International Journal of General Medicine and Pharmacy (IJGMP)
ISSN (P): 2319–3999; ISSN (E): 2319–4006
Vol. 14, Issue 1, Jan–Jun 2025; 1–26

International Academy of Science, Engineering and Technology
Connecting Researchers; Nurturing Innovations

MEDICINAL PLANTS AS THERAPEUTICS AGENTS AND EMERGING THERAPIES FOR DIABETES INDUCED NEUROLOGICAL DISORDERS: A COMPREHENSIVE REVIEW

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ABSTRACT

Diabetes mellitus (DM) is a prevalent endocrine disorder impacting over 100 million individuals globally. It arises from insufficient insulin production or ineffective utilization, leading to hyperglycemia and damage to multiple organ systems, including nerves. Among DM complications, diabetic neuropathy is significant due to its high prevalence and contribution to morbidity and mortality. Current pharmacological approaches for diabetic neuropathy often have adverse effects, prompting interest in herbal formulations as safer alternatives. Medicinal plants with neuroprotective, antioxidant, anti-inflammatory, and hypoglycemic properties have demonstrated promise in managing diabetes and its neurological complications. Notable examples include Pouteria ramiflora, which reduces oxidative stress and regulates apoptosis-related proteins; Calendula officinalis, known for improving cognitive impairment via antioxidant mechanisms; and Hydrolea zeylanica, which mitigates neuroinflammation and oxidative stress. Other plants, such as Centella asiatica, Erythrina indica, Passiflora ligularis, Trigonella foenum-graecum, Ginkgo biloba, and Lannea coromandelica, also exhibit therapeutic potential. These plants' phytochemicals contribute to their beneficial effects in addressing diabetic neuropathy and related complications. This review highlights the therapeutic applications of these medicinal plants, providing a comprehensive overview of their potential in managing diabetes-related neurological disorders.

KEYWORDS: *Diabetes Mellitus, Diabetic Neuropathy, Medicinal Plants, Neuroprotection, Antioxidant Properties, Herbal Formulations*

Article History

Received: 20 Jan 2025 | Revised: 22 Jan 2025 | Accepted: 28 Jan 2025

INTRODUCTION

Diabetes mellitus (DM) is commonest endocrine disorder that affects more than 100 million people worldwide (6% population). It is caused by deficiency or ineffective production of insulin by pancreas which results in increase or decrease in concentrations of glucose in the blood. It is found to damage many of body systems particularly blood vessels, eyes, kidney, heart and nerve(1) Insulin allows the glucose enter into the cells which provide energy to every cell of body, without insulin glucose cannot enter into the cell. Firstly, the presence of sugar in the urine of Diabetics was demonstrated by Dobson in 1755. In 1989 von Mering and Minkowski that pancreatectomized dose become diabetic in addition to developing digestive disturbances (2)

Types of Diabetes Mellitus

Type 1 diabetes mellitus (T1DM)-is a chronic autoimmune condition characterized by elevated blood glucose levels (hyperglycemia), resulting from insufficient insulin production due to the destruction of pancreatic islet β-cells. This condition predominantly affects children and is among the most prevalent endocrine and metabolic disorders in this age group. In approximately 70–90% of cases, the loss of β-cells is attributed to autoimmune processes associated with the development of T1DM-specific autoantibodies. These individuals are diagnosed with autoimmune T1DM, also referred to as type 1 diabetes mellitus [3]

Type 2 diabetes mellitus (T2DM)- Type 2 diabetes mellitus (T2DM) is characterized by dysregulation of carbohydrate, lipid and protein metabolism, and results from impaired insulin secretion, insulin resistance or a combination of both. T2DM is far more common (accounting for more than 90% of all cases) than either type 1 diabetes mellitus (T1DM). Its main cause is progressively impaired insulin secretion by pancreatic β-cells, usually upon a background of pre-existing insulin resistance in skeletal muscle, liver and adipose tissue [4]

Pre-diabetes- Prediabetes, generally defined as blood glucose levels above normal but below the thresholds for diabetes, represents a state of elevated risk for the onset of diabetes. It occurs when your blood sugar is higher than normal range ,but it is not high enough for a diagnosis of Type 2 diabetes[5]

Gestational diabetes-High blood sugar occurring during pregnancy is attributed to the production of insulin-blocking hormones by the placenta. Gestational diabetes typically resolves after childbirth. However, experiencing gestational diabetes increases the likelihood of developing type 2 diabetes later the prevalence of gestational diabetes mellitus (GDM) is estimated at 2–4% of all pregnancies in various populations, although there have been reports of prevalence as low as 0.5% in low-risk populations and as high as 10% in subjects with multiple diabetes risk factors [6,7]

DM complications can be divided into two groups: macrovascular and microvascular complications. The most frequent neuropathy and one of the microvascular consequences of diabetes that result from persistently inadequate glucose control is diabetic neuropathy

The brain accounts for 2% of our total body weight and uses 25% of body oxygen and 20% of blood glucose. The hypothalamus works in conjunction with several hormones to regulate dietary intake, energy consumption, the secretion of insulin, the production of glucose by the liver, and glucose/fatty acid metabolism in fat tissue and skeletal muscle. The energy essential for the brain to function ideally, from cellular upkeep to the production of neurotransmitters, is provided by glucose. In addition to contributing to the pathogenesis of neurological illnesses, glucose plays a critical role in the control of oxidative stress, cellular death, and pathways whose processes are involved in disturbed hypothalamic pathways and monitoring of glucose and insulin [8]. Complications of DM, and the morbidity and mortality associated with DM are a major cause of healthcare burden [9]. Higher diabetes complications, which have a major impact on patients' living standards, are linked to higher DM prevalence [10] DM (T1DM or T2DM) is often associated with long-term complications which include retinopathy, nephropathy, peripheral vascular disease, and heart disease. Nervous system complications of DM include peripheral and autonomic neuropathies, cerebrovascular stroke, epilepsy, cognitive deficits, and depression [6]. Several studies reported experimental, clinical, neuroimaging, and neuropathological evidence of brain injury with DM (whether uncontrolled or controlled on anti-diabetic or hypoglycemic agents) which range from microstructural to macrostructural changes and manifested as progressive cognitive deterioration, brain infarctions, brain atrophy, and neurodegeneration [11]

In modern medicine, there are multiple strategies aimed at mitigating the adverse impacts of diabetes and its complications. Herbal formulations are increasingly favoured due to their reduced side effects and lower cost. Over recent years, interest in plant-based medicine has surged, with these remedies gaining popularity in both developed and developing nations for their natural origin and minimal adverse effects. Consequently, current research is concentrating on herbal remedies and medicinal plants utilized in managing diabetes mellitus and its associated conditions like cardiomyopathy and neuropathy [(12)]

Various system of medicines such as Ayurveda, Homeopathy, Naturopathy, Siddha, unani and other alternative practices have effectively utilized plants to treat diseases like diabetes neuropathy Natural products have been used to treat various ailments and improve human health for thousands of years. Natural products are an important source for the drug discovery and development in many parts of the world. The traditional use of herbal medicine often gives strong evidence for the beneficial effects of their phytoconstituents. Researchers found that people in the different parts of the world use similar medicinal plants for the same purposes. Almost one-fourth of pharmaceutical drugs are derived from natural products. The World Health Organization has estimated that around 80% of people worldwide rely on herbal medicines in the primary health care. Herbal medicines are used to treat diabetes mellitus as well as its associated neurological complications in many parts of the world [(13)]

In this review we will discuss various medicinal plants that has shown promising effect in diabetes complication such as neurological disorders. Various herbs can enhance cognitive functions, reduce oxidative stress and addresses multiple pathway involved in the diabetes complication such as cognitive impairment. By examining these plants we aim to provide a comprehensive overview of their therapeutic potential and applications

