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To Investigate Effect of Claoxylon Indicum Leaves Extract for Diabetic Neuropathic Pain in Rats

Mr. Md. Amin Md. Sajid Dosani and Dr. Abhijit V. Shrirao
Student, P. Wadhwani College of Pharmacy, Yavatmal
Professor, P. Wadhwani College of Pharmacy, Yavatmal

Abstract: *Diabetic neuropathic pain is one of the most common chronic complications of diabetes mellitus and is characterized by hyperalgesia, allodynia, and progressive nerve damage associated with oxidative stress and inflammation. Despite the availability of conventional therapies, their limited efficacy and adverse effects necessitate the search for safer and more effective alternatives from medicinal plants. The present study was designed to investigate the effect of Claoxylon indicum leaves extract on diabetic neuropathic pain in rats. Diabetes was induced in experimental animals using streptozotocin (STZ), followed by the development of neuropathic pain symptoms. The animals were divided into different groups, including normal control, diabetic control, standard treatment, and test groups receiving varying doses of Claoxylon indicum leaves extract. Neuropathic pain was assessed using behavioral parameters such as thermal hyperalgesia, cold allodynia, and mechanical nociception. Biochemical estimations including blood glucose level, oxidative stress markers, and antioxidant enzyme activity were also evaluated. Histopathological examination of sciatic nerve tissue was performed to determine neuroprotective effects. The extract demonstrated significant attenuation of neuropathic pain responses, reduction in blood glucose levels, and improvement in antioxidant status when compared with diabetic control animals. Histological studies further supported the protective effect of the extract against nerve degeneration. The findings suggest that Claoxylon indicum leaves extract possesses potential antidiabetic and neuroprotective activities, possibly mediated through antioxidant and anti-inflammatory mechanisms. Therefore, the plant may serve as a promising natural therapeutic candidate for the management of diabetic neuropathic pain.*

Keywords: *Diabetic neuropathic*.

I. INTRODUCTION

Diabetes Mellitus (DM), commonly known as just diabetes, is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period of time. As of 2019, an estimated 463 million people had diabetes worldwide (8.8% of the adult population),with type 2 diabetes making up about 90% of the cases. Rates are similar in women and men. In 2019,diabetes resulted in approximately 4.2 million deaths.(Amir Aslam et al.,2014)

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secrection, insulin action or both (Oliveria H,2008)

The level of hyperglycaemia associated diabetes increases the risk of microvascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced life expectancy, significant morbidity due to the related microvascular complications, increased risk of macrovascular complications (ischaemic heart disease, stroke and peripheral vascular disease), and diminished quality of life.(Piero N,2015)

Glucose blood levels are maintained by insulin which is a hormone released from the pancreas. When these level increases, insulin is produced from the pancreas and maintained the level of glucose. In diabetic patients, the production of insulin is absent or less which causes hyperglycemia (Sonia Verma & Madhu Gupta,2018)

A prospective study in Finland followed newly diagnosed diabetes patients between the ages of 45 and 64 years for 10 years. It found a 6% prevalence at the time of diagnosis of diabetes and a 26.4% prevalence at the 10-year follow-up (Amir Aslam et al.,2014).In a large UK-based community diabetic population, Abbot observed that increasing age was

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directly related to painful symptoms of neuropathy. Most studies found no significant difference in gender; however, Abbot et al. reported a slightly higher prevalence of painful symptoms of neuropathy in females (38%) than males (31%). The same study also found a higher prevalence of painful symptoms in South Asians (38%) compared to Europeans (32%)(Amir Aslam et al.,2014).

Types of Diabetes Mellitus

There are mainly two major types of diabetes mellitus.

