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Role of phytotherapy in diabetic neuropathy and neurodegeneration: from pathogenesis to treatment

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ABSTRACT

Diabetes mellitus is a metabolic disorder associated with structural and functional alterations of various organ systems. The tissue injury is attributed primarily to chronic hyperglycemia. Diabetic complications are associated with microvascular and macrovascular damage to the major organs of the body, here in this topic role of herbals for complications of Nervous system in diabetes is discussed as a new therapeutic horizon. Peripheral neuropathy along with the small and large blood vessel disease can explain most of the diabetes-related organ failure, over the last two decades that the deleterious effects of chronic hyperglycemia extend beyond neuropathy and angiopathy. Examples of such diabetic complications include opacification of the lens and central nervous system [CNS] dysfunction. In contrast to the high prevalence rate of renal failure in diabetic patients, except for retinal disease, the chronic diabetic complications of the CNS are subtle and often unrecognized. Whereas the CNS effects of acute alterations in blood glucose level are well known, the effect of chronic hyperglycemia on brain metabolism and cognitive function is not widely appreciated. All the conventional therapies for the diabetic neuropathy with neurodegeneration do have disadvantage from the point of view of efficacy and side effects. Since last few decades Herbals getting more attraction towards neuroprotection in CNS complications of diabetes, further more studies are going on herbals for neuroprotection in diabetes. In the treatment of diabetic neuropathy [DN] herbals and phytoconstituents were proved better option, because excellent efficacy and cost effectiveness compared to conventional treatment.

Keywords: Diabetic complications, neurodegeneration, neuropathy, phytoconstituents.

INTRODUCTION

Neuropathy is a common and costly complication of both type 1 [T1DM] and type 2 diabetes [T2DM]. Diabetic neuropathy [DN] is a heterogenous complication in diabetes, it is late finding in type-1 diabetes, but it can be early finding in type-2 diabetes. The selected animal model of DN should exhibit features present in human pathology. Diabetic animals showed many abnormalities that are seen in the diabetic patients with neuropathy, hyperalgesia, allodynia, slow nerve conduction velocity [NCV] and progressive sensory and motor deficit. The pathophysiology of neuropathy is very complex & it has been associated with peripheral demyelination, a decrease in peripheral nerve conduction and degeneration of myelinated and unmyelinated sensory fibers [2]. The DN depends upon various causative factors including persistent hyperglycemia, microvascular insufficiency, oxidative stress, nitrosative stress, defective neurotrophism, & autoimmune-mediated nerve destruction [3, 4]. When we look at the annual costs of diabetic neuropathy and its associated morbidities in the US have been estimated to exceed $10.9 billion [5]. Neurodegeneration is the term relate to progressive loss of structural or functional neurons, including death also. Many neurodegenerative diseases including Parkinson's, Alzheimer's and Huntington's occur as a result of neurodegenerative processes. Diabetes appears to contribute to cognitive impairment during early childhood, when the brain undergoes structural and developmental changes. Longitudinal studies report lower intelligence quotient [IQ], decreased mental efficiency, and worse school performance in children with type-1 diabetes compared to children without diabetes. The reduced insulin production in type-1 diabetes and insulin resistance in type-2 diabetes both can generate AD-like pathology in the CNS. Depression is also associated with both type-1 and type-2 diabetes and this association is bi-directional, with each influencing the presentation of the other. Still information available about the effect of diabetes on neurodegeneration is not sufficient. Animal models of 'induced diabetes' suggest a direct neurodegenerative effect of diabetes, the majority of studies show results in the hippocampus which is the area associated with learning and memory and the first structure to be affected by the neurodegeneration of Alzheimer's disease. Recent clinical study involving more than 1000 people has shown that those with diabetes have greater cortical atrophy, independent of hypertension, total cholesterol, smoking, BMI, coronary heart disease and socio-demographics than people without the

condition [1]. Conventional therapeutic approaches for DN are Glycemic control, Symptomatic therapies includes antidepressants, SSRIs, anticonvulsants, opiates, NSAIDs, NMDA receptor antagonists and Causal therapies include aldose reductase inhibitors, drugs acts on hexosamine pathways, protein kinase C pathways, AGE receptors, many animals studies shows promise of these pharmacological agents but were withdrawed in clinical study either due to lack of efficacy or due to their side effects on major organs [6, 7], Therefore development of non-pharmacological approaches, alternative medicines for prevention & treatment of diabetes and prediabetes-associated neuropathic changes is highly needed. In recent years, progress has been made toward understanding the biochemical and molecular mechanisms leading to diabetic neuropathy. Herbal based approaches are current area of focus in diabetic neuropathy with neurodegeneration.

DIABETES AND NERVOUS SYSTEM

It is now generally accepted that diabetes can alter central nervous system [CNS] function. Even in the absence of overt cerebrovascular accidents or repeated hypoglycemic reactions, uncontrolled hyperglycemia is associated with cognitive changes. These changes are documented both in patients with diabetes as well as in animal models of experimental diabetes. The contributory causes of CNS dysfunction in diabetes include the presence of hypertension, uremia, peripheral and autonomic neuropathy and multiple drug use [8].