PATHOPHYSIOLOGY

The pathological mechanisms implicated in diabetic neuropathy, include microvascular damage, metabolic disorders, and changes in the interactions between neuronal and immunological systems in parallel with glial cell activation. [(14)] Changes in the blood vessels supplying the peripheral nerves underlie the mechanisms involved in microvascular damage and hypoxia. These changes are based on increases in wall thickness with the hyalinization of the vessel walls and the basal lamina of arterioles and capillaries, leading to nerve ischemia [(15).] Metabolic disorders are the primary cause of diabetic neuropathy. A hyperglycaemic state accompanying diabetes type 1, which is induced through de creased insulin secretion, is responsible for the enhanced activation of the polyol pathway (Fig. 1). In the hyperglycaemic state, the affinity of aldose reductase for glucose is increased, leading to the increased production of sorbitol. Sorbitol does not cross cell membranes and accumulates intracellularly in the nervous tissue, thus generating osmotic stress. Osmotic stress increases the intracellular fluid molarity as well as water influx, Schwann cell damage and nerve fibre degeneration [(16).] Furthermore, up regulation of the NADPH oxidase complex results in oxidative stress through reduced glutathione production, decreased nitric oxide concentrations and increased reactive oxygen species concentration Free radicals, oxidants, and some unidentified metabolic factors activate the nuclear en zyme poly(ADP-ribose) polymerase (PARP), which is a fundamental mechanism in the development of diabetic complications, including neuropathy[(17)] Moreover, a nitric oxide deficit and increased oxygen free radical activity are responsible for microvascular damage and hypoxia[(18).] Myo-inositol depletion also causes diabetic neuropathy. Excess sorbitol accumulates in nervous tissue, which leads to and causes osmotic stress and tissue damage. Simultaneously, decreases in the concentration of myo-inositol reduce ATP-ase Na+/K+ activity, which is important in impulse conduction. Under nor mal conditions, the myo-inositol content is approximately 30-fold higher in

peripheral nerves than in plasma [19]. In diabetes, myo-inositol deficiency is observed in the nerves, resulting from the inhibition of the sodium-dependent uptake of myo-inositol and severe changes to the polyol pathway. The reduced myo-inositol concentration causes the insufficiency of renal ATP-ase Na+/K+, the enzyme necessary to generate nerve depolarization (Fig. 1). As a result, the conduction of stimuli is reduced [14] Sundkvist et al. showed that high myo-inositol levels are associated with nerve regeneration, despite the low levels of this polyol observed in diabetic patients in the clinic. Therefore, the elevation of myo-inositol levels might be considered a compensatory mechanism to prevent nerve damage [20]

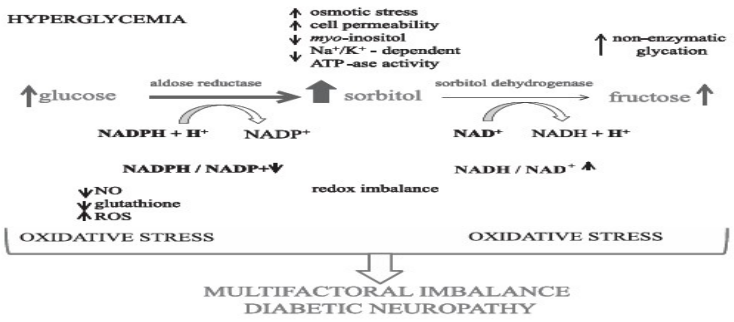

Figure 1

Increased non-enzymatic glycation/glycoxidation (glycation processes involving oxidation) of proteins also plays an important role in the development of diabetic neuropathy [21] In a hyperglycaemic state, the increased levels of glucose and fructose result in covalent binding of these sugars to proteins, nucleotides or lipid molecules without control by an enzyme. This process applies to the structural proteins of the nerve and the blood vessels supplying these nerves, and the products of these transformations, advanced glycation products (AGE), alter cellular functions. AGEs cause a number of disorders, including focal thrombus formation and vasoconstriction, and affect cellular DNA. Furthermore, protein glycation might decrease cytoskeletal assembly, induce protein aggregation, and provide ligands for cell surface receptors [21] AGEs have been identified not only in myelinated and unmyelinated fibres but also in the perineurium, endothelial cells, and pericytes of endoneuria micro vessels. Moreover, the receptors for advanced glycation (RAGE) and glycation products are expressed in peripheral neurons [21]. Interactions between macrophages and AGE-myelin might also influence or contribute to the segmental demyelination associated with diabetic neuropathy[22]

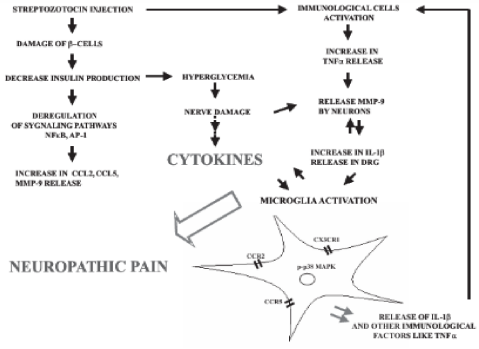

Fig. 2. A proposed diagram of the cytokine network in the pathogenesis of streptozotocin-induced peripheral neuropathic pain [3, 49, 68]

Figure 2

Recent reports suggest the involvement of proinflammatory factors derived from activated microglia in diabetes-induced allodynia and the involvement of the p38 MAPK pathway in dorsal horn microglia in diabetes-induced hyperalgesia [(14)] There are many reports implicating the re lease of pro-inflammatory cytokines from glia and immune cells as a path mechanism for neuropathic pain of different origins. In rats, painful neuropathy accompanies type 1 diabetes and is associated with the release of pro-inflammatory cytokines, such as IL-1b, IL-6 and TNFa[(23)] significantly increased levels of proinflammatory cytokines (IL-1b, IL-6, and TNFa) in the spinal cord in a rat model of diabetes induced through streptozotocin (STZ) administration. Thus, the initiation of the pain process during diabetic neuropathy is mediated through proinflammatory cytokines, such as TNFa, IL-1b, IL-2, and IL-6, that are released from activated microglia[(14)]

MATERIALS AND METHODS

A review of publication on diabetes and neurological disorders effective plants was conducted using databases such as Science Direct, PubMed, Wiley, Scopus and springer. The study employed keywords such as “medicinal plants”, “diabetes”, “neurological disorder”, “symptoms”, “herbal”, and “treatment”. Out of 300 articles collected (published between 2010 an 2024) , 190 were excluded due to either non relevance or lack of access to the original articles

Pouteria Rami Flora (Mart.)

Pouteria rami flora (Mart.) consist of the phytoconstituents such as Phenolic compounds, flavonoids, saponins, and tannins. Exhibits neuroprotective effects by reducing oxidative stress and regulating apoptosis-related proteins. Pouteria rami flora has neuroprotective effects against oxidative damage it restores levels of myosin-Va protein in the brain and is able to prevent hippocampal neuronal loss in the CA3 and hilus subfields of diabetic rats. Pouteria rami flora had a hypoglycaemic effect due to the inhibition of enzymes, including α-amylase and α-glucosidase, that hydrolyse carbohydrates. Pouteria ramiflora treatment increased glutathione peroxidase activity and reduced superoxide dismutase activity and TAS levels in the brains.. Pouteria ramiflora treatment can increase the antioxidant capacity of the brain. This inhibits the α glycosidase plays a major role in glycemic control. It exhibits high levels of expression in the soma of the pyramidal neurons of the frontal cortex and in the cytoplasm of the mossy cells in the dentate gyrus of the brains. Overall it is used in the treatment of cognitive impairment in diabetes [(24)]

Calendula Officinalis

The plant is rich in many pharmaceutical active ingredients such as auroxanthin, carotenoids, flavonoids, flavaxanthin, glycosides, triterpenoid esters, sterols, and steroids. Flavonoids and carotenoids present in CO are potent antioxidants at very low concentrations. The chemo preventive properties of flavonoids are generally believed to reflect their ability to scavenge endogenous ROS. By inhibiting or stimulating various signaling pathways, flavonoids at low concentration could affect cellular function. These constituents may contribute to the antioxidant potential of this extract. The administration of acetylcholinesterase (AChE) inhibitors effectively decreased hyperglycemia and incidence of diabetes. AChE inhibitors enhance cholinergic function in the brain when loss or decline in memory and cognitive impairment has occurred. CO can improve cognitive impairment in diabetic rats. Because of the easy access to the CO in various countries, this plant can be used to treat diseases associated with diabetes such as memory and learning impairment [(25)]

