of renal glucose reabsorption, Stimulation of insulin secretion from pancreatic β cells, Reduction in insulin resistance, Regeneration of pancreatic β cells [33]. Increase the number of β cells in the islets of Langerhans, Increase sensitivity of insulin receptor, Stimulation of glycogenesis and hepatic glycolysis, Inhibition of destruction of the β cells, Improvement in digestion of blood sugar and urea, Prevention of pathological conversion of starch to glucose etc [34].

Recent Approach for Treating Diabetic Nephropathy

Diabetic nephropathy is one of the most important causes of end-stage renal disease (ESRD). In 2011, 15.6% of the 1950 patients developed ESRD due to diabetic nephropathy [35]. In recent times, treatment is multifactorial and involves prevention or treatment of cardiovascular and renal risk factors (hypertension, albuminuria, glycemic control, overweight, smoking, dyslipidemia).and secondary metabolic complications of renal failure (anemia, mineral and bone disease, acidosis, malnutrition). Here we discuss some specific treatment goals for diabetic nephropathy [36].

Reduction of albuminuria

Diabetic patients also suffer from risk of (micro) albuminuria. Reduction of microalbuminuria is associated with increased l endpoints as well as cardiovascular morbidity and mortality in patients with longstanding type1 diabetes and type two diabetes [37]. In line with this, lowering albuminuria predicts better renal outcomes in patients with diabetic kidney disease treated with rennin angiotensin aldosterone system blocking agents [38].

Prevention of albuminuria

Albuminuria progress the risk of higher cardiovascular and renal disease and preventing albuminuria lowers cardiac and renal risk. Therefore, trials have been undertaken to determine whether treating diabetic patients without albuminuria or signs of renal disease with RAAS-inhibiting agents will lower the risk of developing albuminuria and subsequently prevent cardiovascular and renal endpoints [39]. Lower blood pressure played an important role in type 2 diabetes. Prevention of albuminuria at the expense of too low blood pressures is thus undesirable in patients with type 2 diabetes. Therefore, RAAS-inhibiting agents in type 2 diabetic patients with normal blood pressure levels and without albuminuria are not indicated [40].

Glycemic control

Metabolic abnormalities including hyperglycemia are seen in the diabetic mellitus. Elevation in blood-glucose level is the predominant metabolic disorder and glycemic control is an ideal therapeutic approach to reduce the risk of hyperglycemia [41]. The formation of Advance glycation end products promote chronic hyperglycemia is also associated with increased inflammation and expression of associated inflammatory cytokines, such as MCP-1 (monocyte chemoattractant protein-1) and CTGF (connective tissue growth factor), generation of ROS (reactive oxygen species) and activation of number of signaling pathways involved in progression of diabetic nephropathy [42]. Glycemic control is achieved through improving insulin sensitivity via agents such as glutamines, sulfonylureas, meglitinides, biguanides, and α - glucosidase inhibitors. A newer approach to amend post-prandial glucose assimilation is via targeting glucagon-like peptide-1 (GLP-1). GLP-1 is an incretin hormone which is known to stimulate insulin secretion, increase pro-insulin biosynthesis and improve pancreatic beta-cell viability [43].

Lipid management

Hyperlipidemia mostly occurs in type 2 diabetes and increase the risk of cardiovascular disease. The risk of having a fatal myocardial infarction is as high as a person with diabetes as it is in a person without diabetes who has already had a heart attack, and multiple studies have demonstrated that reduction of LDL cholesterol in patients with diabetes using statins will reduce this risk [44]. Therefore, all patients with diabetes should be treated with a statin unless their LDL cholesterol is already less than 100 mg/dl or a contraindication is present. Hyperlipidemia is also associated with an increase at the rate of progression of the diabetic nephropathy, and statin therapy does not appear to reduce cardiovascular disease in patients with end-stage kidney disease but does benefit patients with less severe renal disease [45].

Hyperlipidemia is a common in diabetic patients and is thought to be an important contributor to progressive micro and macro vascular complications. This is most obviously confirmed by the reno protection which is apparently afforded with HMG CoA reductase inhibitors. Obesity is one of the leading factors, which drive the development of type 2 diabetes and its complications such as nephropathy [46]. Moreover, it has also been shown to lead to kidney disease despite the absence of diabetes. As one of the leading causes of chronic kidney disease, the WHO has recommended that lifestyle changes such as dietary and exercise are the most cost-effective approaches to combating this epidemic. We have recently reported the benefits of dietary intervention and renal function in an obese, nondiabetic population [47].

