CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
http://doi.org/10.5281/zenodo.3258857

Available online at: http://www.iajps.com *Review Article*

A REVIEW ON PLANTS USED IN DIABETIC NEUROPATHY

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Article Received: April 2019 **Accepted:** May 2019 **Published:** June 2019

Abstract:

Diabetes mellitus is an endocrinological and/or metabolic disorder with an increasing global prevalence and incidence. High blood glucose levels are symptomatic of diabetes mellitus as a consequence of inadequate pancreatic insulin secretion or poor insulin-directed mobilization of glucose by target cells. Diabetes mellitus is aggravated by and associated with metabolic complications that can subsequently lead to premature death. Currently available treatment options in modern medicine have several adverse effects. Therefore, there is a need to develop safe and effective treatment modalities for diabetes. Medical plants play an important role in the management of diabetes mellitus especially in developing countries where resources are meager. This article presents a review on some reported antidiabetic medicinal plants (with their botanical name, Family and part used)

Key Words: *Insulin, blood glucose levels, medicinal plants, hyperglycemia.*

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Please cite this article in press Kiran K.J et al., ***A Review on Plants used in Diabetic neuropathy.,*** *Indo Am. J. P. Sci, 2019; 06[06].*

INTRODUCTION:

Diabetes mellitus (DM) is a chronic metabolic disorder of impaired metabolism of carbohydrates, fat and proteins characterized by hyperglycemia resulting from decreased utilization carbohydrate and excessive glycogenolysis and glucogenolysis from amino acids. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. Diabetes mellitus can produce can produce micro vascular complications like diabetic neuropathy, nephropathy, retinopathy and cataract [1].

TYPES OF DIABETES MELLITUS

Diabetes mellitus mainly classified into three types.

Type 1: DM or insulin-dependent diabetes mellitus (IDDM) in which body fails to produce insulin. Type 1 diabetes occurs because the insulin-producing cells of the pancreas (beta cells) are damaged. In type 1 diabetes, the pancreas makes little or no insulin, so sugar cannot get into the body's cells for use as energy. People with type 1 diabetes must use insulin injections to control their blood glucose.

Type 2: DM or non-insulin-dependent diabetes mellitus (NIDDM), in type 2 diabetes (adult onset diabetes), the pancreas makes insulin, but it either doesn't produce enough, or the insulin does not work properly. Type 2 diabetes may sometimes be controlled with a combination of diet, weight management and exercise. However, treatment also may include oral glucose-lowering medications (taken by mouth) or insulin injections (shots).

The third main type is gestational diabetes which occurs when women without a previous history of diabetes develop a high blood glucose level during her pregnancy. It may precede development of type 2 DM.

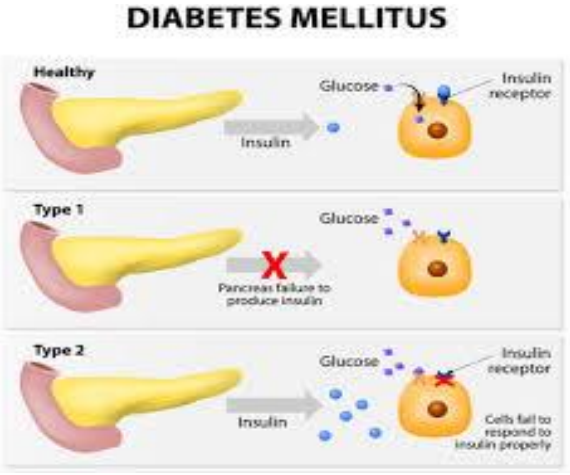

Figure: Types of Diabetes mellitus

Diabetes mellitus often leads to microvascular complications that includes nephropathy, retinopathy, neuropathy and macrovascular complications that includes coronary artery disease, leading to myocardial infarction (heart attack) or angina, stroke (mainly is- chemic type), peripheral vascular disease.

Diabetic neuropathy is type of nerve damage that can be occurs in diabetic patient. High blood sugar (glucose) can injure nerve throughout body. Diabetic neuropathy most often damage nerves in legs and feet. Depending on the affected nerves, symptoms of diabetic neuropathy can range from pain and numbness in legs and feet to problems with digestive system, urinary tract, blood vessels and heart.

Allopathic medicines are not effective in treating the disease leading to various adverse effects. Herbal medicines are currently in demand and their necessity is increasing eventually. Traditional Medicines derived from medicinal plants are used by about 60 % of the world's population. This review focuses on plants used in the treatment of diabetes. In India it is proving to be a major health problem, especially in the urban areas. Though there are various approaches to reduce the ill effects of diabetes and its secondary complications, herbal formulations are preferred due to lesser side effects. A list of medicinal plants with proven antidiabetic and related beneficial effects and of herbal drugs used in treatment of diabetes is compiled. Many clinical studies have confirmed the therapeutic importance of medicinal plants in the treatment of diabetic mellitus. The World Health Organization (WHO) has listed 21,000plants which are used for medicinal purposes around the world. Among these 2500species are in India, out of which 150 species are used commercially on a fairly large scale.

The effect of medicinal plants may delay the diabetic complications and rectify the metabolic abnormalities. They showed hypoglycemic activity with more efficacies. The various herbal drugs have been also proved effective due to their beneficial contents in treatment of diabetes.

DIABETIC NEUROPATHY

Diabetic neuropathy is the most common complication associated with diabetes mellitus. Diabetic neuropathy is type of nerve damage that can be occurs in diabetic patient. High blood sugar (glucose) can injure nerve throughout body. Diabetic neuropathy most often damage nerves in legs and feet. Depending on the affected nerves, symptoms of diabetic neuropathy can range from pain and numbness in legs and feet to

problems with digestive system, urinary tract, blood vessels and heart [2].

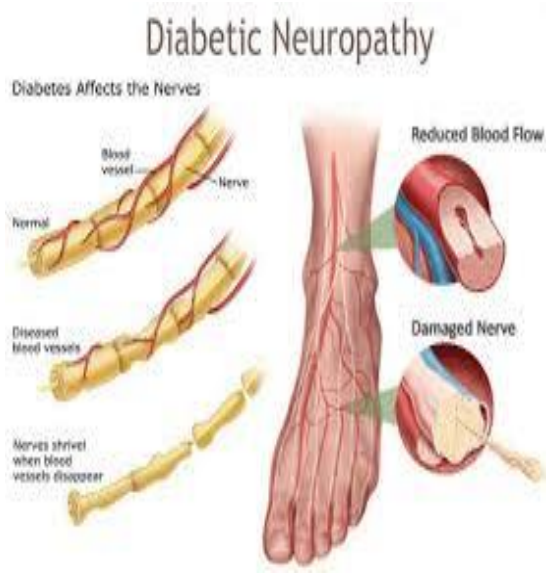

Figure2: Diabetic neuropathy

EPIDEMIOLOGY

Globally diabetic neuropathy affects approximately 422 million people as of 2014 (1.9% of the population)[3].Diabetes is the leading known cause of neuropathy in developed countries, and neuropathy is the most common complication and greatest source of morbidity and mortality in diabetes. It is estimated that neuropathy affects 50% of people with diabetes. Diabetic neuropathy is implicated in 50–75% of nontraumatic amputations.