Hydro Lea Zeylanica

Plants are rich source of Quercetin, caffeic acid, rutin, gallic acid, ferulic acid. Hydro lea zeylanica improves cognitive impairment by regulating oxidative stress, neuroinflammation, and neurotransmission in the brain. Cholinergic

neurotransmitters e.g., acetylcholine (ACh) and butyrylcholine (BCh) are highly expressed in the hippocampus and cerebral cortex of brain and responsible for cognitive functions which are catalysed by the hydrolysis of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). The increase in cholinesterase activities cause neuronal function impairment as found mostly in chronic diabetes patients. But, Hydrolea Zeylanica reduced the cholinesterase activities by managing oxidative stress which regulates glucose metabolism, insulin signalling in diabetic encephalopathy. The rich source of flavonoids (quercetin, caffeic acid, rutin, gallic acid, ferulic acid) and nutrients, and vitamins in Hydrolea Zeylanica were responsible for anticholinesterase activities in the brain of encephalop athy rats. β-secretase e.g., BACE1 and BACE2 prominently expressed in brain, and pancreas are involved in initiating Abeta-generation by the cleavage of amyloid-precursor protein (APP) at β-site, or within β-amyloid (Aβ) peptide .So, BACE is a prime target site for the ther apeutic intervention to inhibit Abeta-generation in AD. Hydro lea zeylanica inhibited the β-secretase activities and prevented the formation and accumulation of Aβ-plaques [(26)]

Cucumis Melo Var. Flexuosus

Exerts neuroprotective effects by lowering blood glucose, glycated hemoglobin, brain tumor necrosis factor-alpha, interleukin levels, brain malondialdehyde content, and caspase-3 activity, while increasing plasma dopamine, melatonin, brain vascular endothelial growth factor-A levels, brain catalase, and superoxide dismutase activities. The nervous system in diabetes undergoes a proinflammation process that leads to developing the neuropathy symptoms. A marked increase in the release of proinflammatory cytokines (TNF-α and IL-6) was observed in brains of diabetic and that may be due to Hyperglycemia. Hyperglycemia activated numerous metabolic pathways like polyol pathway, protein kinase c path way, advanced glycation end products pathway, and the hexosamine pathway. All these pathways could directly or indirectly initiate and progress the neuroinflammation and nerve damage leading to the neuropathic pain. Treatment with C. melo var. flexuosus significantly inhibits the increased of proinflammatory cytokines in brains of diabetic, thus blocking the inflammatory path ways involved in the progression of diabetic neuropathy [(27)]

Centella Asiatica

Plants are rich in phytochemicals such as triterpenoids (asiaticoside, madecassoside), flavonoids, phenolic acids, and essential oils. Centella asiatica was found to improve working memory deficits and ameliorate neuronal loss in the hippocampus regions (CA1, CA2, CA3, and Dentate Gyrus). It demonstrates potential therapeutic effects by increasing neuronal density and mitigating cognitive impairment, likely through reducing oxidative stress and amyloid-beta levels in the brain CA enhances dendritic arborization and synaptogenesis by modulating ERK1/2 and Akt signalling pathways (Gray et al., 2018). It is suggested that asiatic acid enhances doublecortin and NOTCH1 protein levels in the hippocampus, which promote hippocampal neurogenesis. Strikingly, it has been demonstrated that CA increases synaptic markers in the hippocampus and frontal cortex through augmen tation of the cAMP/PKA signaling pathway. In addition, CA improves synaptic trafficking by increasing the expression of the AMPAR GluA1 subunit in the hippocampus. Taken together, there is ameliorative impact of CA on diabetes-induced working memory impairment and hippocampal neural damage

Date Fruit

According to studies there are various phytochemicals accessed from Date fruit such as Vitamin C, melatonin, magnesium, Vitamin B3, alkaloids, flavonoids, saponins. Some of the established neuroprotective constituents of DF are as follows melatonin, a potent antioxidant and free radical scavenger. Vitamin C, an accepted antioxidant agent magnesium, an antagonist of NMDA receptors Vitamin B3, a water-soluble vitamin with neuroprotective properties Therefore, the

possible mechanism that maybe responsible for DFE protection against neuropathy is inhibition of oxidative damage due to ROS as indicated by studies in STZ-diabetic rats treated with DFE. However, it seems that the neuroprotective effect[29]

Erythrina Indica

Plants containing various phytoconstituents such as Phytosterols, fixed oils, carbohydrates, alkaloids, flavonoids, saponins, phytosterols, phenolics and tannins, proteins and amino acids, fixed oils and fats. These have been shown to possess sedative and anxiolytic effects. Some alkaloids in Erythrina indica interact with GABAergic systems, which can help in reducing anxiety and promoting relaxation. These have antioxidant properties, which can protect neuronal cells from oxidative stress, a contributing factor to neurodegenerative diseases. These have shown potential neuroprotective effects by reducing inflammation and oxidative stress in the brain. Erythrina indica can reduce blood glucose levels in diabetic models. This hypoglycemic effect may be due to enhanced insulin secretion or improved insulin sensitivity. Chronic inflammation is a known factor in the progression of diabetes and its complications. The anti-inflammatory properties of Erythrina indica can help mitigate these effect[30].

Aloe Vera

Phytochemicals revealed from aloe vera are aloin, aloe-emodin, chrysophanol, Ace Mannan, vitamin A (beta-carotene), C and E, vitamin B12, folic acid, choline, amylase, lipase, and brady kinase, Saponin, Lignin, Salicylic Acid. Aloe vera's polysaccharides, vitamins (like vitamin E and C), and flavonoids combat oxidative stress in the brain by neutralizing free radicals, which helps protect neurons from damage. Compounds such as acemannan and glycoproteins reduce inflammation in the brain by inhibiting pro-inflammatory cytokines and enzymes (e.g., COX-2), potentially lowering the risk of neurodegenerative diseases. Aloe vera can activate AMP-activated protein kinase (AMPK), a key regulator of energy homeostasis. Activation of AMPK improves glucose uptake and lipid metabolism, aiding in glycaemic control. Aloe vera's compounds protect pancreatic beta cells from oxidative damage and apoptosis, preserving their function and insulin secretion[31]

Passiflora Ligularis

Plants contain various phytoconstituents such as apigenin, luteolin, quercetin, chlorogenic acid, p-coumaric acid, Harman and harmin, vitamins A, C, and K P. ligularis reduces blood glucose, serum lipids which could be due to improvement in insulin secretion by recovery of pancreatic β cells. P. ligularis possesses antioxidant potential which may be used for therapeutic purposes mainly in the prevention of oxidative damage that occurs during diabetes and neurodegenerative diseases. It indicates a significant reduction in the nonenzymatic antioxidants like glutathione (GSH) vitamins C and E in diabetic. The levels of the antioxidants were significantly increased [32]

Brassica Juncea

Phytochemicals consist such as isothiocyanates, indoles, caffeic acid, ferulic acid, p-coumaric acid, quercetin, kaempferol, isorhamnetin. The phenolic acids (such as caffeic acid and ferulic acid) and flavonoids (like quercetin and kaempferol) in Brassica juncea have strong antioxidant properties, which help protect brain cells from oxidative damage. The presence of vitamins, particularly vitamin K, supports cognitive function and brain health. Vitamin K is known to play a role in brain cell health and cognitive function. These compounds have been found to improve insulin sensitivity and help regulate blood glucose levels, making them beneficial for managing diabetes. The anti-inflammatory properties of these compounds can help reduce systemic inflammation, which is often elevated in individuals with diabetes and can lead to insulin

resistance. Brassica juncea leaves was triggered initially by the reports revealing antidepressants and anxiolytics-like efficacies of two BJ constituents isorhamnetin and sinapic acid [33]

Urtica Dioica

Phytochemicals revealed are scopoletin, gentisic acid, protocatechuic acid, quinic acid, caffeic acid, ferulic acid, quercetin, 5-O-caffeoylquinic acid, esculetin and rutin. Urtica dioica modulated glucose homeostasis in hippocampus as well as showed anti-inflammatory and antioxidant effects resulting in neurocognitive improvement. Phytochemical analysis revealed the presence of flavonoids and phenolics in UD extract which is known to improve cognitive performance. UD extract might prove to be effective for diabetes and its associated central nervous system complications[34]

Blumea Laciniata (Roxb.)