Intensive blood pressure control

About 40% of type 1 and 70% of type 2 diabetic patients with noctalbuminuria have blood pressure level 140/90 mmHg. Blood pressure targets for patients with diabetes are lower (130/80 mmHg) than those for patients without diabetes [48]. In the HOT (Hypertension Optimal Treatment) study, a reduction of diastolic blood pressure from 85 to 81 mmHg resulted in a 50% reduction

in the risk of cardiovascular events in diabetic but not nondiabetic patients [49].

Renin-angiotensin system blocker

The role of ACE inhibitors for the prevention of diabetic nephropathy in patients with type I diabetes has not been defined. The use of perindopril during 3 years in normotensive normoalbuminuric type 1 diabetic patients deferred the increase in albuminuria [50]. In patients with type 2 diabetes, ACE inhibitors and ARBs both reduce the menace for diabetic nephropathy and reduce the incidence of cardiovascular events [51]. In the MICRO-HOPE (Heart Outcomes Prevention Evaluation) study, ramipril (10mg/day) decreased the risk of overt nephropathy by 24% and the risk of cardiovascular death in patients with type 2 diabetes who was 55 years of age with one additional cardiovascular risk factor by 37%. Therefore, ACE inhibitors have been revealed to be helpful for reno- and cardioprotection in patients with type 2 diabetes [52].

Inhibition of protein kinase C (PKC) activity

Protein Kinase C is one of the important factors in the proper functioning of the nerves and the progression of DN. PKC is a family of 11 isoforms, out of which 9 are linked to the production of oxidative stress [53]. Hyperglycemia stimulates the formation of Di-acyl glycerol (DAG) which activates these 9 isoforms. These isoforms lead to stimulation of the expression of signaling pathways involving PAI-1 (Plasminogen Activator Inhibitor-1), NF-κB and TGF-β. They then lead to overproduction of cytokines and induce an inflammatory response [54]. It affects the nerves in terms of their contractibility and permeability. Furthermore, it leads to inhibition of Na+/K+ ATPase. PKC also actuates stress genes, phosphorylating transcription factors, affects the balance of gene expression and induces oxidative stress [55].

PKC pathway is known to be activated by many factors like Elevations in diacylglycerol, hydrogen peroxide, increased activity of polyol pathway, mitochondrial superoxide activity and following AGE-RAGE interactions [56]. PKC isoforms have been associated with many cellular and vascular alterations and processes, including endothelial dysfunction, angiogenesis, vascular permeability, cell growth and apoptosis, basement membrane thickening, extracellular matrix (ECM) expansion [57]. PKC pathway is known to be activation of numerous cellular pathways including NADH, ROS, Na+/K+ ATPase, Endothelin (ET-1), Ang II, MAPK and phospholipase A2, and VEGF[58]. Activation of PKC pathway produces free radicals leading to diabetic microvascular complications. Studies propose that hyperglycemia leads to the activation of PKCβ, which is considered to have potential role in microvascular complications of DN [58]. Hyperglycemic activation of PKCβ causes abnormal signaling and other complications like cytokine activation and inhibition, vascular alterations, cell cycle and transcriptional factor deregulation, and abnormal angiogenesis [59]. Ruboxistaurin, which inhibits PKC-β activation, has been particularly successful in curbing the progress of DN [60]. We have recently found the attenuation of PKC-α phosphorylation and translocation with ALA in both in vivo models of DN and in vitro studies. It remains to be determined if this action of alagebrium on PKC-α phosphorylation partly explains its renoprotective actions. Modulation of PKC activity within the diabetic kidney has also been exhibited by various vitamin B derivatives. Interestingly, both ACEi and aminoguanidine prevent diabetes-associated increases in PKC activation in renal glomeruli [61]. The effects of aminoguanidine and ACEi on PKC α activity were also observed at other sites of vascular injury including the retina and mesenteric vascular bed. In addition, AT-1 receptor antagonists, also attenuate diabetes-induced increases in PKC-epsilon activity within the diabetic heart. The modulation of PKC has been demonstrated in vascular endothelial cells with the insulin-sensitizing agent metformin and the anti-thrombotic therapeutic, aspirin [62]. We have demonstrated that in our experimental models of diabetes translocation of PKC α to the membrane is associated with parallel increases in superoxide production and elevated urinary VEGF thus highlighting the importance of this pathway in DN [63]. On the other hand, PKCδ plays a major role in islet cell function and insulin response. The changes in the level and activity of PKCδ in mice strains correlates with risk of glucose tolerance and insulin resistance. Along with it, loss of inflammation is also associated with insulin resistance in PKCδ deficient mice. Therefore, inhibition of PKCδ may also offer a treatment for metabolic syndrome [64].