Relation between Diabetes and Neurodegeneration

Diabetes dramatically increase risk of neurodegenerative diseases. Diabetes has been shown to have a specific and detrimental effect on the hippocampus, the area of the brain involved in memory processing, is the area that is at risk in Alzheimer's disease. Research has revealed that the hippocampus is damaged by glucose. Therefore, we have another advanced glycosylated end product of importance which is beta-amyloid. Beta-amyloid can be modified by glucose, and this enhances its inflammatory predisposition in the brain. Beta-amyloid is one of the hallmarks of Alzheimer's disease. Alzheimer's plaques and neurofibrillary tangles have glycosylated proteins. Animal models of 'induced diabetes' suggest a direct neurodegenerative effect of diabetes. The issues like, vascular disease, glycation protein, and beta-amyloid has directly link diabetes with an increased risk for Alzheimer's disease. Fundamentally, these are all inflammatory issues [9]. People with diabetes are at increased risk for stroke, still less information is available about the effect of diabetes on neurodegeneration. Recent work involving more than 1000 people has shown that those with diabetes have greater cortical atrophy, independent of hypertension, total cholesterol, smoking, BMI, coronary heart disease and socio-demographics than people without the condition [1]. Evidence emerged recently that obesity is in fact a risk factor for dementia and Alzheimer's disease. The prevalence of obesity is increasing rapidly and it has never been timelier to focus on a healthy weight, especially for people with diabetes.

Alzheimer's disease, Dementia and Diabetes

Alzheimer's disease, the most common type of dementia. Over half of all dementia is due to Alzheimer's – a neurodegenerative disease that is characterized by memory loss, cognitive decline and ultimately, severe behavioural changes and complete loss of the ability to care for oneself. The usual first noticeable symptom is shortterm memory loss, which progresses from simple forgetfulness to a consistent loss of short-term memory, and finally, the most devastating part of the disease, the loss of well-known skills and inability to recognize familiar people. Alzheimer's involves changes in the brain, part of the progression of the disease. People with Alzheimer's loss neurons and develop atrophy, a sign of neurodegeneration. People with the disease also have amyloid (protein) plaques and neurofibrillary tangles (protein aggregates found in neurons) in their brain – the pathological hallmarks of Alzheimer's. Many population-based studies have found an association between Alzheimer' disease, vascular dementia and type 2 diabetes. In one study, the risk was stronger for people with type 2 diabetes who used insulin compared with those who used oral blood glucose-lowering medications; both groups had a higher risk of Alzheimer's compared to people without diabetes [10]. Although initially, the association between type 2 diabetes and vascular dementia appeared to be more consistent than the relationship between type 2 diabetes and Alzheimer's [11], recent work has shown more consistent evidence for diabetes and 'pure' Alzheimer's [12]. Vascular dementia is the second most common type of dementia in elderly people with age between 60 and 75. It refers to a number of syndromes which result in vascular lesions in the brain.

Relation between diabetes and Neuropathy

Diabetic neuropathy is characterized by diffuse or focal damage to peripheral somatic or autonomic nerve fibers resulting from diabetes mellitus. The syndromes may be grouped under two general headings: diffuse and focal neuropathies. The diffuse neuropathies, i.e., distal symmetrical sensorimotor polyneuropathy (DPN) and diabetic autonomic neuropathy (DAN) are common, usually chronic, and often progressive. The focal forms of diabetic neuropathy reflect damage to single (mononeuropathy) or multiple peripheral nerves (mononeuropathy multiplex), cranial nerves, regions of the brachial or lumbosacral plexuses (plexopathy), or the nerve roots (radiculopathy). The most common peripheral nerve mononeuropathies, medial and ulnar neuropathy, are essentially indistinguishable from entrapment neuropathies in nondiabetic subjects, suggesting that the diabetic nerve has increased susceptibility to compression. The most common cranial neuropathy affects the third nerve, producing unilateral headache, diplopia, and ptosis with papillary sparing (diabetic ophthalmoplegia) [3].

Signs and Symptoms

Diabetic neuropathy affects all peripheral nerves: pain fibers, motor neurons, autonomic nerves. It therefore necessarily can affect all organs and systems since all are innervated. There are several distinct syndromes based on the organ systems and members affected, but these are by no means exclusive. A patient can have sensorimotor and autonomic neuropathy or any other combination. Symptoms vary depending on the nerve[s] affected and may include symptoms other than those listed. Symptoms usually develop gradually over years.