Phytochemicals are Acarbose, Galantamine,Orlistat, 3,4 Dihydroxybenzoic acid, Caffeic acid,Vanillic acid, Syringic acid, p-Coumaric acid, Rosmarinic acid, Myricetin, Quercetin. This species exhibited very strong antioxidant capacity as measured from various antioxidant assays models which include free radical scavenging assay, reducing power assay, metal chelation assays, and phosphomolybdenum assay. Enzyme inhibition assays revealed that this species has very strong α-amylase and moderate α-glucosidase and lipase inhibition activity. This species also shown appreciable cholinostearases and tyrosinase inhibition activity.Furthermore, various solvent extracts of this plant have the potential to suppress postprandial blood glucose in normal mice and to improve impaired fasting glucose. In particular, it is an important candidate for preparing alternative medicine formulations in the management of diabetes mellitus and its related complications such as neurodegenerative disorders[35]

Trigonella Foenum-Graecum L

Phytochemicals revealed Trigonelline, Diosgenin, Yamogenin, gitogenin, tigogenin,Vitexin, isovitexin, quercetin, kaempferol, 4-Hydroxyisoleucine, Galactomannan, Protodioscin, vitamin A, B6, C, and folic acid. Na+K+ATPase and Ca2+ATPase play a role in the fine tuning of neuron functions which are decreased in diabetes due to oxidative stress and membrane damages, a decrease in Ca2+ATPase in diabetic brain could be due to excessive nonenzymatic glycation of the enzyme itself or of calmodulin, TSP and insulin treatment restored the altered Ca2+ATPase activity to control levels. TSP treatment decreased the oxidative stress and lipid peroxidation. Presence of steroid saponins in TSP seeds. 4-hydroxyisoleucine, a modified amino acid extracted and purified from Trigonella seeds, increases stimulated insulin secretion.[36]

Sida Linifolia Linn

Sida linifolia consist of various phytoconstituents such as Ellagic acid, Quercetin, 4-Methoxycinnamic acid, Sinapic acid, Chlorogenic acid, 3,4-Dimethoxybenzoic acid. The result of the present study showed that S. Linifolia ethanolic leaf fraction demonstrated appreciable antioxidant, anti-diabetic, anti-inflammatory, and neuromodulatory potentials, which could be anchored on its rich phytochemistry. Perhaps, the plant leaves could be a rich source of bioactive phytoconstituents which will be of valuable essence to the health and pharmaceutical industry. The rich phytochemistry and antioxidant properties of the leaf fraction suggest that the plant extracts could also be considered for investigating anticancerous activities[37]

Ginkgo Biloba

Ginkgo biloba consist of various phytochemicals such as flavonoids (flavone glycosides, primarily composed of quercetin) and terpenoids (ginkgolides and bilobalide). Gingko biloba possesses various biological activities and has been shown to be useful in diabetes treatment. Oxidative stress has been known to play an important role in the development and progression of diabetes mellitus (DM), and reactive oxygen species (ROS) production is a direct consequence of hyperglycemia. Chronic hyperglycemia in diabetes is involved in direct neuronal damage caused by intracellular glucose which leads to altered neurotransmitter functions and reduced motor activity. Oxygen free radicals are also thought to play an important role in the diabetic and hypoxic condition of cells. Success of Ginkgo biloba application is determined by its main active substances, flavonoids (flavone glycosides, primarily composed of quercetin) and terpenoids (ginkgolides and bilobalides). Ginkgo biloba can improve hemodynamics, scavenge ROS, suppress platelet-activating factor (PAF), neutoprotective and relax vascular smooth muscle.[38]

Luteolin

Luteolin, a flavonoid isolated from Cirsium japonicum Luteolin, a flavonoid isolated from Cirsium japonicum, has antioxidant, anti-inflammatory and neuroprotective activities. However, no report is available on influence of luteolin on streptozotocin-induced memory impairment, choline esterase (ChE) activity as marker of cholinergic function and oxidative stress were assessed in the cerebral cortex and hippocampus to evaluate the neuropathological changes and the effects of luteolin on diabetic rats.[39]

Actinidia Arguta Leaf

Phytochemical present are Quercetin,Kaempferol, Myricetin, Caffeic Acid, Chlorogenic Acid, Ellagitannins, Saponins, Vitamin C,, kaempferol-3-O-rutinoside. Actinidia arguta leaf in improving cognitive decline caused by hyperglycemia-induced oxidative stress. Improvement of the insulin signaling pathway with the reduction of Tau phosphorylation and decrease in amyloid beta (Aβ) by increasing IDE expression in EFAL group was also observed. Finally, oxo-dihydroxy-octadecenoic acid (oxo-DHODE), rutin, and kaempferol-3-O- rutinoside were identified.[40]

Lannea Coromandelica

Alkaloids, Flavonoids, Saponins, Tannins, Steroids, Cardiac glycosides, Terpenoids are the phytochemicals found in the plants. Can be beneficial in neuroprotection, as oxidative stress and inflammation are critical factors in neurodegenerative diseases. Lannea coromandelica may protect against neurotoxicity, potentially due to its antioxidant compound. .It may improve insulin sensitivity, which is crucial for managing diabetes.By reducing inflammation, it can potentially mitigate some diabetic complications, particularly those related to cardiovascular health and neuropathy.[41]

Crataegus

Quercetin, Rutin, Vitexin, Oleanolic Acid, Ursolic Acid, Chlorogenic Acid, Caffeic Acid are the phytochemicals present in the plant. Crataegus decrease the mRNA expression levels of inflammatory factors, including interleukin 6 (IL-6,) and tumor necrosis factor-α (TNF-α) in the pancreatic tissues and concluded that fasting blood glucose lowering effects of Crataegus are mediated by its anti-inflammatory effect.f Crataegus oxyacantha extract on oxidative stress biomarkers in ischemia reperfusion–induced oxidative stress in diabetic rats. . Moreover, it has been demonstrated that extracts of the Crataegus possess considerable antioxidant potential because they inhibited oxidation of β-carotene and 2,2-azobis(2-

amidino-propan) dihydrochloride. Crataegus may have a therapeutic role via its antioxidant potential, anti-inflammatory and hypoglycemic effects.[42]

Sesamol

Sesamol (3,4-methylenedioxyphenol), a phenolic molecule. Acetylcholine, a neurotransmitter associated with learning and memory, is degraded by the enzyme acetylcholinesterase, terminating the physiological action of the neurotransmitter. Chronic treatment with sesamol attenuated increase in acetylcholinesterase activity in the cerebral cortex. However, sesamol did not alter hippocampal acetylcholinesterase activity in diabetic rats Besides the enhanced level of reactive oxygen species, NO levels are also increased, and expression of mitochondrial nitric oxide synthase appears to be signicantly increased in the brain mitochondria of diabetic rats A signicant inhibition of TNF- levels by sesamol observed in our study is indicative of the fact that sesamol contributes to beneWcial eVects seen in diabetic encephalopathy. Thus, sesamol treatment ameliorated cognitive deWcit, cholinergic dysfunction, reduced oxidative stress, nitric oxide and TNF- in the diabetic rats and thus may Wnd clinical application in treating neuronal disturbances in the diabetic patients.[43]