The main risk factor for diabetic neuropathy is hyperglycemia. In the DCCT (Diabetes Control and Complications Trial, 1995) study, the annual incidence of neuropathy was 2% per year but dropped to 0.56% with intensive treatment of Type 1 diabetics. The progression of neuropathy is dependent on the degree of glycemic control in both Type 1 and Type 2 diabetes. Duration of diabetes, age, cigarette smoking, hypertension, height, and hyperlipidemia are also risk factors for diabetic neuropathy.

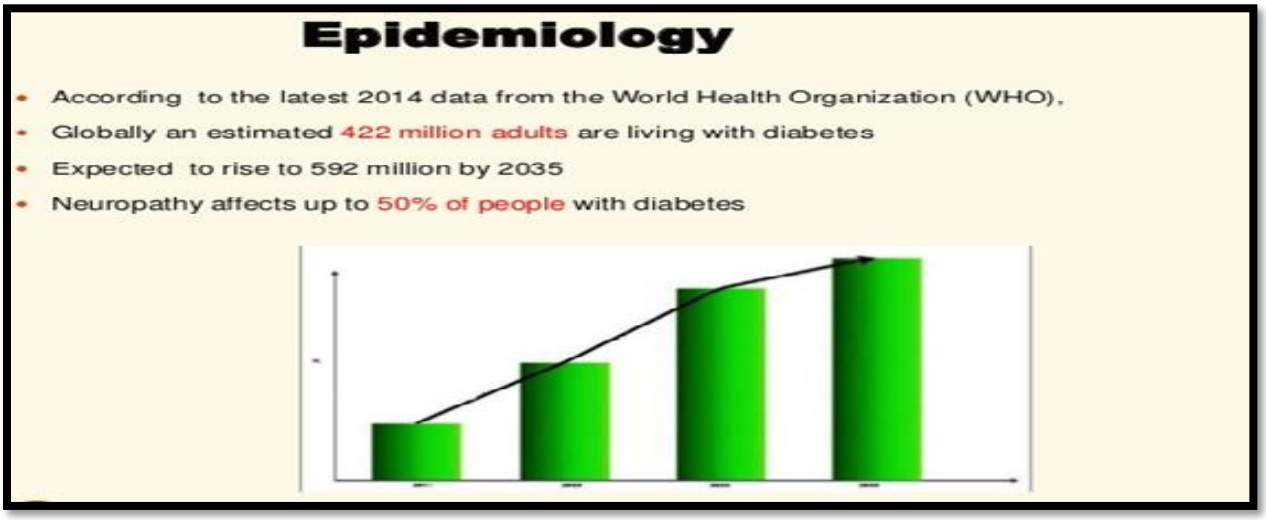

Figure 3: Epidemiology of Diabetic neuropathy

CLASSIFICATION OF DIABEIC NEUROPATHY

Diabetic neuropathy consist mainly five types. Such as the peripheral neuropathy, motor neuropathy, proximal neuropathy, autonomic neuropathy, and mono neuropathy [4].

PERIPHERAL NEUROPATHY

Peripheral neuropathy commonly referred to as sensory neuropathy can involve pain, tingling, numbness, or a combination of all, generally beginning in the feet [5]. The nerves that run from the spinal cord to the feet are the longest in the body and must carry signals the farthest of all the nerves. There is more opportunity for damage to these nerves just because there are more of them. This is the most common type of neuropathic condition caused by diabetes.

PROXIMAL NEUROPATHY

Proximal neuropathy can also be called diabetic amyotrophy. That myo in the word means muscle, so this is a form of neuropathy that can cause muscle weakness. It specifically affects the muscles in the upper part of the legs, buttocks, and hips. Sometimes, proximal neuropathy can also involve nerve pain, especially pain that shoots from the low back and down the leg. The technical medical term for that

is radiculopathy, although most people refer to it as sciatica. If there's also shooting nerve pain involved, this form of neuropathy can also be called polyradiculopathy - diabetic amyotrophy.

Proximal neuropathy is the second most common type of diabetic neuropathy. It usually affects elderly people with diabetes; as opposed to peripheral neuropathy, it usually resolves with time or treatment.

Figure 4: Proximal Neuropathy

MONO NEUROPATHY

Mononeuropathy, sometimes called focal neuropathy, can occur suddenly and mostly affects nerves in the eyes and other parts of the head. It usually presents itself very suddenly and can cause shooting pains behind the eyeball and in other parts of the head. Sometimes mononeuropathy will affect other parts of the body and is often confused with motor neuropathy because the symptoms are similar: weakness and cramps. This type of neuropathy also imitates peripheral neuropathy and can cause tingling and sharp pains in the legs.

AUTONOMIC NEUROPATHY

Autonomic neuropathy tends to take the body out of balance, or homeostasis and gives the person a feeling of uneasiness because the functions that are usually automatically handled without conscious thought are interrupted. This type of neuropathy will affect many of the systems which keep the body functioning but the most heavily affected will be the systems served by the most damaged nerves. This type of neuropathy doesn't involve pain, but weakness, generally in the arms, can be diagnosed with tests and is often confused with other nerve diseases such as ALS. Autonomic neuropathy can involve symptoms such as weakness, loss of control of certain muscles, cramps, and even paralysis.

The various types of neuropathy often mimic each other and can be difficult or impossible to diagnose specifically because of crossover symptoms. Only a physician can perform this diagnosis and will usually handle this through blood tests or reflex test.