Symptoms may include:

- Numbness and tingling of extremities
- Dysesthesia [abnormal sensation to a body part]
- Diarrhea
- Erectile dysfunction
- Urinary incontinence [loss of bladder control]
- Facial, mouth and eyelid drooping
- Vision changes
- Dizziness

- Muscle weakness
- Difficulty swallowing
- Speech impairment
- Fasciculation [muscle contractions]
- Anorgasmia
- Burning or electric pain

Pathophysiology of Diabetic Neuropathy

There may be multiple etiologies which account for the various neuropathic syndromes seen in patients with diabetes. Hyperglycemia clearly plays a key role in the development and progression of diabetic neuropathy as well as the other microvascular complications of diabetes. All of these pathways are related to the metabolic and/or redox state of the cell. Pathways which are mainly driven by metabolism are: glucose flux through the polyol pathway; the hexosamine pathway; excess/inappropriate activation of protein kinase C (PKC) isoforms; accumulation of advanced glycation endproducts (Fig-1). While each pathway may be injurious alone, collectively they cause an imbalance in the mitochondrial redox state of the cell and lead to excess formation of reactive oxygen species (ROS) [3]. Increased oxidative stress within the cell leads to activation of the Poly [ADP-ribose] polymerase [PARP] pathway, which regulates the expression of genes involved in promoting inflammatory reactions and neuronal dysfunction. This section will discuss each of these mechanisms and the central role of ROS. Diabetic neuropathy is thought to occur from both hyperglycemia-induced damages to nerve cells and from neuronal ischemia caused by hyperglycemia-induced decreases in neurovascular flow. Important Pathways/Mechanism involved in the pathophysiology of DN are listed as followings:

a] Polyol Pathways
b] Hexosamine Pathways
c] Protein Kinase C pathways
d] Advanced glycation endproduct pathways
e] Poly[ADP-ribose] polymerase pathway
f] Mechanism of Oxidative stress and Apoptosis
g] Role of Inflammation
h] Role of Growth factors

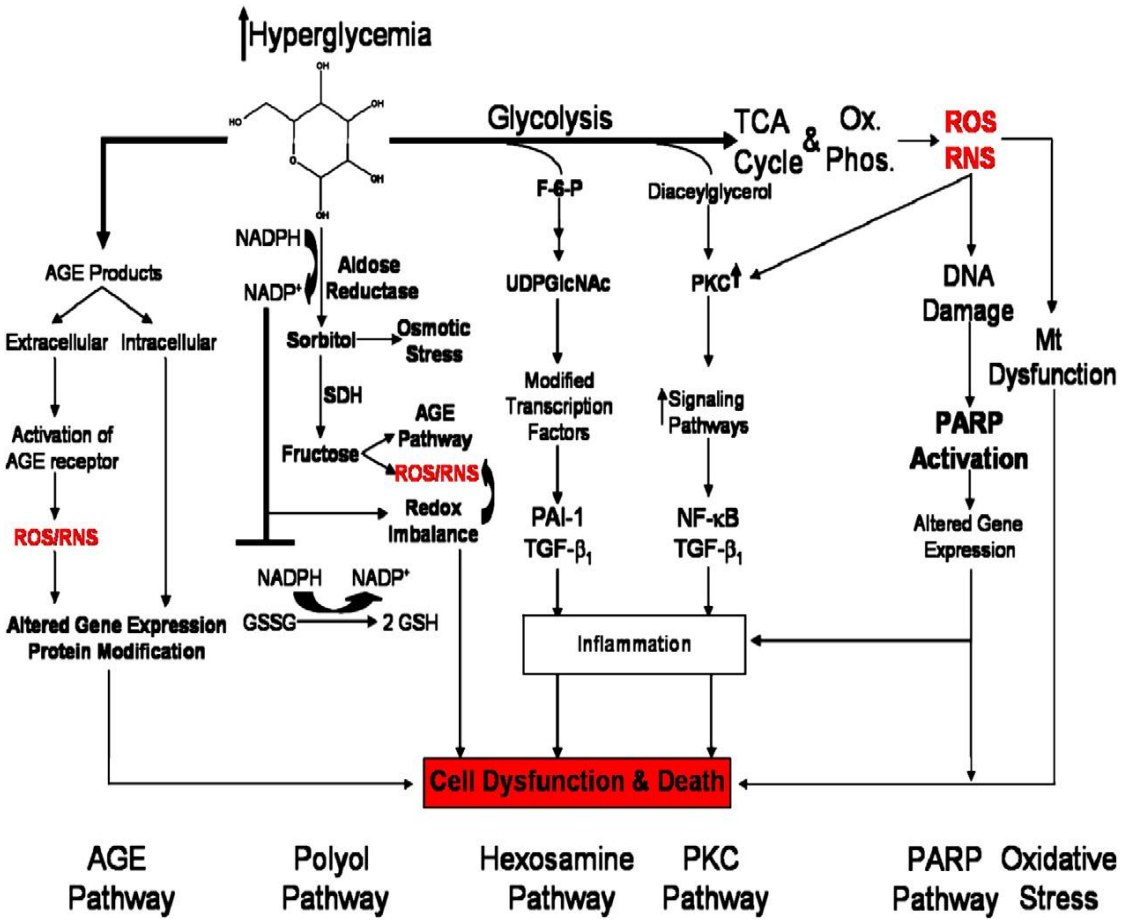

Figure 1: Schematic of hyperglycemic effects on biochemical pathways in diabetic neuropathy.