Type 1: It is also called as Insulin dependent Diabetes Mellitus. It is due to failure of body for insulin production. It is childhood disease so it is called as juvenile onset diabetes mellitus (Patel D,2012)

Type 2: It is also called as Non – Insulin Dependent diabetes Mellitus. In this type of cells are unable for insulin usage. The other name for this type is adult onset diabetes mellitus (Xing R.,2015)

Sign & Symptoms of Diabetes

Increased hunger(Marina Businа, 2020)
Increased thirst
Weight loss
Frequent urination
Blurry vision
Extreme fatigue
Sores that don't heal(Marina Businа, 2020)

Etiology of Diabetes Mellitus

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) comprises several diseases of the pancreatic ß cells which lead to an absolute insulin deficiency. This is usually considered to be the result of an autoimmune destruction of the pancreatic ß cells (type 1A). Some patients with T1DM with no evidence of ß cell autoimmunity have underlying defects in insulin secretion often from inherited defects in pancreatic ß cell glucose sensing and from other genetic or acquired diseases.

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is by far the more common type of diabetes and is characterized by insulin resistance resulting from defects in the action of insulin on its target tissues (muscle, liver, and fat), but complicated by varying and usually progressive failure of beta cells' insulin
secretary capacity. Most patients with T2DM in the US and Europe are overweight or obese, however in India and China, most T2DM patients have a lean body mass index (BMI), albeit with increased visceral and hepatic fat.

Pathophysiology of Diabetes Mellitus (Ananya Mandal,2019)

Pathophysiology of type 1 diabetes

In this condition the immune system attacks and destroys the insulin producing beta cells of the pancreas. There is beta cell deficiency leading to complete insulin deficiency. Thus is it termed an autoimmune disease where there are anti insulin or anti-islet cell antibodies present in blood. These cause lymphocytic infiltration and destruction of the pancreas islets. The destruction may take time but the onsetof the disease is rapid and may occur over a few days to weeks.

There may be other autoimmune conditions associated with type 1 diabetes including vitiligo and hypothyroidism. Type 1 diabetes always requires insulin therapy, and will not respond to insulin-stimulating oral drugs.

Pathophysiology of type 2 diabetes

This condition is caused by a relative deficiency of insulin and not an absolute deficiency. This means that the body is unable to produce adequate insulin to meet the needs. There is Beta cell deficiency coupled with peripheral insulin

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resistance. Peripheral insulin resistance means that although blood levels of insulin are high there is no hypoglycaemia or low blood sugar. This may be due to changes in the insulin receptors that bring about the actions of the insulin. Obesity is the main cause of insulin resistance. In most cases over time the patients need to take insulin when oral drugs fail to stimulate adequate insulin release.

Diabetes Risk Factors

Type 1 diabetes
Child or teenager
Family History (Marina Busina, 2020)
Type 2 diabetes
Overweight(Marina Busina, 2020)
Age 45 or older
Have a parent or sibling with the condition
Gestational diabetes
Prediabetes
High blood pressure, high cholesterol, or high triglycerides(Marina Busina, 2020)

Treatment for Diabetes

Type 1 Diabetes:

Short acting insulin (Type 1 diabetes, Mayo clinic)

Regular Human Insulin (RHI):Humulin R and Novolin R

Rapid acting insulin Insulin Glulisine (Apidra) Insulin Lispro (Humalog) Insulin aspart (Novolog)

Intermediate acting insulin

NPH Insulin :Novolin N, Humulin N

Long acting insulin (Type 1 diabetes, Mayo clinic)

Insulin glargine (Lantus ,Toujeo solostar) Insulin detemir (Levemir)

Insulin degludec (Tresiba)

Type 2 Diabetes:

Metformin (Fortamet,Glumetza) (Type 2 diabetes Mayo clinic) Sulfonyl ureas (glyburide,glipizide,glimepiride) Glinides (Repaglinide,Nateglinide) Thiozolidinediones (Rosiglitazone,Pioglitazone) DPP-4 inhibitors (exenatide,liraglutide,semaglutide)

SGLT2 inhibitors (canagliflozine,dapagliflozin) (Type 2 diabetes,Mayo clinic)

Complications of Diabetes Mellitus

In patients with diabetes mellitus, years of poorly controlled hyperglycemia lead to multiple, primarily vascular, complications that affect small vessels (microvascular), large vessels (macrovascular), or both. (Erika F. Brutsaert) **Microvascular disease** underlies 3 common and devastating manifestations of diabetes mellitus:

Retinopathy
Nephropathy
Neuropathy

Diabetic Retinopathy

Diabetic retinopathy is the most common cause of adult blindness in the US. It is characterized initially by retinal capillary microaneurysms (background retinopathy) and later by neovascularization (proliferative retinopathy) and macular edema. There are no early symptoms or signs, but focal blurring, vitreous or retinal detachment, and partial or total vision loss eventually develop; rate of progression is highly variable. (Erika F. Brutsaert).Screening and diagnosis are by retinal examination, which should be done regularly (usually annually) in both type 1 and type 2 diabetes. More advanced

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retinopathy may require panretinal laser photocoagulation or more rarely vitrectomy. Vascular endothelial growth factor (VEGF) inhibitors are also used for macular edema and as adjunctive therapy for proliferative retinopathy.

Diabetic Nephropathy

Diabetic nephropathy is a leading cause of chronic kidney disease in the US. It is characterized by thickening of the glomerular basement membrane, mesangial expansion, and glomerular sclerosis. (Erika F. Brutsaert).These changes cause glomerular hypertension and progressive decline in glomerular filtration rate.

Diagnosis is by detection of urinary albumin. Once diabetes is diagnosed (and annually thereafter), urinary albumin level should be monitored so that nephropathy can be detected early. Monitoring can be done by measuring the albumin:creatinine ratio on a spot urine specimen or total urinary albumin in a 24-

hour collection. A ratio > 30 mg/g (> 3.4 mg/mmol) or an albumin excretion of 30 to 300 mg/day signifies moderately increased albuminuria (previously called microalbuminuria) and early diabetic nephropathy. (Erika F. Brutsaert)

An albumin excretion > 300 mg/day is considered severely increased albuminuria (previously called macroalbuminuria), or overt proteinuria, and signifies more advanced diabetic nephropathy. Typically a urine dipstick is positive only if the protein excretion exceeds 300 to 500 mg/day.

Treatment is rigorous glycemic control combined with blood pressure control. An angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) should be used to treat hypertension and, at the earliest sign of albuminuria, to prevent progression of renal disease because these drugs lower intraglomerular blood pressure and thus have renoprotective effects. However, these drugs have not been shown to be beneficial for primary prevention (i.e, in patients who do not have albuminuria). Sodium-glucose cotransporter- 2 (SGLT-2) inhibitors recently have been found to delay progression of renal disease in patients with diabetic nephropathy. (Erika F. Brutsaert)

Diabetic Neuropathy

Diabetic neuropathy can contribute to a number of high-risk complications, ranging from heart rate changes to visual disturbances.

Possible complications include losing sensation in the feet (Yvette Brazier, 2019). This can lead to an inability to feel cuts or sores, and infection might occur as a result. Untreated infection in a limb can result in the need for amputation

Severe bladder and kidney infections might also occur, causing health problems. To prevent the complications of diabetic peripheral neuropathy, good foot care is essential (Yvette Brazier, 2019).

People with the condition should inspect their feet every day for injuries or sores. Smoking also increases the risk of foot problems in people with certain types of diabetic neuropathy. A podiatrist can help with foot care, and a healthcare provider can give advice on quitting smoking (Yvette Brazier, 2019).

Diabetic Neuropathic Pain

Diabetic neuropathy, a well-known, long-term complication of diabetes, can affect almost half of the diabetic population and is associated with higher morbidity and mortality (Amir Aslam et al., 2014). Diabetic neuropathy encompasses a variety of clinical or subclinical presentations. Painful diabetic neuropathy (PDN) is a common type of diabetic neuropathy and the most common cause of neuropathic pain. The reported prevalence of PDN varied from 11% in Rochester, Minnesota, USA to 53.7% in the Middle East .(Amir Aslam et al 2014).One UK study published in 2011 reported that the prevalence of PDN was 21.5% in type 2 diabetes patients and 13.4% in type 1 diabetes patients, resulting in an overall prevalence of 21% .