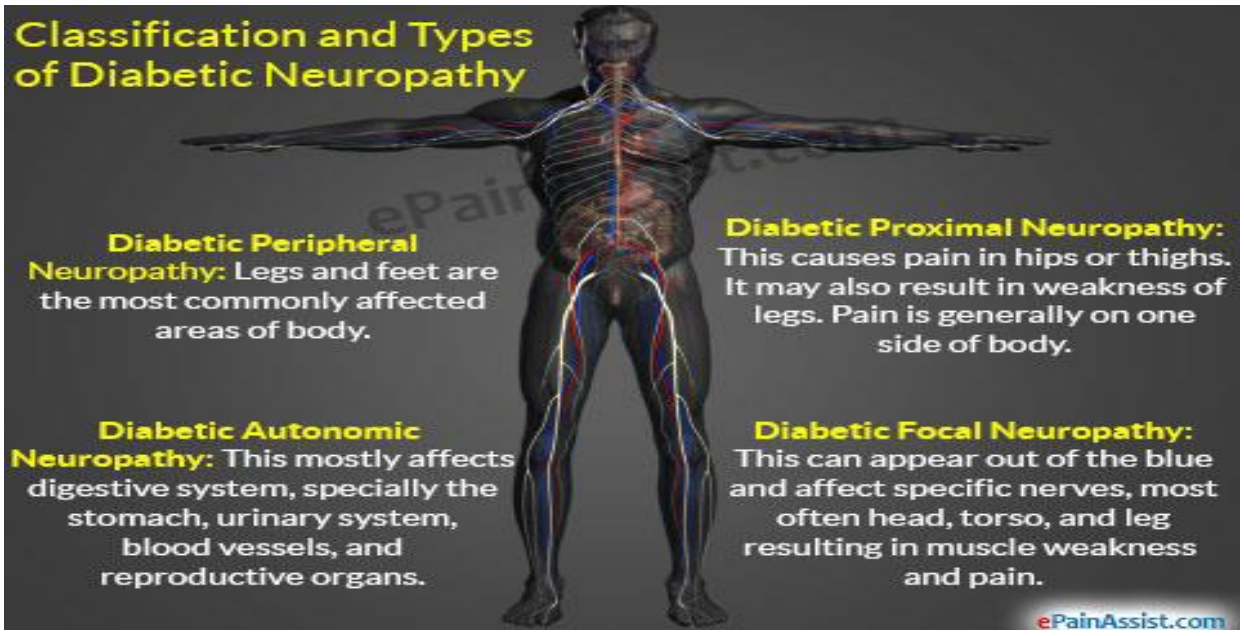

Figure 5: Types of Diabetic Neuropathy

AETIOLOGY

Damage to nerves and blood vessels: High blood sugar also weakens the walls of the small blood vessels (capillaries) that supply the nerves with oxygen and nutrients [6]. However, a combination of factors may lead to nerve damage, including.

Inflammation in the nerves: caused by an autoimmune response. The immune system mistakes nerve as foreign and attacks them.

Genetic factors: unrelated to diabetes may make some people more likely to develop nerve damage.

Smoking and alcohol abuse: damage both nerves and blood vessels and significantly increase the risk of infection.

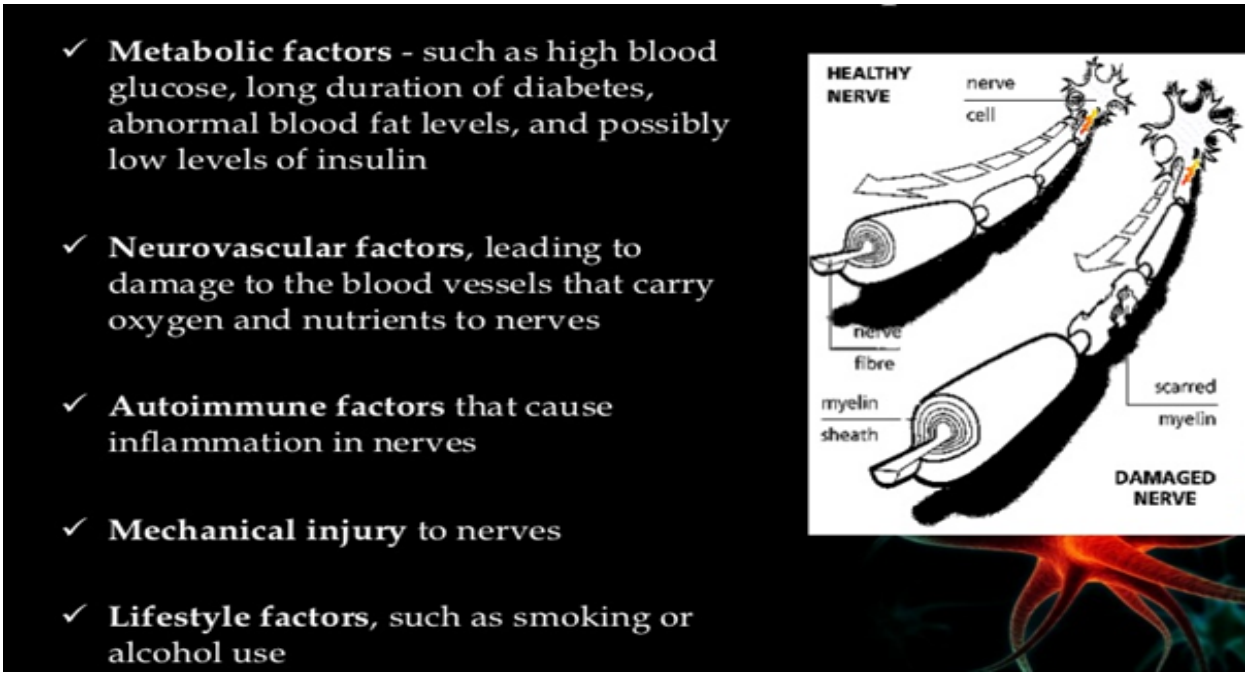

Figure 6: Aetiology of Diabetic neuropathy

Table 1: Aetiology of Diabetic Neuropathy

CLASSIFICATION	EXAMPLES
Traumatic	➢ Surgery ➢ Phantom limb pain ➢ Spinal cord injury ➢ Peripheral nerve injury
Complex regional pain syndrome type II	➢ Following a nerve lesion/injury
Neurological and neuromuscular disease	➢ Gullain-Barre disease ➢ Trigeminal neuralgia ➢ Multiple sclerosis
Metabolic disease	➢ Fabry's disease
Chronic infection	➢ HIV/AIDS ➢ Postherpetic neuralgia
Cancer	➢ Nervous system tumour ➢ Invasion/compression by tumour ➢ Effect of treatment(eg: chemotherapy)
Genetic	➢ Erythromelalgia ➢ Paroxysmal extreme pain disorder

SIGNS AND SYMPTOMS:

Figure7; Illustration depicting areas affected by diabetic neuropathy:

PERIPHERAL NEUROPATHY:

Signs and symptoms of peripheral neuropathy are often worse at night, and may include [7]

- Numbness or reduced ability to feel pain or temperature changes
- Tingling or burning sensation
- Sharp pains or cramps
- Increased sensitivity to touch — for some people, even the weight of a bed sheet can be painful
- Muscle weakness
- Loss of reflexes, especially in the ankle
- Loss of balance and coordination
- Serious foot problems, such as ulcers, infections, and bone and joint pain

AUTONOMIC NEUROPATHY:

The autonomic nervous system controls your heart, bladder, stomach, intestines, sex organs and eyes. Diabetes can affect nerves in any of these areas, possibly causing:

- A lack of awareness that blood sugar levels are low (hypoglycemia unawareness)
- Bladder problems, including urinary tract infections or urinary retention or incontinence
- Constipation, uncontrolled diarrhea or both
- Slow stomach emptying (gastroparesis), causing nausea, vomiting, bloating and loss of appetite
- Difficulty swallowing
- Increased or decreased sweating
- Problems controlling body temperature
- Changes in the way your eyes adjust from light to dark
- Increased heart rate at rest
- Sharp drops in blood pressure after sitting or standing that may cause you to faint or feel lightheaded
- Erectile dysfunction
- Vaginal dryness
- Decreased sexual response

RADICULOPLEXUS NEUROPATHY:

Symptoms are usually on one side of the body, but sometimes may spread to other side. May include:

- Severe pain in a hip and thigh or buttock that occurs in a day or more
- Eventual weak and shrinking thigh muscles
- Difficulty rising from a sitting position
- Abdominal swelling, if the abdomen is affected
- Weight loss

MONO NEUROPATHY:

Signs and symptoms depend on which nerve is involved. May have pain in the:

- Shin or foot
- Lower back or pelvis
- Front of thigh
- Chest or abdomen

Mononeuropathy may also cause nerve problems in the eyes and face, leading to:

- Difficulty focusing
- Double vision
- Aching behind one eye
- Paralysis on one side of your face (Bell's palsy)

PATHOGENESIS OF DIABETIC NEUROPATHY:

Hyperglycemia plays an important role in the pathogenesis of diabetic neuropathy. Other metabolic consequences like increased polyol pathway activity, myo-inositol depletion, Na+/K+ - ATPase activity, microvacular disease, sensorimotor poly neuropathy and autonomic neuropathy also contributes to the pathogenesis of diabetic neuropathies[8].