Excessive glucose metabolism generates excess NADH and leads to overload of the electron transport chain causing oxidative stress, damage to Mt, activation of PARP. PARP activation by ROS acts in conjunction with the hexosamine and PKC pathway to induce inflammation and neuronal dysfunction. A combination of oxidative stress and hyperglycemia activate the detrimental pathways of AGE, polyol, hexosamine and PKC pathways which lead to redox imbalance, gene expression disturbances, and further oxidative stress. These pathways also induce inflammation and neuronal dysfunction. NF-κB: Nuclear factor kappa B; PARP: Poly[ADP-ribose] polymerase; PKC: Protein kinase C; AGE: Advanced glycation endproducts; RNS: Reactive nitrogen species; ROS: Reactive oxygen species, GSH: glutathione; GSSG: oxidized glutathione; UDPGlcNAc: UDP-N-Acetyl glucosamine; VEGF: Vascular endothelial growth factor [13].

Role of herbal drugs in the treatment and management of diabetic induced neuropathy & neurodegeneration.

Patients suffering from neurodegenerative and neuropathy with/without diabetes, currently have inadequate therapies available to them. Various experimental model by using various animals have been developed, for the same newer therapies also been tried, only few of them lead to the initiation of human clinical trials. Clearly, more work needs to be done as we pursue effective pharmaceutical treatments for these devastating diseases. Multi-target and synergistic properties are the common features in the actions of herbals and neutraceuticals, due to the variety of constituents within a single natural product. Herbal medicines and neutraceuticals may be beneficial in dealing with diabetes itself, as well as its complications. Many prescription medicines have narrow therapeutic windows and possess unwanted side effects, while herbal medicines and neutraceuticals provide a valuable resource of effective and safe therapeutic agents due to better efficacy profile. This has resulted in a commercially significant market and hence got the international attention, recognition and usage of herbal medicines [14].

In this topic we focus mainly on Diabetic neuropathy [DN] and neurodegeneration, various novel treatment options available for this complications. In recent times area which will contribute towards drug discovery strategy against diabetic Neurological and neuropathic complications are in the herbal medicines and neutraceuticals. In addition to dietary and lifestyle modifications, herbal medicines and neutraceuticals may offer extra health benefits for the management of diabetes and diabetic vascular complications.

Importance of Herbal Medicines in Diabetes

Various oral antidiabetic agents such as sulfonylureas, biguanides, α-glucosidase inhibitors, glinides and oral hypoglycemic agents like sulphonylureas and biguanides are still the major players in the management of the disease, but there is growing interest in herbal remedies due to the side effects associated with the antidiabetic agents and hypoglycemic agents. Herbal medicines have been the highly esteemed source of medicine throughout human history and are widely used today indicating that herbs are a growing part of modern, high-tech medicine. The medicinal plants and herbals, besides having natural therapeutic values against various diseases and considerable works have been done on these plants to treat diabetes mellitus, describes that the antidiabetic activity of medicinal plants is due to the presence of phenolic compounds, flavonoids, terpenoids, coumarins and other constituents which show reduction in blood glucose levels. Some of these herbal plants and their active chemical constituents which have a role in the management of diabetes mellitus.

Possible Herbals & Phytoconstituents target for DNN having antidiabetic activity / hypoglycaemic activity

Currently, there is growing interest in herbal remedies due to the side effects associated with the oral hypoglycemic agents and other antidiabetic drugs for the treatment of diabetes mellitus. So the traditional herbal medicines are mainly used which are obtained from plants, it plays important role in the management of diabetes mellitus [15]. Here the list of some important herbal plants having antidiabetic potential are given in Table-1 [16] which might prove beneficial for the treatment of Diabetic neuropathy and neurodegeneration.

Table 1: Important anti-diabetic potential herbal plants source and their active principles

Botanical name	Family	Parts used	Major Active components
Allium sativum	Alliaceae	Bulbs	Allyl propyl disulphide, allicin
Areca catechu	Arecaceae	Seed	Arecaine and arecoline
Azadirachta indica	Meliaceae	Leaves, flowers & Seed	Azadirachtin and nimbin
Bauhinia forficate	Leguminosae	Leaf	Astragalin, kaempferitrin
Camellia sinensis	Theaceae	Leaves	caffeine and catechins
Combretum Micranthum	Combretaceae	Leaves	Polyphenols
Elephantopus scaber	Asteraceae	Whole plant	Terpenoid and 2,6,23-Trienolide
Gymnema sylvestre	Asclepiadaceae	Leaf	Dihydroxy gymnemic triacetate
Momordica charantia	Cucurbitaceae	Leaves	Charantin, sterol
Ocimum sanctum	Labiatae	whole plant	Eugenol
Phyllanthus amarus	Phyllanthaceae	whole plant	Phyllanthin
Pterocarpus marsupium	Leguminosae	Whole plant	Kenotannic acid, pyrocatechin
Swertia punicea	Gentianaceae	Whole plant	Methyl swertianin and Bellidifolin
Tinospora cordifolia	Menispermaceae	Root	Tinosporone, tinosporic acid
Vernonia anthelmintica	Asteraceae	Seed	Epoxy acid or vernolic acid

Individual & or combinations of Herbals and phytoconstituents in the treatment of Diabetic neuropathy and neurodegeneration