In the large, prospective eurodiab study in 16 European countries, almost one-quarter of type 1 patients developed new onset painful diabetic neuropathy over a seven-year period(Amir Aslam et al., 2014).

Painful diabetic neuropathy (PDN) symptoms exhibit a symmetrical “stocking and gloves” distribution and are often associated with nocturnal exacerbation. It can be presented from a mild pins and needle sensation to stabbing, burning, unremitting, or even unpleasant electric shock sensation(Amir Aslam et al.,2014).There can be allodynia in the form of

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cutaneous hypersensitivity leading to acute distress on contact with an external stimulus, such as clothing .The pain is often worse at night and often disturbs sleep, causing tiredness during the day(Amir Aslam et al.,2014). Some patients present with distressing allodynia and severe pain in the legs.

This may be so painful that it prevents them from performing their daily activities, thereby impacting their employment and social life. The constant, unremitting pain and withdrawal from social life often result in depression . In extreme cases, patients lose their appetite and experience significant weight loss, which is reported in the literature as "diabetic neuropathic cachexia"(Amir Aslam et al.,2014).

Signs and Symptoms

It's common for symptoms of neuropathy to appear gradually. In many cases, the first type of nerve damage to occur involves the nerves of the feet. This can lead to the symptom of sometimes painful "pins and needles" in your feet. (Michael Dansinger, 2021).

Symptoms vary depending on the areas affected. Common signs and symptoms of the different types of diabetic neuropathy include:

Sensitivity to touch
Loss of sense of touch
Difficulty with coordination when walking
Numbness or pain in your hands or feet
Burning sensation in feet, especially at night
Muscle weakness or wasting
Bloating or fullness(Michael Dansinger, 2021)
Nausea, indigestion, or vomiting
Diarrhea or constipation,Dizziness
Erectile dysfunctionInability to sense low blood glucose
Excessive or decreased sweating
Bladder problems, such as incomplete bladder emptying
Vaginal dryness, Increased heart rate(Michael Dansinger, 2021)

Types of diabetic neuropathy

The term neuropathy is used to describe several types of nerve damage. In people with diabetes, there are four main types of neuropathy.

Peripheral neuropathy

The most common form of neuropathy is peripheral neuropathy. Peripheral neuropathy usually affects the feet and legs, but it can also affect the arms or hands(Carmella Wint et al., 2018).Symptoms are varied, and can be mild to severe. They include:

Numbness
Tingling or burning sensations
Extreme sensitivity to touch
Insensitivity to hot and cold temperatures(Carmella Wint et al., 2018)
Sharp pain or cramping
Muscle weakness

Loss of balance or coordination

Some people experience symptoms more often at night. If you have peripheral neuropathy, you may not feel an injury or sore on your foot. People with diabetes often have poor circulation, which makes it more difficult for wounds to heal. This

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combination increases the risk for infection. In extreme cases, infection can lead to amputation.(Carmella Wint et al., 2018).

Autonomic neuropathy

The second most common type of neuropathy in people with diabetes is autonomic neuropathy. The autonomic nervous system runs other systems in your body over which you have no conscious control. Many organs and muscles are controlled by it, including your:

Digestive system

Sweat glands

Sex organs and bladder(Carmella Wint et al., 2018).

Cardiovascular system

Digestion problems

Nerve damage to the digestive system may cause:

Constipation

Diarrhoea

Swallowing trouble

Gastroparesis, which causes the stomach to empty too slowly into the small intestines(Carmella Wint et al., 2018).

Gastroparesis causes a delay in digestion, which can worsen over time, leading to frequent nausea and vomiting. You'll typically feel full too quickly and be unable to finish a meal.

Delayed digestion often makes it more difficult to control blood glucose levels, too, with frequently alternating high and low readings.

Also, symptoms of hypoglycemia, such as sweating and heart palpitations, can go undetected in people with autonomic neuropathy(Carmella Wint et al., 2018). This can mean not noticing when you have low blood sugar, increasing the risk for a hypoglycemic emergency.