Polyol pathway: In the presence of excess hyperglycaemia, there is an intracellular accumulation of glucose. This excess glucose gets converted into sugar alcohol i.e. sorbitol by enzyme aldose reductase. Sorbitol accumulation has deleterious effect on nerve conduction velocity. This is attributed to schwann cell damage caused by an increase in osmolarity due to sorbitol and fructose.

Myo-inositol metabolism: Myo-inositol is an important constituent of phospholipids and cell membranes. It is found in higher concentration in peripheral nerves. Hyperglycemia causes increased intracellular concentrations of glucose, resulting in increased activity of polyol pathway leading to depletion of myo-inositol concentrations that inhibits Na/K ATPase tissue activity. Reduced activity of Na/K ATPase activity results in diminished myo-inositol uptake in the nerve.

Protein Kinase C pathway activation (PKC): Hyperglycemia increases the formation of diacylglycerol, which in turns activates PKC. In addition, hyperglycemia activates polyol pathway which causes depletion of myoinositol. PKC mediates a vascular response to hyperglycemia that involves both endothelium and smooth muscles. PKC regulates the vascular permeability, contractility, basement membrane synthesis and cellular proliferation. Inhibition of PKC due to euglycemia plays a pivotal role in decrease of vascular permeability and deregulation of basement membrane synthesis of the endothelium [9].

Advanced glycation end products (AGE): Non-enzymatic addition of glucose of glucose to proteins is called glycation. Glucose forms a chemically reversible product with protein called as Schiff base. The degree to which glycation occurs depends on blood plasma glucose concentration.

Hexosamine pathway: Hexamine pathway is activated when excess intermediates are formed from increased glycolytic activity. These intermediates alter gene function and protein expression that contribute to diabetic microvascular complications.

Microvascular disease: Vascular and neural diseases are closely related and intertwined. Blood vessels depend on normal nerve function, and nerves depend on adequate blood flow. The first pathological change in the small blood vessels is narrowing of the blood vessels. As the disease progresses, neuronal dysfunction correlates closely with the development of blood vessel abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia, which contribute to diminished oxygen tension and hypoxia. Neuronal ischemia is a well-established characteristic of diabetic neuropathy.

Sensorimotor polyneuropathy: Longer nerve fibers are affected to a greater degree than shorter ones because nerve conduction velocity is slowed in proportion to a nerve's length. In this syndrome, decreased sensation and loss of reflexes occurs first in the toes on each foot, and then extends upward. It is usually described as a glove-stocking distribution of numbness, sensory loss, dysesthesia and night time pain. The pain can feel like burning, pricking sensation, achy or dull. A pins and needles sensation is common. Loss of proprioception, the sense of where a limb is in space, is affected early. These patients cannot feel when they are stepping on a foreign body, like a splinter, or when they are developing a callous from an ill-fitting shoe. Consequently, they are at risk of developing ulcers and infections on the feet and legs, which can lead to amputation.

Autonomic neuropathy: The autonomic nervous system is composed of nerves serving the heart, lungs, blood vessels, bone, adipose tissue, sweat glands, gastrointestinal system and genitourinary system. Autonomic neuropathy can affect any of these organ systems. The most commonly recognized autonomic dysfunction in diabetics is orthostatic hypotension, or becoming dizzy and possibly fainting when standing up due to a sudden drop in blood pressure. In the case of diabetic autonomic neuropathy, it is due to the failure of the heart and arteries to appropriately adjust heart rate and vascular tone to keep blood continually and fully flowing to the brain. This symptom is usually accompanied by a loss of respiratory sinus arrhythmia – the usual change in heart rate seen with normal breathing. These two findings suggest autonomic neuropathy.

History & Physical examination: Includes taking a medical and family history and finding about their lifestyle such as drinking habits and any infection in the past.

A **neurological examination:** which includes checking the reflexes, muscle tone and strength, evidence of cramps or spasms, posture, coordination and ability to feel sensations like pain and temperature is also done.
Other tests are suggested based on the results of neurological and physical examination and history.

Blood tests can detect diabetes, vitamin deficiencies, liver or kidney dysfunction, other metabolic

disorders, signs of abnormal immune system activity or any other condition that can indicate peripheral neuropathy.

Imaging tests like **computed tomograpy (CT)** or **magnetic resonance imaging (MRI)** can help rule out tumors, herniated discs, or other abnormalities that may be causing the neuropathy [10].

Nerve biopsy involves removing a small portion of a nerve, usually a sensory nerve, often from the lower leg to look for abnormalities. It is an invasive procedure that is difficult to perform and causes neuropathic side-effects.

Skin biopsy - A small portion of skin is removed to look for a reduction in nerve endings. It helps to reveal damage present in smaller fibers. It is less invasive than nerve biopsy, is easier to perform and has lesser side-effects.

Electromyography **(EMG) involves inserting a fine needle into a muscle** torecord electrical activity in the muscles. It detects abnormal electrical activity in motor neuropathy and can help differentiate between muscle and nerve disorders.

Nerve conduction velocity (NCV) test measures the speed at which electrical signals pass through the nerves. Special electrodes are placed on the skin over the nerve being tested. These electrodes give off very small electrical impulses or shocks to the nerves which responds by generating its own electrical impulse. In peripheral neuropathy, this speed and strength of the impulses is reduced and impulses are blocked.

Figure 8: Diagnosis of Diabetic neuropathy

COMPLICATIONS

Diabetic neuropathy can cause a number of serious complications, including:

Loss of a toe, foot or leg: Nerve damage can make lose feeling in feet. Foot sores and cuts may silently become severely infected or turn into ulcers. Even minor foot sores that don't heal can turn into ulcers. In severe cases, infection can spread to the bone, and ulcers can lead to tissue death (gangrene). Removal (amputation) of a toe, foot or even the lower leg may be necessary [11].

Joint damage: Nerve damage can cause a joint to deteriorate, causing a condition called as Charcot joint. This usually occurs in the small joints in the feet. Symptoms include loss of sensation and joint swelling, instability and sometimes joint deformity. Prompt treatment can help heal and prevent further joint damage.

Urinary tract infections and urinary incontinence: If the nerves that control bladder are damaged, may be unable to fully empty bladder. Bacteria can build up in the bladder and kidneys, causing urinary tract infections. Nerve damage can also affect ability to feel when need to urinate or to control the muscles that release urine, leading to leakage (incontinence).

Hypoglycemia unawareness: Low blood sugar (below 70 milligrams per deciliter, or mg/dl) normally causes shakiness, sweating and a fast heartbeat. But if have autonomic neuropathy, may not notice these warning signs.