Butea monosperma and Sapindus trifoliatus

Experimental studies with herbals proved beneficial for diabetic neuropathy condition, like Butea monosperma [Fabaceae] is a medium sized tree native of the mountainous regions of India and Burma and now grows wild throughout India stated in "Wealth of India", 1988, various parts of this plant having different activities/properties like antitumour, antiulcer, antifungal, aphrodisiac, analgesic, anthelmintic, antimicrobial, liver disorders and anthelmintic [17-20]. Sapindus trifoliatus Linn. family Sapindaceae is medium-sized deciduous tree found in south India. High content of saponins and sugars have been reported in the plant stated in "The Wealth of India", 1972. various parts of the plant having different activities/properties

like antiemetic, tonic, astringent and anti-asthma, anti diarrherial, and as antiepileptic [21, 22]. Extracts of Butea monosperma (AEBuM) and Sapindus trifoliatus (EEST) investigated on thermal and chemical hyperalgesia in STZ induced diabetic rats targeted at adenosine receptor. AEBuM and EEST with dose of 200 mg/kg produced significant reversal of hyperalgesia in diabetic animals. Results of this study are further supported by a report in which adenosine administration showed improvement in motor nerve conduction and nerve blood flow in diabetic rats [23]. Adenosine and directly acting adenosine receptor agonists have been shown to reduce nerve injury and carrageenan induced hyperalgesia in rats. The result of the study suggest a significant role of Butea monosperma and Sapindus trifoliatus targeted at adenosine receptor in regulating neuropathic pain. This study revealed molecular level mechanism of Butea monosperma and Sapindus trifoliatus stimulates the adenosine receptor subtype A1 which is linked to a number of effectors namely, adenylate cyclase, ionositol phosphate,K+ channel, Ca2+ channel and neurotransmitters release. Activation of adenosine A1-receptors results in a decrease in adenylate cyclase activity leading to decrease in intracellular level of cyclic adenosine monophosphate, while activation of adenosine A2-receptors stimulates adenyl cyclase activity [24]. In conclusion of this study, the protective effect of AEBuM and EEST with dose of 200 mg/kg was reversed by DPCPX (8-Cyclopentyl-1, 3-dipropyl xanthine), an adenosine A1-receptor antagonist but not by DMPX (3,7-dimethyl-l-propargylxanthine), an adenosine A2A-receptor antagonist, indicating there is involvement of adenosine A 1-receptors in alleviating diabetic neuropathic pain hyperalgesia in rats [25]. So, these findings suggest that the potential of adenosinergic agents in diabetic neuropathic pain, may offer a therapeutic alternative to existing treatment. In recent times antioxidants and neutraceuticals approach proved better to overcome certain condition related to stress, Experimental studies to combat oxidative stress in diabetic neuropathy with antioxidants treatment has been tried in both animals and diabetic patients. Administration of the antioxidants vitamin C or α-lipoic acid, as well as free amino acids, also improves responses to insulin and thus can provide additional benefit to the proposed reduction of oxidative stress in tissues [26-29]. Vitamin E decreases blood glucose in type 1 diabetic rats through an unknown mechanism [30].

Enicostemma littorale Blume [EL]

Rural folk herbal plants found in Gujarat, which has been tried as Antidiabetic agent in one experimental study such as Enicostemma littorale Blume (EL), a small herb of family Gentianaceae, some earlier studies had confirmed its hypoglycemic potential in alloxan-induced diabetic rats [31-34] & also used as an antidiabetic herbomineral preparation [35]. In an experimental study [33] significant reduction was observed in nociception with EL treatment for 45 days. This could be due to hypoglycemic and antioxidant activity of EL. Several reports have showed free radical induced oxidative stress under diabetic conditions to hyperglycemia [36, 37]. Hence, from the above reported results it was convincing to assume that the amelioration of oxidative stress using potent hypoglycemic and antioxidants can be beneficial in diabetic neuropathy.

Eugenia jambolana, Mucuna pruriens and Tinospora cordifolia

In another experiment study narrated that, extracts of Eugenia jambolana [200 mg/kg], Mucuna pruriens [200 mg/kg] and Tinospora cordifolia [400 mg/kg] was administered for 50 days in STZ induced diabetic mice, the plasma glucose concentration was reduced by 24.4, 20.84, 7.45% respectively. Tail flick latency [TFL] and gastric transit percentage [which are parameters for evaluation of diabetic neuropathy] were significantly higher in diabetic controls versus normal controls. Eugenia jambolana modified this effect favorably while Mucuna pruriens and Tinospora cordifolia did not exert any favorable changes of TFL and gastric transit percentage [38].

Artemisia Species

Artemisia plant having over 1500 species, has been a rich source of herbal remedies in many countries [39]. Several studies on Artemisia species showed lower blood glucose concentrations and have been used for treatment of diabetes [40]. An ethanolic extract of Artemisia dracunculus L. [PMI-5011] with a good safety profile [41], has been found to inhibit activity of aldose reductase [42], the first enzyme of the sorbitol pathway, known to play an important role in the pathogenesis of both diabetic and prediabetic neuropathy [43, 44]. Earlier study based on demonstrated that a high-fat diet fed mouse with alimentary obesity, hyperinsulinemia, and impaired glucose tolerance develops nerve conduction velocity deficit and small sensory fiber neuropathy and displays increased sorbitol pathway activity, oxidative-nitrosative stress, and pro-inflammatory changes in PNS. This mouse, therefore, represents an ideal model for evaluating PMI-5011 on functional and biochemical manifestations of prediabetic neuropathy.