AGE-receptors

AGE receptors are important modulators of the harmful effects of these compounds. Receptors for AGEs may be loosely grouped as either inflammatory (RAGE, AGE-R2) or clearance type receptors vascular, renal, and neuronal and haematopoietic cells are all known to express receptors for AGEs [65]. AGEs contribute to the pathogenesis of diabetic nephropathy via receptor-mediated mechanisms and indirectly via the generation of reactive oxygen species and by altering extracellular matrix (ECM) integrity [66]. Diabetes alters the expression of a number of AGE-receptors thought to drive the development and progression of diabetic nephropathy, in particular, the expression of RAGE on cells such as podocytes and tubular epithelial cells. Another AGE receptor postulated to be involved throughout the development of diabetic nephropathy is AGE-R1, although the converse to RAGE this is likely via a decrease in expression [67]. In an experimental model of type 1 diabetes, renal AGE-R1 expression is reduced in association with a concurrent increase in AGE deposition and progression to diabetic nephropathy. In addition, we recently reported that in a small cohort of type 2 diabetic patients, we found a positive correlation with AGE-R1 expression on the cell surface of peripheral blood mononuclear cells and renal function. We found that this was the most predictive biomarker for renal function and further investigation in a larger cohort is required [68]. Furthermore, AGE-R3 deficient mice develop albuminuria, mesangial expansion and fibrosis within the kidney cortex which is more pronounced with diabetes. Importantly, the deletion of AGE-R3 was also associated with a decrease in AGE-R1 and increased expression of RAGE demonstrating the existence of AGE-receptor cross talk. This study highlights that the role of AGE-R3 in the clearance of AGEs is likely more important in diabetic nephropathy than its ability to modulate immune function [69].

Reactive oxygen species

Reactive oxygen species are important intermediates in the formation of AGEs and are often excessively generated within the kidney in diabetes. In addition, associated dysregulation of anti-oxidant enzymes in diabetes leads to a state of oxidative stress [70]. It is unclear as to why the exogenous administration of antioxidants has demonstrated such a poor renoprotection in humans. Vitamins may not be the ideal antioxidant strategy in human DN. Vitamin B6 derivatives, metformin, ACEi, AT1 antagonists, ALA, and sRAGE have exhibited beneficial effects on excess superoxide generation within tissues, associated with improvements in the development and/or progression of diabetic complications [71]. Vitamin B-related therapeutic is an effective scavenger of ROS intermediates. Pyridoxamine, inhibits superoxide radical generation, as well as preventing the progression of neuropathy and retinopathy. In addition benfotiamine and thiamine, Vitamin B1 derivatives, have shown beneficial effects in normalizing ROS production and reducing the activity of aldose reductase. Paradoxically, thiamine administered to be human with diabetic renal disease actually worsened renal function. The role of ROS in diabetic kidney disease has been extensively reviewed previously [72].

HEMODYNAMIC PATHWAY

Hyper filtration, which presents as a marked increase in glomerular filtration rate, is widely recognized as being an early marker of diabetic nephropathy. Elevations in intra-renal pressure or glomerular capillary pressure are thought to induce the development of hyperfiltration thus highlighting the importance of the hemodynamic pathways in DNA. There is a wealth of evidence from experimental diabetic models that intraglomerular pressure is raised, due to relative constriction of the efferent arteriole. The increased pressure is thought to precipitate glomerular damage by direct pressure effects and indirectly by

increasing proteinuria. Recently, in elegant experimental studies, it has been demonstrated that stretch of human mesangial cells activates p38 mitogen-activated protein kinase via a protein kinase C dependent mechanism, which in turn induces transforming growth factor-b1 and fibronectin expression. Thus raised intraglomerular pressure may also exacerbate cellular and biochemical changes [73].

CONCLUSION

Diabetic nephropathy is a serious condition associated with patient suffering from Diabetes. It is really a curse of diabetes because still there is no medication available in the market for its treatment. Herbal plant from the age of Ayurveda has prove to be a vital tool for the treatment of various diseases. There is various medicinal plants that are used by the traditional healer for the treatment of diabetic nephropathy. This article provides the various possible mechanisms of occurrence of nephropathy and the list of plant which may be used for its treatment.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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