Rubus Fruticosus

Rubus fruticosus consist of various phytochemicals such as Anthocyanins, ellagitannins, flavonols and ellagic acid,. Cyanidin-3-O-glucoside. Blackberries were capable of improving performance on motor tests, which relied on balance and fine motor coordination, and on measures of spatial working memory. However, these effects were not accompanied by an improvement in dopamine release and consequently by an improvement of receptor sensitivity, events usually related with the observed effects. Ellagic acid prevented brain and sciatic nerve damage. Compounds such as vitamin C and E, ellagic acid, a-tocopherul, anthocyanins and phenolic compound are anti-oxidantand protect brain against oxidative stress induced by diabetes[44]

Chrysin

Chrysin (CH) is an important natural plant flavonoid which can be extracted from many plants, honey and propolis. Chrysin exhibits strong antioxidant properties, which help in reducing oxidative stress, a significant factor in the progression of neurodegenerative diseases like Alzheimer's and Parkinson's diseases. It scavenges free radicals and upregulates the expression of antioxidant enzymes, thereby protecting neuronal cells from damage.Chronic inflammation is a hallmark of many neurodegenerative diseases. Chrysin can inhibit the release of pro-inflammatory cytokines and downregulate the activity of inflammatory pathways (e.g., NF-κB pathway), reducing neuroinflammation and potentially slowing disease progression.Chrysin promotes neuroprotection by enhancing the expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), which supports neuron survival and function. It also inhibits apoptosis (programmed cell death) in neuronal cells.Chrysin influences the levels and activity of various neurotransmitters, such as dopamine and serotonin, which play critical roles in mood regulation and cognitive function. This modulation can be beneficial in conditions like Parkinson's disease, where dopaminergic neurons are particularly affected.Chrysin has been shown to improve insulin sensitivity and enhance glucose uptake in cells, which can help in managing blood glucose levels. It activates the AMP-activated protein kinase (AMPK) pathway, a key regulator of glucose and lipid metabolism. Chrysin helps protect pancreatic beta-cells from oxidative damage and apoptosis, which is crucial for maintaining insulin production and secretion. This action can aid in preserving pancreatic function in diabetes.Chrysin can improve lipid profiles by reducing triglycerides, total cholesterol, and low-density lipoprotein (LDL) levels while increasing high-density

lipoprotein (HDL) levels. This lipid-modulating effect can be beneficial in preventing cardiovascular complications associated with diabetes.[45]

Terminalia Chebula Fruit

Terminalia chebula fruit consist of various phytochemicals such as tannins, polyphenols and triterpenoids. T. chebula is rich in the highest concentrations of total polyphenolic and total tannins, and hence it possesses high antioxidant and scavenging, activities. Furthermore, it exhibited high antidiabetic, anti-Alzheimer's and anti-infammatory activities. The exhibited the highest ameliorative effect[46]

Alpha Lipoic Acid

ALA has been shown to have a variety of properties which can interfere with the pathogenesis or progression of AD. For example, LA increases acetylcholine (ACh) production by activation of choline acetyltransferase and increases glucose uptake, thus supplying more acetyl-CoA for the production of ACh. LA chelates redox-active transition metals, thus inhibiting the formation of hydroxyl radicals and also scavenges reactive oxygen species (ROS), thereby increasing the levels of reduced glutathione. In addition, LA down-regulates the expression of redox-sensitive pro-inflammatory proteins including TNF and inducible nitric oxide synthase. . Furthermore, LA can scavenge lipid peroxidation products such as hydroxynonenal and acrolein. In human plasma, LA exists in an equilibrium of free and plasma protein bound form. Up to 150 μM, it is bound completely, most likely binding to high affinity fatty acid sites on human serum albumin, suggesting that one large dose rather than continuous low doses. LA could be combined with nutraceuticals such as curcumin, (−)-epigallocatechin gallate (from green tea) and docosahexaenoic acid (from fish oil) to synergistically decrease oxidative stress, inflammation, Aβ levels and Aβ plaque load and thus provide a combined benefit in the treatment of AD.[47]

Rosmarinic Acid

Rosmarinic acid (RA) is an abundant phytochemical of Lamiaceae species. Increases the expression of key genes associated with mitochondrial biogenesis Increases GLUT4 translocation Reduces the levels of blood glucose, advanced glycation end (AGE) products, cholesterol, lipid peroxides, and triglycerides Inhibits MARK and NF-κB pathways Inhibits proinflammatory T helper and Treg cells Increases diabetes-resistant bacteria Shows neuroprotective effects on neurons Restores loss of function in neurons by reducing free radical-mediated oxidative stress Neuroprotective role against oxidative stress in N2A cells Reduces Amyloid-β-induced neurotoxicity by inhibiting oxidative stress. Reduces t-BHP-induced oxidative damage Neutralizes free radicals, chelates pro-oxidant ions and reduces lipid peroxidation Inhibits release of IL-6 and ROS Reduces H2O2-induced cell damage[48]

Artemesia Nilgarica

Alkaloids, Flavonoids, Saponins, Tannins, Steroids, Cardiac glycosides are the phytochemicals found in the plant These have been shown to possess sedative and anxiolytic effects. Some alkaloids in Artemesia nilgarica interact with GABAergic systems, which can help in reducing anxiety and promoting relaxation. These have antioxidant properties, which can protect neuronal cells from oxidative stress, a contributing factor to neurodegenerative diseases. This has the property of enhanced hypoglycemic effect may be due to enhanced insulin secretion or improved insulin sensitivity. Chronic inflammation is a known factor in the progression of diabetes and its complications[49]

Limonium Spathulatum (Desf.)

It has shown the presence of fatty acids and phenolic compounds including flavonoids, tannins, hydroxycinnamic acids, anthocyanins, flavones, and flavonols. These extracts exhibits strong inhibitory effects on AChE, BchE, and a-glucosidase. These findings have demonstrated the potential of L. sphathulatum to exert various therapeutic effects and promote its use as a natural source for bioactive substances with several pharmacological actions[50]

Astragalus Polysaccharides

Astragalus polysaccharides are constituents of A. membranaceus that are potential candidate therapeutic agents for the treatment of memory deficit in diabetes. APS are the most important components in Astragalus membranaceus and have been clinically applied in the treatment of cancer as an adjunctive medicine enhancing immune activity. APS is also effective for the treatment of diabetic nephropathy, possibly through ameliorating glucose metabolism and decreasing the levels of transform growth factor beta 1. In addition, APS are involved in oxidative stress elimination and insulin resistance. Based upon this evidence, APS present a high potential to reverse memory deficit in diabetic animal models[51].

Calotropis Procera

Calotropis procera has been investigated previously for its phytoconstituents, which revealed the presence of cardenolides, antho cyanins, and triterpenoids The α-amyrin, β-amyrin flavonoids, alkaloids, tannins and saponins Calotropis procera roots, stem and leaves such as alkaloids, flavonoids, tannins, phenolic compounds, triterpene, saponins, steroids, fixed oils and fats. The bioactive compounds in Calotropis procera, such as cardenolides and flavonoids, reduce inflammation, which is a critical factor in diabetic neuropathy. The phytochemicals may improve insulin sensitivity, aiding in better glucose control and reducing the progression of diabetic complications, including neuropathy. It is potent anti-hyperglycemic and antioxidant attenuating actions may be responsible for the observed ameliorative effects[52]

Ligustrum Vulgare Leaf

Ligustrum vulgare showed oleacein, secoiridoid precursor, oleuropein, secoiridoid aglycone, oleocanthal. Oleuropein and other compounds may enhance insulin sensitivity and improve glucose metabolism, leading to better blood sugar control and reducing the risk of neuropathic complications. Compounds such as oleuropein and hydroxytyrosol exhibit strong antioxidant properties, reducing oxidative stress which is a major contributor to nerve damage in diabetic neuropathy.The flavonoids and iridoid glycosides in Ligustrum vulgare reduce inflammation by inhibiting pro-inflammatory cytokines and pathways, which helps alleviate inflammatory responses in diabetic neuropathy[53]