The findings reported herein provide evidence of alleviation of HFD-induced nerve conduction slowing and small sensory nerve fiber dysfunction after PMI- 5011 treatment, potentially due to inhibition of oxidative nitrosative stress and pro-inflammatory response in the peripheral nervous system (PNS). So, this study provides evidence of the therapeutic efficacy of an ethanolic extract of *Artemisia dracunculus L.* on Motor Nerve Conduction Velocity and Sensory Nerve Conduction Velocity deficits, thermal and mechanical hypoalgesia, and tactile allodynia in the model of peripheral neuropathy associated with prediabetes and alimentary obesity. The beneficial effects of PMI-5011 may at least partially be related to inhibition of oxidative-nitrosative stress and LO upregulation in peripheral nerve and spinal cord. It was concluded in this study that PMI-5011, is a safe and nontoxic product, may find use in management of clinical diabetic neuropathy at the earliest stage of disease. Several other Herbal plants and Phytoconstituents with their activity for Diabetic Neuropathy (DN) and Diabetic Peripheral Neuropathy (DPN) are given in Table-2.

Table 2: Herbals/Medicinal Plants and Nutraceuticals for the Treatment of Diabetic Neuropathy (DN), Diabetic peripheral Neuropathy (DPN).

Herbals/ medicinal plants/ Neutraceuticals	Common Name	Effect on DN and DPN	Scientific Evidence	References
Angelica sinensis	--	DPN	Animal studies [*In vivo*]	45
Eugenia jambolana/ Syzgium cumini	Jambul	DN	Animal studies [*In vivo*]	46, 38, 47
Tinospora cordifolia	Guduchi	DN	Animal studies [*In vivo*] , A systematic review and a randomised controlled trial	38,48
Vitis vinifera	Grapes	DN	Animal studies [*In vivo*]	49-51
Zingiber officinale	Ginger	DN	Animal studies [*In vivo*]	52
Ficus racemosa	Gular	DN	Animal Studies [*In vivo*]	80
Operculina turpethum	turpeth	DN	Animal Studies [*In vivo*]	81

Curcumin

In one experimental study antinociceptive effect of curcumin on TNF-α and nitric oxide (NO) was observed. The experimental design of the study; Four weeks after a single i.p injection of streptozotocin [200 mg/kg], mice were tested in the tail immersion and hot-plate assays. Diabetic mice exhibited significant hyperalgesia along with increased plasma glucose and decreased body weights as compared with control mice. Chronic treatment with curcumin [15, 30 and 60 mg/kg body weight; p.o.] for 4 weeks starting from the 4th week of streptozotocin injection significantly attenuated thermal hyperalgesia and the hot-plate latencies. Curcumin also inhibited the TNF-α and NO release in a dose dependent manner. These results indicate an antinociceptive activity of curcumin possibly through its inhibitory action on NO and TNF-α release and point towards its potential to attenuate diabetic neuropathic pain [53]. Important phytoconstituents having Neuropathic potential in Diabetes with activity in DN and DPN listed in the Table-3.

Table 3: Phytochemicals having activity in DN and DPN.

Phytochemicals	Herbal Source	Beneficial Effects in DN and/ DPN	Level of Scientific Evidence	References
Astragaloside IV	*Astragalus membranaceus*	DPN	Animal studies [*In vivo*]	54
Eugenol	*Syzygium aromaticum*	DN		55
Isoliquiritigenin	*Glycyrrhiza glabra*	DN		56
Quercetin	*Centella asiatica*	DPN		57
Resveratrol	*Vitis vinifera Propolis*	DN		53,58

All these experimental study of Herbals plants and imp phytocontituents having different mechanisms of action on Diabetic neuropathy [DN] and similar conditions proved to be beneficial, with lesser side effects, better efficacy profile which provide background for the further research in the same direction, with proper mechanism based approach for the treatment and management in early stages of DN which ultimately leads for betterment of life of person with DN. Cost effectiveness criteria should also be taken in consideration because all the conventional and novel treatment approach for DN were very much costly.

Ginseng

Ginseng, a root of Panax species, is a well-known herbal medicine. It has been used as a traditional medicine in various countries for thousands of years and is now a popular and worldwide used natural medicine. The active ingredients of ginseng are ginsenosides which are also called ginseng saponins. Recent research has suggested that some of ginseng's active ingredients also exert beneficial effects on aging, central nervous system [CNS] disorders, and neurodegenerative diseases and diabetic complications of CNS. In general, antioxidant, anti-inflammatory, anti-apoptotic, and immune-stimulatory activities are mostly underlying the possible ginseng-mediated protective mechanisms. Next to animal studies, data from neural cell cultures contribute to the understanding of these mechanisms that involve decreasing nitric oxide [NO], scavenging of free radicals, and counteracting excitotoxicity.