Sharp drops in blood pressure: Damage to the nerves that control blood flow can affect your body's ability to adjust blood pressure. This can cause a sharp drop in pressure when you stand after sitting (orthostatic hypotension), which may lead to dizziness and fainting.

Digestive problems: If nerve damage strikes digestive tract, can have constipation or diarrhea, or bouts of both. Diabetes-related nerve damage can lead to gastroparesis, a condition in which the stomach empties too slowly or not at all. This can interfere with digestion and severely affect blood sugar levels and nutrition. Signs and symptoms include nausea, vomiting and bloating.

Sexual dysfunction: Autonomic neuropathy often damages the nerves that affect the sex organs. Men may experience erectile dysfunction. Women may have difficulty with lubrication and arousal.

Increased or decreased sweating: Nerve damage can disrupt sweat glands work and make it difficult for body to control its temperature properly. Some people with autonomic neuropathy have excessive sweating, particularly at night or while eating. Too little or no sweating at all (anhidrosis) can be life-threatening.

PREVENTION:

Diabetic neuropathy and its complications prevented by keeping tight control of blood sugar and taking good care of your feet.

Blood sugar control: Use an at-home blood sugar monitor to check blood sugar and make sure it consistently stays within target range. It's important to do this on schedule. Shifts in blood sugar levels can accelerate nerve damage.This blood test indicates average blood sugar level for the past two to three months. If blood sugar isn't well-controlled or change medications, may need to get tested more often.

Foot care: Foot problems, including sores that don't heal, ulcers and even amputation, are a common complication of diabetic neuropathy. But you can prevent many of these problems by having a comprehensive foot exam at least once a year, having doctor check feet at each office visit and taking good care of feet at home.

To protect the health of feet:

Check your feet every day: Look for blisters, cuts, bruises, cracked and peeling skin, redness, and swelling. Use a mirror or ask a friend or family member to help examine parts of your feet that are hard to see.

Keep your feet clean and dry: Wash your feet every day with lukewarm water and mild soap. Avoid soaking feet. Dry feet and between toes carefully by blotting or patting with a soft towel.

Moisturize feet thoroughly to prevent cracking. Avoid getting lotion between toes, however, as this can encourage fungal growth.

Trim your toenails carefully: Cut your toenails straight across, and file the edges carefully so there are no sharp edges.

Wear clean, dry socks: Look for socks made of cotton or moisture-wicking fibers that don't have tight bands or thick seams.

Wear cushioned shoes that fit well: Always wear shoes or slippers to protect feet from injury. Make sure that shoes fit properly and allow toes to move. A podiatrist (foot doctor) can teach you how to buy properly fitted shoes and to prevent problems such as corns and calluses.

MANAGEMENT

PHARMCOLOGICL MANAGEMENT OF DIABETIC NEUROPATHY

Various pharmacolcogical therapies have been proposed that might have a curative effect on the neuropathic pain that is usually perceived in diabetic peripheral neuropathy.

Antidepressants: DN is associated with an unbalanced release of norepinephrine and serotonin from neurons [12]. For that reason, serotonin–norepinephrine reuptake inhibitors (SNRIs), such as duloxetine and venlafaxine, are a promising category of antidepressants for DN treatment. Tricyclic antidepressants (TCAs), such as amitriptyline and nortriptyline, have also shown promise in patients with DN and are considered first-line treatment for DPN at many centers. The use of TCAs, however, is restricted by the frequency and severity of their adverse effects, which can include sedation, cardiac arrhythmias, and postural hypotension. In general, SNRIs are better tolerated than TCAs.

Duloxetine:

Dose: Duloxetine 20 - 60 mg daily, or 60 mg twice daily [120 mg per day]) : Duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake. Although the exact mechanism of action of the drug's central pain-inhibitory activity is unknown, it is believed to be related to the potentiation of serotonergic and noradrenergic activity in the central nervous system (CNS). The blockade of norepinephrine reuptake, in particular, is known to have a beneficial effect on neuropathic pain [13].

Amitriptyline: The mechanism of action of TCAs such as amitriptyline is unclear, but they are believed to inhibit the reuptake of serotonin and norepinephrine. In addition, they are known to antagonize *N*-methyl-d-aspartate (NMDA) receptors, which mediate hyperalgesia and allodynia., the use of amitriptyline is limited by the potential for serious adverse events (AEs), including cardiac arrhythmias and orthostatic hypotension, which are related to the drug's anticholinergic effects.

Desipramine:
Dose: Desipramine 10 to 25 mg at bedtime initially, increasing as tolerated to 100 or 150 mg as a single bedtime dose.

Desipramine is indicated for the treatment of depression. It takes place serotonin/norepinephrine reuptake inhibition (particularly norepinephrine blockade) and NMDA receptor antagonism [14]. However, unlike amitriptyline, desipramine has a low affinity for cholinergic (muscarinic) receptors and is therefore associated with less-severe anticholinergic AEs.

ANTICONVULSANTS

Anticonvulsants comprise two general categories: traditional agents (e.g., carbamazepine and valproate sodium) and newer agents (e.g., pregabalin and gabapentin).

Pregabalin: It is a structural derivative of gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the CNS. It is structurally related to the antiepileptic drug gabapentin, and both agents have the same site of action: the alpha$_2$-delta protein, an auxiliary subunit of voltage-gated calcium channels. Although pregabalin's precise mechanism of action is unknown, binding of the alpha$_2$-delta subunit may be related to the drug's antinociceptive activity. Preclinical findings were consistent with a mechanism of action that might involve the reduction of abnormal neuronal excitability through reduced release of the GABA neurotransmitter [15]. Treating the pain associated with DPN, pregabalin is indicated for patients with postherpetic neuralgia, fibromyalgia, and neuropathic pain associated with spinal-cord injury in adults, and for adjunctive therapy in adults with partial-onset seizures.

Gabapentin: Gabapentin is the treatment of postherpetic neuralgia in adults, and for adjunctive therapy of partial-onset seizures in adult and pediatric patients 3 years of age and older with epilepsy. It is not indicated for the treatment of DPN patients.

Valproate Sodium: Valproate sodium is the sodium salt of valproic acid, is one of several valproate products. Others include valproic acid and divalproex sodium, along with their generics. Valproate sodium and the other valproate products are FDA-approved to treat seizures and manic or mixed episodes associated with bipolar disorder (manic-depressive disorder), and to prevent migraine headaches. They are also used off-label for other conditions, particularly psychiatric disorders [16].

OPIOIDS: The use of opioids for the treatment of chronic, nonmalignant pain has increased during the last decade. Opioid drugs, however, can cause novel pain syndromes, such as rebound headaches, and their chronic use may lead to tolerance, frequent dose escalation, and hyperalgesia. For this reason, the use of opioids in the setting of DPN is controversial. Monotherapy with these medications should be reserved for patients who do not achieve pain relief with other therapies. Despite concerns about dependency, consensus guidelines have suggested that chronic opioid therapy may benefit DPN patients.
Oxycodone: Oxycodone is an opioid analgesic drug. The precise mechanism of action behind the analgesic effect of oxycodone is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the drug's analgesic activity. Oxycodone is often combined with aspirin or acetaminophen in immediate-release pain medications, such as Percodan (oxycodone/aspirin).