Zingiber Officinale

It consists of phytochemicals such as 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, 8-shogaol, 10-shogaol, Zingiberene, beta-bisabolene, camphene, farnesene, Quercetin, kaempferol, Alpha-pinene, beta-pinene, cineole, borneol and citral. Gingerols, shogaols, and zingerone exhibit strong antioxidant properties, which help in reducing oxidative stress. This is crucial as oxidative stress is a significant factor in the pathogenesis of diabetic neuropathy, causing damage to nerves. Gingerols and shogaols have potent anti-inflammatory properties that help in reducing inflammation. They inhibit the production of pro-inflammatory cytokines and pathways, such as NF-κB and COX-2, thereby reducing inflammation associated with diabetic neuropathy. The antioxidant and anti-inflammatory properties of gingerols and shogaols contribute to the protection of neurons from hyperglycemia-induced damage. This helps in maintaining nerve function and preventing

the degeneration of nerve cells. Helps in enhancing insulin sensitivity and improving glucose metabolism. This leads to better blood sugar control, reducing the risk and severity of diabetic complications, including neuropathy[54]

Green Tea

It consist of phytochemicals such as (-)-epigallocatechin gallate (EGCG), (-)-epicatechin gallate (ECG), (-)-epigallocatechin (EGC), and (-)-epicatechin (EC). Catechins have strong antioxidant properties that protect neural cells from oxidative damage, reducing the risk of neurodegenerative diseases like Alzheimer's and Parkinson's. L-theanine, in combination with caffeine found in green tea, enhances cognitive function, improves attention, and increases alertness. Catechins reduce neuroinflammation, which is beneficial in managing neurodegenerative conditions and improving overall brain health[55]

Elaeocarpus Tuberculatus Roxb.

It consist of various phytochemicals such as Alkaloids, Flavonoids, Steroids, Glycosides, Terpinoids, Saponin, Phenol, Quinones, Coumarins. Claimed for Anti diabetes and neurodegenrative diseases[56]

Acmape Praemorsa

Claimed for Anti diabetes and neurodegenrative diseases[57]

Folium Mori

Folium mori increases insulin sensitivity and curbs insulin resistance. In the present study, treatment with Folium mori was shown to increase the number of BrdU-positive cells in the dentate gyrus in normal rats and those with STZ-induced diabetes. Although the precise mechanism of cell proliferation is unknown, other studies have suggested that cell proliferation could be mediated by NPY among other factors. reported that NPY increases the number of neuronal precursor cells undergoing cell division and thus produces more olfactory neurons and that the action of NPY in increasing neuronal precursor proliferation is mediated by protein kinase C (PKC), indicating an upstream PKC-dependent activation of ERK1/2. it can be suggested that Folium mori treatment may aid in the recovery from the central nervous system complications of diabetes mellitus by enhancing cell proliferation in the dentate gyrus via augmented NPY expression[58]

Intestinal Microbiome

The endogenous bile acid, tauroursodeoxy-cholic acid (TUDCA) is a potent neuroprotective agent and acts as a mitochondrial stabilizer and anti-apoptotic agent in several models of neurodegenerative diseases. TUDCA has been shown to be neuroprotective in several models of AD, including amyloid precursor protein and presenilin 1 double-transgenic mice. In Huntington's disease, increased level of TUDCA was also found to be neuroprotective, but still little is known about the role of bile acids in neurodegenerative disease. However, it has been reported that TUDCA is playing a fundamental role to modulate the process of p53-mediated apoptosis in AD. The bile acids, especially glycocholate, glycodeoxycholate and glycochenodeoxycholate have been shown to be altered in plasma profile of AD patients. Bifidobacterium spp. significantly increases in prebiotic treated-mice and correlated with low-grade inflammation and improved glucose-tolerance. Several studies have shown that gut bacteria through modulation of plasma Lipopolysaccharides levels can activate the inflammatory processes associated with obesity and insulin resistance. The triggering role of bacterial LPS derived from gut microbes to develop low-grade chronic inflammation, insulin resistance and T2DM was subsequently studied in both genetically and nutritionally obese mice through specific transition of the gut

microbiota composition. Changing the gut microbiota of host by antibiotic treatment protects against diet-induced adiposity, oxidative stress, glucose intolerance, insulin resistance and low-grade inflammation . Dysbiosis, or an imbalance in the gut microbiota, can lead to chronic inflammation. In diabetes, high blood sugar levels can exacerbate this imbalance, promoting inflammatory responses that can affect the brain. Chronic inflammation is a key factor in the development of neurodegenerative diseases like Alzheimer's and Parkinson's. The gut and brain are connected through the gut-brain axis, involving direct and indirect pathways such as the vagus nerve, immune system, and metabolic pathways. Dysregulation in the gut microbiome can disrupt these communication pathways, affecting brain function and contributing to neurodegeneration. Beneficial gut bacteria produce SCFAs, such as butyrate, which have anti-inflammatory and neuroprotective properties. In diabetes, a reduction in SCFA-producing bacteria can diminish these protective effects, potentially accelerating neurodegenerative processes[59]

Peristrophe Bicalyculata

Flavonoids, Alkaloids, glycosides, saponins and tannins are the phytoconstituents present in the plant. Flavonoids and alkaloids help in reducing oxidative stress and inflammation, which are key factors in neurodegenerative diseases. The antioxidants in Peristrophe bicalyculata protect neurons and support cognitive function. Reduces neuroinflammation, which is linked to various brain disorders. Phytochemicals like flavonoids and tannins combat oxidative stress, a major contributor to diabetes complications. Alkaloids and saponins may improve insulin secretion and reduce blood glucose levels. Some phytochemicals can inhibit enzymes like alpha-glucosidase, reducing glucose absorption and managing blood sugar levels[60]

Physalis Pubescens L.

Withanolide, Flavonoids, Phenolic compounds, Carotenoids, Vitamins (C and A). Withanolides and flavonoids protect neurons from oxidative damage and inflammation. Withanolides, flavonoids, and phenolic compounds combat oxidative stress, which is crucial in managing diabetes and its complications. Reduces systemic inflammation, improving insulin sensitivity and overall metabolic function. Certain compounds may inhibit enzymes like alpha-glucosidase, reducing glucose absorption and assisting in blood sugar management[61]

Sterculia Tragacantha Lindl Leaf

Triterpenoids, Flavonoids, Saponins, Alkaloids, Phenolic compounds are the various phytoconstituents present. Flavonoids and triterpenoids protect neurons from oxidative stress and inflammation, which are key factors in neurodegenerative diseases like Alzheimer's and Parkinson's. Reduces neuroinflammation, thereby protecting the brain from damage associated with chronic inflammation. Triterpenoids, flavonoids, and phenolic compounds help mitigate oxidative stress, which is crucial in preventing and managing diabetes complications. Saponins and alkaloids may enhance insulin secretion and action, helping to regulate blood glucose levels[62]

Cinnamon Cassia

Cinnamaldehyde, Eugenol, Cinnamic acid, Polyphenols, Proanthocyanidins. Cinnamaldehyde and eugenol protect neurons by reducing oxidative stress and inflammation, which are major contributors to neurodegenerative diseases like Alzheimer's and Parkinson's. Cinnamic acid and proanthocyanidins neutralize free radicals, preventing oxidative damage to neurons and supporting cognitive function. Some studies suggest that cinnamon compounds can inhibit the aggregation of tau protein, potentially reducing the formation of amyloid plaques associated with Alzheimer's disease. Cinnamaldehyde

and polyphenols improve insulin sensitivity and glucose uptake, helping to regulate blood sugar levels. Some compounds in cinnamon mimic insulin, enhancing glucose metabolism and lowering blood sugar levels. Cinnamaldehyde and other compounds inhibit enzymes like alpha-glucosidase and alpha-amylase, reducing glucose absorption and aiding in blood sugar management[63]