Role of Ginseng in Neuroprotection:

Ginseng and its components, ginsenosides, have a wide range of actions in the CNS. These effects include increased cell survival, extension of neurite growth, and rescuing of neurons from death in consequence of different insults either *in vivo* & *in vitro* [59-61] studies had reported that ginseng roots appeared to facilitate survival and neurite extension of cultured cortical neurons, and recent research [62] showed that ginsenosides Rb1 and Rg3 protected neurons from glutamate-induced neurotoxicity. In spinal neuron model, ginsenosides Rb1 and Rg1 proved to be potentially effective therapeutic agents for spinal cord injuries as they protected spinal neurons from excitotoxicity induced by glutamate and kainic acid and oxidative stress induced by hydrogen peroxide [63]. Number of studies have recently described the beneficial effect of ginseng and its main components, ginsenosides, on some neurodegenerative disease models. Special interest has been paid on Parkinson's disease [PD] models either *In vivo* or in vitro. In an experimental *In vivo* study reported that prolonged oral administration of ginseng extract G115 significantly protected against neurotoxic effects of parkinsonism inducing agents such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP] and its active metabolite 1-methyl-4-phenylpyridinium [MPP+] in rodents. It was found out that ginseng-treated animals sustained less damage and TH+ neuronal loss in

substantia nigra pars compacta [SNpc] after MPP+ exposure. So it would be beneficial for diabetic CNS complications. *In vitro* studies showed that ginseng saponins enhanced neurite growth of dopaminergic SK-N-SH neuroblastoma cells [64].

Although the processes and mechanisms underlying the neuroprotective effects of ginseng upon dopaminergic neurons remain to be elucidated specially in diabetic neurodegeneration. Several reports demonstrate the inhibitory role of ginseng on MPP+ uptake in dopaminergic neurons, the suppression of oxidative stress induced by autooxidation of dopamine, the attenuation of MPP+-induced apoptosis, and the potentiation of nerve growth factor [NGF]. It has been shown that certain ginsenosides inhibit dopamine uptake into rat synaptosomes [65]. Ginsenoside Rg1 was shown to interrupt dopamine-induced elevation of reactive oxygen species [ROS] or NO generation in pheochromocytoma cells [PC12] [66]. Studies have reported that Ginseng radix attenuated MPP+-induced apoptosis as it decreased the intensity of MPP+-induced DNA laddering in PC12 cells and ginsenoside Rg1 had protective effects against MPTP-induced apoptosis in the mouse substantia nigra, while ginsenosides Rb1, Rg1, Rc, and Re inhibited tyrosine hydroxylase activity and exhibited anti-dopaminergic action since they reduced the availability of dopamine at presynaptic dopamine receptors [62, 67]. One research report also suggest link between diabetes [Type-2] and AD [11], hence ginseng proved to be a beneficial neuroprotectant in diabetes by above possible mechanism.

Resveratrol [RES]

The efficacy of nutritionally derived compounds as neuroprotective agents is increasingly supported by empirical evidence. Plant-derived molecules including polyphenols have demonstrated neuroprotective activities in cell culture and animal models. However, the molecular mechanisms that give rise to their protective effects are generally not well understood. Elevated levels of oxidative damage and an increased occurrence of cell death are common observations in chronic neurodegenerative diseases and acute ischemic injury. Polyphenols are small molecule antioxidants that are hypothesized to offer protection against the negative effects of oxidative stress in many tissues including brain, and this may underlie their ability to protect against cell death. Although dietary sources of antioxidants are extensive, a great deal of research interest has been directed towards the compounds found in red wine. RES, a compound found in high concentrations in red wine, and related polyphenols, have inherent antioxidant capacity due to their chemical structure. Direct antioxidant properties were once posited to be responsible for their broad range of biological effects; however, limited bioavailability and relatively weak scavenging abilities make this unlikely. An alternative to direct chemical interactions is the possibility that RES and related polyphenols work to enhance endogenous intracellular defense systems and in turn protect against cellular stress, dysfunction and death. In this sub-topic supporting the neuroprotective actions of RES, followed by a critical review of recent findings regarding putative mechanisms of RES's actions at the cellular level. We then extend this discussion to dietary delivery strategies that may increase RES's bioavailability and thereby maximize its neuroprotective effects.

Role of RES in Neuroprotection

RES's neuroprotective activity has been demonstrated in a wide range of different experimental models including neuronal cell cultures and live animals. Experiments with neuronal cell lines are too numerous to summarize here, so only selected examples are described. Micromolar concentrations of RES have been shown to prevent apoptotic cell death in cultured cerebellar [68] and dopaminergic [69] neurons exposed to MPP+, a model of Parkinson-like neurodegeneration. Similarly, RES protects rat brain hippocampal slices against oxygen and glucose deprivation, a model of ischemic brain injury. *In vivo*, dietary administration of RES to mice [70] or rats [71] confers protection against acute brain injury caused by transient middle cerebral artery occlusion or cardiac arrest, respectively. Delivery of RES in the diet also protects mice [72] and rats [73] against 1-methyl-4-phenyl-1,2,3,3-tetrahydropyridine [MPTP]- and 6-hydroxydopamine [6-OHDA]-induced neurodegeneration in experimental models of Parkinson's disease. Thus, regular dietary supplementation with RES can provide neural protection against a variety of potentially cytotoxic stresses and ameliorates neurodegeneration resulting from both acute and chronic insults. In diabetic neurodegenerative complications this approach of RES proved beneficial for neuroprotection.