Morphine Sulfate: Morphine sulfate is a potent, relatively selective mu-opioid receptor agonist. Its principal therapeutic effect is analgesia, which it produces by interacting with one or more classes of opioid receptors throughout the body.Long-acting formulations of morphine sulfate include Avinza ER capsules and MS Contin CR tablets [17]. Numerous generic formulations of morphine sulfate are also available in the form of long-acting tablets (Endo, Mallinckrodt, Milan, Nesher, Ranbaxy, Rhodes) and capsules (Watson).

OPIOID LIKE ANALGESIC

Tramadol: Tramadol is a centrally acting synthetic analgesic agent in an ER formulation. Its analgesic activity appears to involve at least two complementary mechanisms: binding of the parent drug and its metabolite to mu-opioid receptors and weak inhibition of both norepinephrine and serotonin reuptake.

Tramadol is indicated for the management of moderate to moderately severe chronic pain in adults who require around-the-clock treatment of their pain for an extended period. It is not approved specifically for patients with DPN.

Dextromethorphan: Dextromethorphan (DXM) is a synthetic NMDA receptor antagonist. DXM has proven useful in controlling pain because of its ability to bind to NMDA receptors in the spinal cord and CNS, thereby blocking the generation of central acute and chronic pain sensations [18].

TOPICAL MEDICATIONS

Capsaicin: Capsaicin is an alkaloid derived from chili peppers that desensitizes afferent sensory nerves, resulting in pain relief. Topical treatment, however, may cause burning, stinging, and erythema in some patients. Capsaicin cream or vehicle cream was applied four times daily for eight weeks. At the final visit, capsaicin showed significant superiority over vehicle in the proportion of patients with pain relief (58% versus 45%, respectively) and decreased pain intensity (38% versus 27%). Capsaicin cream was well tolerated, with the exception of transient burning, sneezing, and coughing.

Lidocaine: Lidocaine is an amide-type local anesthetic agent that blocks neuronal sodium channels, thereby blunting the sensitization of peripheral nociceptors and, ultimately, CNS hyperexcitability. Early studies suggested that IV lidocaine might be beneficial in relieving neuropathic pain, but the inconvenience and potential complications of IV administration, along with possible AEs, proved to be problematic. Today, lidocaine 5% patches (Lidoderm, Endo Pharmaceuticals) are a common topical treatment for patients with painful DPN, although this approach is approved only for patients with postherpetic neuralgia.

NON-PHARMACOLOGICAL MANAGEMENT OF DIABETIC NEUROPATHY

Anodyne therapy: Peripheral neuropathy is prevalent among people with diabetes and has a strong correlation to the majority of diabetic foot ulcers and diabetes-related amputations. One potential option for helping these patients is Anodyne Therapy, a non-invasive treatment that has garnered praise in clinical studies and anecdotal kudos from podiatrists and their patients. The device, which received FDA approval in 1994, reduces pain and increases circulation, according to the company Anodyne Therapy [19].

The Anodyne Therapy System uses monochromatic infrared energy (MIRE) to release nitric oxide from the patient's red blood cells. The company says this improves nerve function and is important for making new blood vessels and healing wounds. As the company notes, "low levels of nitric oxide are common in people with diabetes and are a major factor in the poor circulation, loss of sensation, chronic falls, foot ulcers and pain of diabetic peripheral neuropathy."

The manufacturer also emphasizes that Anodyne Therapy has been clinically proven to increase local microcirculation and reduce pain. It says there are several clinical studies that demonstrate significant clinical outcomes including restoration of protective sensation in patients with diabetic peripheral neuropathy, pain reduction, increased nerve conduction and faster healing of diabetic ulcers and other chronic wounds.

Yoga: Yoga is a thousand-of -years-old physical, mental, and spiritual practice that is beneficial for many disorders of the nervous system. It is not just bending into seemingly impossible poses. The practice of yoga is composed of *asana* (the poses), meditation and deep breathing, which combine to help reduce stress. It is a low impact, strength-building and relaxing exercise [20].

Yoga can significantly improve neuropathy symptoms and quality of life– reducing pain by 25%; fatigue by 31% and depression by 44%. In a group of individuals with diabetic neuropathy, 40 days of yoga improved nerve conduction and blood glucose levels, whereas these parameters continued to deteriorate in the control group. Also, eight weeks of yoga decreased pain and improved grip strength in people with Carpal Tunnel Syndrome, when compared to control subjects. Yoga can help to increase the communication between your nerve cells, spinal cord and brain. In this way, yoga is believed to strengthen the pathways between the nerves and brain, managing symptoms and even reducing progression.

Stem cell therapy: Stem-cell therapy is the use of stem cells to treat or prevent a disease or condition. Bone marrow transplant is the most widely used stem-cell therapy, but some therapies derived from umbilical cord blood are also in use Stem-cell is treating the elevated blood glucose levels and relieving diabetic neuropathy. Stem cell may also improve blood flow to damaged nerves, help to reduce pain and heal neurons crippled by diabetic neuropathy.

Acupuncture: Acupuncture is a component of traditional Chinese medicine. During acupuncture, tiny needle are inserted into the skin at various pressure points across the body. According to the Chinese tradition, acupuncture helps balance the flow of the energy. This new energy balance stimulates the body's healing abilities. Acupuncture stimulates the nerves and muscles. This helps boost the body's response to pain, and improves blood circulation. The treatment is done on the both sides of body. Depending on pain felt, needles are inserted at specified acupuncture points in the hand, feet or both. The ultimate effect of this treatment is to reduce pain and improved functioning of the affected body parts.

Non-viral gene therapy: Diabetes nerve damage can make it difficult to sense injury. The non-viral gene therapy help patients experience sensation without just a light touch. The researchers explain VM202 contain a gene known as Human Hepatocyte Growth Factor (HGF) that is responsible to keep nerve fiber healthy and functioning [21]. The hope of therapy is that it will stimulate new blood vessel growth and nerve pain and heal the body.

Aromatherapy: Neuropathy is the damage of nerve endings. Essential oil treatment can help restore the damage to the nerves. The use of essential oils cannot cure neuropathy but in combination with massage and footbath essential oils improves circulation which improves circulation which may prove useful. Most commonly used essential oils are eucalyptus oil, peppermint oil, lavender oil, lemon grass oil etc.

Peppermint oil: Peppermint oil is made from the herbal extract of the peppermint plant. It has a cooling and calming effect on the body. It also improves blood circulation and regular massage with this oil can help relieve the symptoms and reverse the damage of neuropathy. To use this oil for your massage, mix a few drops of peppermint oil in neutral oil such as olive oil or coconut oil, whichever you prefer for your massage. Dip your fingertips in the oil and massage on the affected parts in circular motion.

Cypress essential oil: Cypress essential oil is extracted from the evergreen Cypress tree. It is amazing for all kinds of nerve related problems as it has anti-inflammatory properties and is great for improving blood circulation. To make massage oil, use three parts of Cypress essential oil with three parts coconut oil. Use this oil to massage your limbs and extremities of the body.