ALTERNATIVE TREATMENTS FOR NEUROLOGICAL COMPLICATIONS IN DIABETES

Si Rna Treatment

Targeting genes using small interfering RNA (siRNA) shows promise for alleviating symptoms of diabetic neuropathy, particularly focusing on neuropathies and distal symmetric polyneuropathy (DSPN). This approach relies on the specific gene-silencing capabilities of siRNA to mitigate nerve damage and pain, potentially preventing or delaying the condition. siRNA shows promise in treating diabetic neuropathy by targeting genes involved in inflammation and oxidative stress. Key factors for successful siRNA therapy include sequence and structural considerations, chemical modifications, and delivery mechanisms like nanoparticles. Ethnicity-based screening and treatment are crucial due to varying prevalence of diabetic retinopathy. Advances in siRNA delivery and understanding enhance its potential for personalized treatment, aiming to reduce nerve damage, pain, and improve quality of life. siRNA silences specific genes responsible for inflammation and oxidative stress, critical factors in diabetic neuropathy[64]

Probiotics

Probiotics are beneficial microorganisms shown to improve human health when consumed regularly and in sufficient quantities. Numerous health benefits can be attained by possessing important metabolites with nutritional and medicinal qualities. It has been shown through scientific research that these living microbial consortiums can influence a variety of mental health outcomes, including but not limited to anxiety, depression, cognitive processes, stress responses, and behavioral patterns. Selected strains of bacteria and yeasts control how the central nervous system (CNS) communicates with the gut-brain axis (GBA) through neuronal, humoral, and metabolic pathways to ease mood. Psychobiotics are substances that can affect the digestive system as well as mood and anxiety. There is scant evidence to validate the beneficial effects of psychiatric drugs in treating neurological diseases or disorders. The therapeutic method of research into psychobiotics opens exciting prospects for the future of the field of development. This review compiles the current evidence available in the scientific literature on the use of probiotics to influence neurological disorders[65].

Antioxidant Therapies for Diabetes with Neurological Complications-

Diabetes often leads to neurological complications due to oxidative stress and inflammation. Antioxidant therapies aim to mitigate these effects, improving neural function and preventing further damage. Key antioxidants used in these therapies include

- **Alpha-Lipoic Acid (ALA)**: Reduces oxidative stress, improves nerve conduction, and alleviates symptoms of diabetic neuropathy.
- **Vitamin E**: Protects cell membranes from oxidative damage and has been shown to improve nerve function in diabetic patients.
- **Vitamin C**: Works synergistically with Vitamin E to neutralize free radicals and improve overall antioxidant status

- **N-Acetylcysteine (NAC)**: Boosts glutathione levels, a critical antioxidant in combating oxidative stress.
- **Polyphenols (e.g., Resveratrol, Curcumin)**: Exhibit strong antioxidant and anti-inflammatory properties, supporting neural health and glucose metabolism.
- **Coenzyme Q10**: Improves mitochondrial function and reduces oxidative damage in nerve cells[65]

Gene Therapy for Diabetes with Neurological Complications-

Gene therapy offers a novel approach to treating diabetes and its associated neurological complications by targeting specific genetic pathways to restore normal function and prevent damage. Here are key strategies and mechanisms involved-

- **Gene Editing (CRISPR-Cas9)-** Directly edits faulty genes responsible for insulin production or glucose regulation. Potentially permanent correction of genetic defects causing diabetes with neurological complications
- **Gene Replacement Therapy**- Introduces healthy copies of genes to compensate for defective ones, such as genes involved in insulin synthesis or secretion. Restores normal metabolic function and improves glucose homeostasis
- **Gene Silencing (siRNA, shRNA)-** Silences genes that contribute to insulin resistance or inflammation. Reduces oxidative stress and inflammation, mitigating neurological damage. Targeting genes to reduce oxidative stress and inflammation, protecting neurons from damage. Modifying genes to improve glucose uptake and metabolism in peripheral tissues, reducing hyperglycemia. Silencing pro-inflammatory genes to reduce chronic inflammation, which is a major contributor to diabetic neuropathy.

Delivery System

- **Viral Vectors**: Using adeno-associated viruses (AAV) or lentiviruses to deliver therapeutic genes to target cells
- **Non-viral Vectors**: Employing nanoparticles or liposomes to deliver genes, offering safer and less immunogenic alternatives.

Benefits

- **Targeted Treatment**: Directly addresses the genetic root causes of diabetes and its complications.
- **Long-lasting Effects**: Potential for long-term or permanent correction of genetic defects
- **Reduced Side Effects**: Minimizes systemic drug exposure and associated side effects

Challenges

- **Delivery Efficiency**: Ensuring efficient and targeted delivery to specific cells or tissues
- **Safety**: Minimizing off-target effects and immune responses to the therapy.
- **Ethical Considerations**: Addressing ethical concerns related to genetic modifications[66]

Table 1: Most commonly used agents for treatment of Diabetes neuropathy and their most common side effects[67]

Agent	Dosage	Common side effects
1) Amitriptyline	10-100 mg daily	Dry mouth, urinary retention, sedation, vertigo, constipation, weight gain, arrhythmias
2) Desipramine	10-150 mg daily	Dry mouth, urinary retention, sedation, vertigo, constipation, weight gain, arrhythmias
3)Duloxetine(FDA approved)	60-120 mg daily	Nausea, somnolence, hyperhidrosis, anorexia, vomiting, constipation, fatigue, dry mouth
4) Venlafaxine	75-225 mg daily	Nausea, somnolence, ECG changes
5)Pregabalin(FDA approved)	150-600 mg daily	Somnolence, dizziness, peripheral edema, weight gain
6) Gabapentin	900-3,600 mg daily	Dizziness, somnolence, diarrhea, fatigue, GI upset, peripheral edema
7) Oxycodone	5-120 mg daily	Constipation, somnolence, dizziness, nausea, vomiting, itchiness
8) Tramadol	50-200 mg daily	Nausea, sedation, constipation, headache, dry mouth, urinary retention, confusion, tremor, seizures
9)Tapentalol(FDA approved)	50-250 mg daily	Nausea, dizziness, somnolence, constipation, vomiting, headache

New Perspective in Diabetes Neuropathy

- **Increased G3BP2-Tau interaction in tauopathies is a natural defence against Tau aggregation**- Many RNA-binding proteins (RBPs), especially those linked to RNA granules, contribute to pathological protein aggregation in neurodegenerative diseases. In this study, we reveal that G3BP2, a key component of stress granules, directly interacts with Tau and prevents its aggregation. In the human brain, the interaction between G3BP2 and Tau is significantly heightened in various tauopathies, and this interaction occurs independently of neurofibrillary tangle (NFT) formation in Alzheimer's disease (AD). Remarkably, the loss of G3BP2 in human neurons and brain organoids leads to a marked increase in Tau pathology. Additionally, we discovered that G3BP2 covers the microtubule-binding region (MTBR) of Tau, thereby blocking its aggregation.[68]

- **Single genomic enhancers drive experience dependent GABAergic plasticity to maintain sensory processing in the adult cortex**- Experience-dependent plasticity of synapses is crucial for cognitive functions and is regulated by non-coding genomic enhancers. In the visual cortex of adult mice, sensory-induced enhancers drive the transcription of the Igf1 gene in vasoactive intestinal peptide (VIP) interneurons. This process enhances GABAergic inputs to VIP INs, maintaining the balance between excitation and inhibition and thus restricting neural activity in both VIP INs and principal excitatory neurons. This homeostatic modulation preserves spatial frequency tuning and sensory processing in the adult cortex.[68]

THERAPIES UNDER STUDY

There is a lot of interest in therapeutic agents focused on other points within the pathophysiology of DN, which is why new drugs are under study. . Desensitization of the temperature-sensitive transient receptor potential channel in nociceptive neurons has been proposed as an interesting therapeutic option considering the pain pathways, through the application of topical capsaicin, which is still only approved for the management of painful DN in feet[69]

The use of low-voltage electrical current stimulation of the spinal cord with success in some studies is also under investigation[70]

Mutations in voltage-gated sodium channels such as Nav1.7 have been implicated in painful DN, and are the target of antagonists such as the drug Xenon402, which is useful in erythromelalgia and has the potential to be used in other types of neuropathic pain[71]