RES ameliorates oxidative stress

In neurons, ROS are produced primarily from the mitochondrial electron transport chain as electrons pass from reduced complexes directly to molecular oxygen. The resulting superoxide anion participates in a variety of reactions that produce hydrogen peroxide, hydroxyl radical and peroxynitrite, which are subsequently involved in the oxidation of DNA, proteins and membranes. An aberrant overproduction of mitochondrial ROS is thought to contribute to both acute and chronic neuronal stress and death. For example Parkinson's disease, which is characterized by the specific loss of dopaminergic neurons, can be induced by injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP] [72, 73]. This toxin is converted to MPP+ in satellite cells, and then taken up by dopaminergic neurons and electrophoretically accumulated within the mitochondrial matrix where it inhibits respiratory complex I [74] and increases superoxide production. Isolated mitochondria from rats treated with rotenone, a similar model of Parkinsonism, display increased levels of superoxide production, as well as an increased propensity to undergo membrane permeability transition pore opening [75]. In these Parkinson's disease models, treatment with mitochondria-targeted antioxidants, such as Szeto-Schiller peptide and MitoQ, can prevent acute neurological injury and neurodegeneration. Szeto-Schiller peptide SS-31 is a short peptide containing aromatic and basic amino acids that accumulates in mitochondria and may reduce ROS concentrations [76]. SS-31 protects neuronal cell lines against exogenous oxidants [77]. It has recently been shown to protect against MPTP neurotoxicity in mice in a dose dependent manner [78]. Thus, rodent models of acute neuronal injury and chronic neurodegenerative disease indicate an important role for mitochondria-derived ROS, and provide evidence for the benefits of mitochondria-targeted antioxidants.

Tocotrienols

In nature, eight substances have been found to have vitamin E activity: α-, β-, γ- and δ-tocopherol; and α-, β-, γ- and δ-tocotrienol. The abundance of α-tocopherol in the human body and the comparable efficiency of all vitamin E molecules as antioxidants, led biologists to neglect the non-tocopherol vitamin E molecules as topics for basic and clinical research. Tocotrienols possess powerful neuroprotective, anti-cancer and cholesterol lowering properties that are often not exhibited by tocopherols. Current developments in vitamin E research clearly indicate that members of the vitamin E family are not redundant with respect to their biological

functions. α-Tocotrienol, γ-tocopherol, and δ-tocotrienol have emerged as vitamin E molecules with functions in health and disease that are clearly distinct from that of α-tocopherol. At nanomolar concentration, α-tocotrienol, not α-tocopherol, prevents neurodegeneration. On a concentration basis, this finding represents the most potent of all biological functions exhibited by any natural vitamin E molecule [79]. There are various ongoing clinical studies which involves tocotrienols. One of the most extensively investigated area is the neuroprotective effects of tocotrienols. Several cellular studies in isolated human neuronal cells using nanomolar concentration of tocotrienol, but not tocopherol, demonstrated potent inhibition of cell signalling pathway which causes neuronal damages and the ability to reverse the condition. Similar conclusions were confirmed during subsequent work in animals, where gene knocked-out mice were employed to assess the efficacy of to cotrienols in preventing stroke and in reversing the effects in post-stroke condition.

So, All these herbal plants and their phytoconstituents proved beneficial for neuroprotection with or without diabetes. In case of diabetic neurodegeneration various herbals which are mentioned here and other having hypoglycaemic, antioxidant, anti-inflammtory & most important Neuroprotective actions proves beneficial for the treatment of this complication.

Summary

Diabetes mellitus is metabolic disorder associated with structural and functional alterations of various organs system & diabetic complications are associated with macrovascular and microvascular damamge to the major organs of the body. Universally the role of herbals for complications of nervous system with or without diabetes is accepted. The normal day to day activity of an individuals and from treatment point of view theses category of diseases are very much costly. In the intial stages of diabetes various complications starts, but when disease progresses these complications increases and in the late stage of diabetes chances of neuropathy and neurodegeneration are very high. Preclinical study of induced diabetes suggest a direct neurodegenerative effect of diabetes. In case of diabetic neuropathy which is characterized by diffuse or focal damage to peripheral somatic or autonomic nerve fibres resulting from diabetes and affects all peripheral nerves: pain fibres, motor neurons, autonomic nerves. There are multiple etiologies involved in the progression of diabetic neuropathy and neurodegeneration. In recent times area which will contribute towards drug discovery strategy against diabetic neurological and neuropathic complications are Herbals medicines, their phytoconstituents and neutraceuticals. Scientific evidence on herbals & other phytoconstituents showed positive results for the treatment and management of neuropathy and neurodegeneration in diabetes. Based on this scientific proofs in future these herbal & phytoconstituents based approach will prove beneficial for betterment of the life of people who are suffering from diabetic neuropathy and neurodegeneration.

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