Lemongrass oil: Lemongrass oil works as an analgesic, that is it provides pain relief; sedative and anti-inflammatory agent. Lemongrass oil mixed with any massage oil can be used to treat diabetic neuropathy. It also has a very soothing and refreshing smell which can help with relaxation of the body.

Lavender oil: The lovely smelling lavender oil is not just famous for its alluring fragrance; in fact its medicinal properties are well known and have been used for hundreds of years to treat common ailments. Lavender oil can work wonders for diabetic neuropathy as it is known for as a nervous system restorative. Regular use of lavender oil for massage can restore the damaged nerve endings. Mix a couple of drops of lavender oil in your massage oil and use it 2-3 times a week for massage.

PLANTS USED IN DIABETIC NEUROPATHY

GYMNEMA SYLVESTRE

It is commonly known as madhunashini belonging to family Asclipidaceae. Its leaves have been widely used ayurvedic traditional medicine and are bitter, acrid, thermogenic, antiinflammatory, anodyne, anticancer properties. Gymnemic acid is the chief constituent responsible for anti-diabetic effect.

Gymnemic acid has the ability to delay the glucose absorption in the blood [22].The atomic arrangement of gymnemic acid molecules is similar to that of glucose molecules. That molecule fills the receptor locations on the taste buds thereby preventing its activation by sugar molecules present in the food. Similarly Gymnemic acid molecules fill the receptor location in the absorptive external layer of the intestine thereby prevents the absorption of sugar molecule by the intestine which results in decreased blood sugar. When Gymnema leaf extract is administered in a diabetic patient there is a stimulation of the pancreas by virtue of which there is an increase in insulin release. It is believed that by inhibiting sweet taste sensation people taking this will limit their intake of sweet foods and this activity is partially responsible for its hypoglycemic effect.

Possible mechanism by which they exert hypoglycemic effects;

- Increases insulin secretion,
- Promotes regeneration of islet of cells,
- Increases the utilization of glucose; it is shown to
- Increase the enzyme responsible for utilization of glucose, by insulin dependent pathway and increase in Phosphorylate activity, decrease in gluconeogenic Enzymes and sorbitol dehydrogenase
- It the inhibition of glucose absorption from intestine.

Figure 9: Gymnema sylvestre

MOMORDICA CHARANTIA

Commonly called as bitter guard belonging to family Cucurbitaceae. It is a popular herbal resource to treat diabetes. Charantin (mixture of sterol glycosides), vicine (pyrimidine nucleotide) and p-insulin (polypeptide) are reported as active ingredients. It is most studied with regard to antidiabetic effect and all part of plant show hypoglycemic activity in normal animals. A polyhedral preparation containing Momordica charantia show a significant reduction in blood glucose, glycosylated haemoglobin and an increase in plasma insulin and total haemoglobin in animals.

Momordica charantia has been shown to enhance the number of β-cells. Another study shows that momordica charantia can act like insulin or promote insulin release. Other studies shows that hypoglycemic effect is due to an extra pancreatic effect which includes GLUT4 transporter proteins in muscle, increased glucose utilization in the liver and muscle, inhibition of glucose 1, 6-bisphosphatase and glucose-6-phosphatase in liver and stimulation of red cell hepatic glucose-6-phosphate dehydrogenase activity which contributes to hypoglycemic activity of Momordica charantia[23].

Administration of momordica charantia not only reduced blood glucose level but also corrected the structural abnormalities of peripheral nerves. Momordica charantia also has potent aldose reductase inhibitory activity in diabetic rats leading to slight increase in the myelinated fiber area.

Figure10: Momordica charantia

COPTIS CHINENSIS FRANCH:

Dried rhizome of Coptis chinensis Franch belonging to the family Ranunculaceae .It is traditionally used in the Chinese medicine for the treatment of diabetes and inflammatory diseases. The alkaloid obtained from these plants has neuroprotective, neurogenerative, anti-diabetic, anti-oxidative and anti-inflammatory effects. The alkaloids present are berberine, palmatine, hydrastine and copistine. The study shows a significant reduction in cell viability, increased apoptotic rate, declined mitochondrial membrane potential and increased ROS (reactive oxygen species) production [24].

Due to these neuroprotective properties, Coptis chinensis Franch might be a potential therapeutic agent for the prevention of diabetic neuropathy and neurodegenerative disorders like Alzheimer's and Parkinson's disease

CALOTROPIS PROCERA

It is one of the ancient traditional shrubs which have been used for the treatment of diabetes, pain and inflammation. The root extract of Calotropis procera is used for the treatment of diabetic neuropathy.

The negative control rats developing diabetes and diabetic neuropathy after 6 weeks of streptozotocin administration were distinguished by significant hyperalgesia and tactile allodynia with enhanced HbA1c% level compared to normoglycemic rats.

Figure 11: Calotropis procera

ARTEMESIA PALLENS:

It is commonly called as davana belonging to Compositae family. Methanolic extract of aerial parts are responsible for anti - diabetic activity. They inhibit glucose absorption and increase peripheral glucose utilization. Davanone, divan ether, divan furan and linalool are the major constituent [25].

Figure 12: Artemesia pallens

AEGELE MARMELOS

It is commonly called holy fruit tree belonging to the family Rutaceae. *Aegle marmelos* is well known for its antidiabetic and anti-oxidant properties. Studies have reported for the leaf extract of the plant to possess analgesic and anti-inflammatory activity. Aegelin, α and β - sitosterol marmalosin, marmesin are the constituents responsible for anti-diabetic activity. It increases utilization of glucose either by direct glucose stimulation or by acting like insulin like glucose for uptake.

Aegeline found in the alcohol extract of *A. marmelos*. It has been generally accepted that both α and β adrenergic receptors allocated on the membrane surface of beta cells of pancreas regulate the insulin release. The α_2 adrenergic receptors are proposed to be the major adrenergic receptor involved in the modulation of insulin release in pancreatic beta cells.The α_2 adrenergic receptors may be mediating the effect of *Aegle marmelos* in diabetic neuropathy.

Figure 13: Aegele marmelos

ALLIUM SATIVA

It is commonly called as garlic, belongs to family Alliaceae. Antihyperglycemic activity was observed in ethyl acetate, ethanol and petroleum ether extract of alloxan induced rabbits[26].Allium, epigenin, allicin-s-allyl cysteine sulfoxide is responsible for hypoglycemic activity. It has been found that ethyl acetate extract is most potent and active principle producing maximum hypoglycemic activity due to increased insulin.

Figure 15: Allium sativa

OCCIMUM SANTUM:

It is commonly called thulsi belonging to Labiatae family. Leaf powder extract was glucose lowering activity. In streptozotocin induced diabetic animals the effect of the extract on three enzymes of carbohydrate metabolism namely glucokinase, hexokinase and phospofructokinase has been revealed. Eugenol, carvacol, linalool, caryophylline, β-sitosterol present in occimum santum has potent hypoglycemic effect in normal and diabetic rats. Administration of leaf extracts leads to decrease in plasma glucose level by 24.6% [27].