The intrathecal administration of drugs such as morphine and ziconotide allows direct release into the cerebrospinal fluid, with fewer side effects than systemic administration; however, their use in DN has not been evaluated, and this could be complicated by the difficulty in healing of wounds that people with DM are prone to[72]

The benefit of topical application of O2 and CO2 nanobubbles for the treatment of DN symptoms is also being studied in more than 50% of patients with success so far[73]

Repurposing of Anti-Diabetic Agents as A New Opportunity to Alleviate Cognitive Impairment in Neurodegenerative and Neuropsychiatric Disorders

Table 2: Preclinical Studies: Targeting Insulin Pathway to Improve Cognitive Deficits

Drug	In vitro/vivo models, dose used, and intervention period	Brief Conclusions
Intranasal insulin	Aβ-induced rat model of AD received normal saline or insulin (0.1, 0.2, and 0.3 IU) for 14 consecutive days	Intranasal insulin treatment improved memory and learning in a rat amyloidbeta model of Alzheimer's disease[74]
Metformin	7-month-old male APP/PS1 mice (C57BL/6) received (200 mg/kg p.o.) metformin for 8 weeks.	i: ↓ brain oxidative stress and inflammation: MDA and SOD; IL-1β and IL-6; ii: ↓ brain Aβ accumulation; ↑insulindegrading enzyme, neprilysin, and p-AMPK expression; iii: ↑ brain function: ↑18F Fluordeoxyglucose uptake (microPET-CT); v: ameliorated learning and memory dysfunction: MWM and Y-maze tests; Metformin could relieve learning and memory dysfunction and improve brain [75]
Dulaglutide	STZ-induced AD-like mice or control mice received vehicle, dulaglutide (0.6 mg/kg/week i.p.), or dulaglutide and exendin (9-39) (0.67 mg/kg/ week i.p.) for 4 weeks.	Dulaglutide improved learning and memory deficits caused by STZ-induced AD-like conditions by regulating the hyperphosphorylation of tau and neurofilaments via the PI3K/AKT/GSK3β signaling pathway[76]
Liraglutide	Male Swiss mice were given daily intraperitoneal injections of liraglutide (25 nmol/kg) or a vehicle (PBS) for 7 days prior to receiving an injection of Aβ oligomers (Aβ O) (10 pmol) or vehicle into the lateral ventricle. Additionally, four non-human primates were injected with Aβ O, two of which received liraglutide treatment, and three served as controls.	Liraglutide reversed cognitive impairment and insulin receptor loss induced by AβOs in mice and provided partial neuroprotective effects in non-human primates. [77]
Insulin combination with exenatide	G2576 mice were treated with an 8-month course of intranasal administration of insulin and exenatide (0.43×10−3 IU insulin, 0.075 μg exenatide, and 5 μg BSA per mouse once daily).	The combination of insulin and exenatide was linked to improved memory and normalized expression of insulin receptor pathway genes in a mouse model of Alzheimer's disease. Improved memory and normalized expression of insulin receptor pathway genes in a mouse model of Alzheimer's disease. Normalized insulin receptor pathway gene expression without affecting Aβ levels. Enhanced spatial learning, though the improvement did not reach statistical significance in the Morris Water Maze (MWM) test.[78]

Table 2: Contd.,

Exenatide	10 months age adult mice received exenatide (500 mg/kg, bw, i.p.) or vehicle 5 days per week for 2 months	Increased expression of BDNF and its phosphorylation, along with increased phosphorylation of TrkB, ERK5, and PSD95 in the hippocampus; decreased expression of pro-BDNF, p75NTR, and phosphorylated ERK1,2 (pERK1,2) and JNK (pJNK). Increased dendritic spine density in hippocampal neurons. Enhanced long-term memory performance as observed in the Morris Water Maze (MWM) test.[79]
Sitagliptin and saxagliptin	3xTg mice were administered sitagliptin (3.5 mg/kg subcutaneously) and saxagliptin (2.6 mg/kg subcutaneously) for a duration of 56 days.	DPP-4 inhibitors enhanced spatial learning and memory, reduced tau and neurofilament aggregation, increased Aβ degradation, and alleviated AD-like neurodegeneration by partially improving GLP-1 signaling pathways, including PI3K-Akt and MAPK.[80]
Vildagliptin	In a rat model of Alzheimer's disease induced by streptozotocin, vildagliptin was administered orally at doses of 2.5, 5, and 10 mg/kg for 30 days.	Vildagliptin improved memory retention, reduced Aβ levels and tau phosphorylation, diminished inflammation, and increased GLP-1 levels[81]
Linagliptin	The 3xTg-AD mouse model of Alzheimer's disease was administered linagliptin orally at doses of 5, 10, and 20 mg/kg for a duration of 8 weeks.	Linagliptin, a dipeptidyl peptidase-4 inhibitor, increases the levels of GLP-1 and GIP in the brain without affecting plasma glucose levels. It also alleviates cognitive deficits and pathology in the 3xTg-AD mouse model of Alzheimer's disease. Additionally, linagliptin reduces Aβ42 levels, phosphorylated tau (p-tau) levels, and neuroinflammation in the brain.[82]
Pioglitazone and exenatide	Male Wistar albino rats were given fructose to induce insulin resistance and then treated for 8 weeks with pioglitazone (10 mg/kg), exenatide (10 or 20 μg/kg), a combination of pioglitazone and exenatide, or a vehicle.	The combination of pioglitazone and exenatide provided neuroprotection to the hippocampus and enhanced cognitive function in insulin-resistant rats. Specifically, it led to reductions in blood glucose levels, insulin levels, and HOMA-IR index, as well as decreased serum advanced glycated end products and lipids (TG, LDL). Additionally, it decreased the percentage of pycnotic cells in the hippocampus, reduced hippocampal Aβ and microglia expression, and improved cognitive performance as assessed by the eight-arm radial maze test.[83]
Pioglitazone	Twelve-month-old APP/PS1 mice were administered pioglitazone intraperitoneally at a dose of 10 mg/kg per day for 15 days.	Pioglitazone inhibited Cdk5 activity by lowering p35 protein levels and improved impaired synaptic plasticity and spatial memory in Alzheimer's disease mouse models.[84]
pioglitazone or rosiglitazone	3xTg-AD mice and wild-type control mice were fed an experimental diet containing pioglitazone hydrochloride or rosiglitazone maleate for a duration of 4 months.	Chronic treatment of 3xTg-AD mice with pioglitazone or rosiglitazone for 4 months enhanced spatial learning and reduced tau hyperphosphorylation and neuroinflammation.[85]
Rosiglitazone	Nine-month-old transgenic mice overexpressing human amyloid precursor protein (hAPP) were administered rosiglitazone orally at a dose of 5 mg/kg per day for 4 weeks.	Rosiglitazone reduced brain Aβ levels and Aβ plaque deposition while decreasing p-Tau aggregates. It alleviated Alzheimer's disease pathology and restored hippocampal function, which improved memory impairment in APP transgenic mice. Additionally, it reduced memory deficits as measured by object recognition and the Morris water maze (MWM) test.[86]

Table 2: Contd.,

Sulforaphane	**Schedule 1:** Male ICR mice were treated with either vehicle + saline, sulforaphane (30 mg/kg/day, i.p.) + saline, vehicle + PCP (10 mg/kg/day, s.c.), or sulforaphane (30 mg/kg/day, i.p.) + PCP (10 mg/kg/day, s.c.) for 10 days. **Schedule 2:** Following Schedule 1, sulforaphane (30 mg/kg/day, i.p.) or vehicle was administered once daily for an additional 14 days.	**Schedule 1:** Pretreatment with sulforaphane mitigated the PCP-induced decrease in spine density and protected against the PCP-induced increase in 8-oxo-dG-positive cells and decrease in PV-positive cells in the mPFC and hippocampus. Sulforaphane exhibited both prophylactic and therapeutic effects on PCP-induced cognitive deficits in mice. **NOR: Schedule 1:** Sulforaphane pretreatment reduced PCP-induced cognitive deficits in mice. **Schedule 2:** Sulforaphane continued to attenuate PCP-induced cognitive deficits in mice[87]

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