Figure 16: Occimum sanctum

PHYLLANTUS AMARUS:

It is an herb of height up to 60 cm, from family Euphorbiaceae. It is commonly known as Bhuiamala. It is scattered throughout the hotter parts of India, mainly Deccan, Konkan and south Indian states. Traditionally it is used in diabetes therapeutics. Methanolic extract of *Phyllanthus amarus* was found to have potent antioxidant activity. This extract also reduced the blood sugar in alloxanized diabetic rats. The plant also shows antiinflammatory, antimutagenic, anticarcinogenic, antidiarrhoeal activity [28].

Figure 17: Phyllanthus amarus

PTEROCARPUS MARSUPIUM:

It is a deciduous moderate to large tree found in India mainly in hilly region. Pterostilbene, a constituent derived from wood of this plant caused hypoglycemia in dog showed that the hypoglycemic activity of this extract is because of presence of tannates in the extract. Flavonoid fraction from *Pterocarpus marsupium* has been shown to cause pancreatic beta cell regranulation. Marsupin, pterosupin and liquiritigenin obtained from this plant showed antihyperlipidemic activity [29].(−) Epicatechin, its active principle, has been found to be insulinogenic, enhancing insulin release and conversion of proinsulin to insulin *in vitro*. Like insulin, (−) epicatechin stimulates oxygen uptake in fat cells and tissue slices of various organs, increases glycogen content of rat diaphragm in a dose-dependent manner.

Figure 18: Pterocarpus marsupium

TRIGONELLA FOENUM GRACEUM:

It is found all over India and the fenugreek seeds are usually used as one of the major constituents of Indian spices. 4-hydroxyleucine, a novel amino acid from fenugreek seeds increased glucose stimulated insulin release by isolated islet cells in both rats and humans. Oral administration of 2 and 8 g/kg of plant extract produced dose dependent decrease in the blood glucose levels in both normal as well as diabetic rats. Administration of fenugreek seeds also improved glucose metabolism and normalized creatinine kinase activity in heart, skeletal muscle and liver of diabetic rats. It also reduced hepatic and renal glucose-6-phosphatase and fructose −1, 6 – biphosphatase activity. This plant also shows antioxidant activity [30].

Figure 19: Trigonella foenum graecum

MOMORDICA CYMBALARIA:

Momordica cymbalaria Fenzl belongs to the family Cucurbitaceae; is a species found in Karnataka and Andhra Pradesh. Its tuber is traditionally used as abortifacient and also for the treatment of diabetes mellitus, its fruit powder and extract were reported to have anti-diabetic activity in experimental type-1.

diabetes mellitus. The anti-diabetic activity of saponins of Momordica cymbalaria is possibly due to reversal of the atrophy of the pancreatic islets of β-cells resulting in increased insulin secretion and hepatic glycogen levels which may attenuate hyperinsulinemia. The α- adrenergic blocking effect may also contribute to their insulin secretion and sensitizing effects. Steroidal saponin of Momordica cymbalaria revealed significant preventive or curative effects on diabetic neuropathy due to improvement in myelination and restoration of neuronal integrity, thereby delaying the progression of neuropathy. The neuronal anti-oxidant activity may facilitate the neuroprotective effect.

Figure 20: Momordica cymbalaria

ZINGIBER OFFICINALE:

It is a perennial herb, having one meter long erected stem and possesses tuberous rhizomes that are used as a spice in cooking throughout the world. Ginger plant bears purple flowers and there are some essential oils present in it, which provides good aroma to the spice. Antibacterial, antimicrobial, neuroprotective, antioxidant and hepatoprotective activity consist of its extract.

Volatile oils, tanins, alkaloids saponins and flavonoids are reported as its active phytochemicals. The juice of *Z. officinale* showed antidiabetic action. Its juice significantly reduced the fasting glucose levels and increased the insulin levels. A compound gingerol is reported as a potential antidiabetic, lipid lowering and antioxidant agent.

Diabetes mellitus results in neuronal damage caused by increased intracellular glucose leading to oxidative stress. Recent evidence revealed the potential of ginger for reducing diabetic induced oxidative stress markers. The studies revealed a protective role of ginger mediated by modulating the astroglial response to the injury, reducing Ach expression (acetylcholine) and improving neurogenesis. The results represent a new insight to the beneficial effects of ginger on structural alterations of diabetes brain and suggest that ginger might be a potential therapeutic source for the treatment of diabetic induced damage in the brain.

Figure 21: Zingiber officinale

HYGROPHILIA ERECTA:

Diabetic cystopathy manifested by an enlarged bladder is mainly caused by peripheral neuropathy. It is well established that diabetes mellitus induces dysfunction of lower urinary tract which occurs in 26.87 % of cases. The first manifestations are usually the insidious onset of impaired bladder sensation due to autonomic neuropathy. If this continues, the inability to perceive distention of the bladder results in a large bladder. In addition, diabetic autonomic neuropathy may progress to a motor disturbance which affects the hypocontractile dextrusor muscle. The tropical plant, hypographilia erecta has been shown to contain some long fatty alcohols that demonstrate neurotropic activities on cultured neurons on from the cerebral cortex. The c-20 alcohol n-hexacosanol was found to increase neurite extension as well as biochemical differentiation of neuron directly. It was also reported that peripheral administration of this compound prevented neuronal death in the brains of rats. These findings are particularly interesting because long chain fatty alcohol have been shown to be synthesized by rat brain as well as sciatic nerve during development.

Figure 22: Hygrophilia erecta

ALOE VERA:

Aloe vera is being used as medicinal plant. Different type of anthraquinones, saccarides, vitamins, essential and nonessential amino acids, enzymes and inorganic compounds are present in Aloe vera. Leaves are the main part, which contains most of these compounds. Locally Aloe vera is known as "Kunwarghandel" and is used as an ingredient of herbal formulation used to treat the diabetes. Aloe vera gel extract is potential agent in preventing the glycoprotein's mediated secondary diabetic complications. Aloin and aloe-emodin are main constituents of Aloe vera extract. Aloe extracts containing high concentrations of aloin and aloe-emodin. They found significant decrease in blood glucose levels along with protective effect on insulin producing β cells. It can be concluded that these compounds are major contributors for antidiabetic activity of Aloe vera. Due to the presence of gibberellin-like active substances it showed anti-inflammatory activity.

Figure 23: Aloe vera

CONCLUSION:

Diabetic neuropathy is type of nerve damage that can be occurs in diabetic patient. It can be prevented mainly by the blood glucose control and healthy life style. Allopathic medicines are effective in treating the disease, but leading to various adverse effects. Various alternative therapies for diabetic neuropathy including yoga, anodyne therapy, stem cell therapy, non –viral gene therapy, decompression surgery, low intensity laser treatment, gene therapy, aromatherapy, acupuncture, homeopathy etc are also there. But this treatment has its own adverse effects. Hence medicinal plants are the best alternative treatment for the treatment of diabetes mellitus and its associated complication neuropathy. The plant species are proved their efficacy. Limiting diabetes mellitus without any side effect is a challenge still to the medical system. In recent years herbs have become a subject of interest because of their effect of beneficial effect on human health. This review article explored the role of herbs in the treatment of diabetic neuropathy. In near future herbal plants will play a crucial role in modern system of medicine for the treatment of diabetes.

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