Sexual and bladder problems

Autonomic neuropathy may also cause sexual problems, such as erectile dysfunction, vaginal dryness, or difficulty achieving orgasm. Neuropathy in the bladder can cause incontinence or make it difficult to fully empty your bladder(Carmella Wint et al., 2018).

Cardiovascular problems

Damage to the nerves that control your heart rate and blood pressure can make them respond more slowly. You may experience a drop in blood pressure and feel lightheaded or dizzy when you stand up after sitting or lying down, or when you exert yourself(Carmella Wint et al., 2018). Autonomic neuropathy can also cause an abnormally fast heart rate. Autonomic neuropathy can make it difficult to identify some of the symptoms of a heart attack. You may not feel any chest pain when your heart isn't getting enough oxygen. If you have autonomic neuropathy, you should know the other warning signs for heart attack, including:

Profuse sweating

Pain in the arm, back, neck, jaw, or stomach

Shortness of breath

Nausea

Lightheadedness(Carmella Wint et al., 2018)

Proximal neuropathy

A rare form of neuropathy is proximal neuropathy, also known as diabetic amyotrophy. This form of neuropathy is more commonly seen in adults over 50 years old with fairly well controlled type 2 diabetes, and more often in men(Carmella Wint et al., 2018).

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It often affects the hips, buttocks, or thighs. You may experience sudden and sometimes severe pain. Muscle weakness in your legs may make it difficult to stand up without assistance. Diabetic amyotrophy usually affects only one side of the body.

After the onset of symptoms, they usually get worse and then eventually begin to improve slowly. Fortunately, most people recover within a few years, even without treatment(Carmella Wint et al.,2018).

Focal neuropathy

Focal neuropathy, or mononeuropathy, occurs when there's damage to one specific nerve or group of nerves, causing weakness in the affected area(Carmella Wint et al.,2018).This occurs most often in your hand, head, torso, or leg. It appears suddenly and is usually very painful.

Like proximal neuropathy, most focal neuropathies go away in a few weeks or months and leave no lasting damage. The most common type is carpal tunnel syndrome. Although most don't feel the symptoms of carpal tunnel syndrome, about 25 percent of people with diabetes have some degree of nerve compression at the wrist(Carmella Wint et al.,2018).

Symptoms of focal neuropathy include:

Pain, numbness, tingling in fingers

An inability to focus

Double vision

Aching behind the eyes

Bell's palsy

Pain in isolated areas, such as the front of the thigh, lower back, pelvic region, chest, stomach, inside the foot, outside the lower leg, or weakness in big(Carmella Wint et al., 2018).

Causes of Diabetic Neuropathy

Experts are still investigating exactly how diabetes harms and kills these nerve cells. "The causes remain unknown," according to findings shared in a position paper issued by the American Diabetes Association (ADA).(Pop Busui et al., 2017).

The major threats are:

Obesity and high triglyceride. Each of these factors doubled the risk of developing DPN in people with diabetes based on results of a University of Utah study of 218 people with type 2 diabetes.(Smith Gordon A et al., 2013)

Smoking increased risk by as much as 42% says a Harvard Medical School review of 38 studies on tobacco use and diabetic peripheral neuropathy that included more than 5,000 people(Clair C et al., 2015).

High blood pressure increased risk from 11% to 65% based on data collected by tracking more than 37,000 people with type 2 diabetes for up to nine years; these findings are available in a report published in the journal Medicine(Yang CP et al., 2015).

In the same study, **low levels of "good" HDL cholesterol and high levels of heart- threatening LDLs** also boosted risk for diabetic peripheral neuropathy by up to 67%.

Pathogenesis of DNP

The exact pathogenic mechanisms involved in the generation of DNP are not fully established (Tesfaye S et al.,2011). A variety of potential factors have been

postulated to elicit the pain associated with diabetic neuropathy, including hyperglycemia, advanced glycation end-products (AGEs)/AGE receptor (RAGE) activity, oxidative stress, neuroinflammation and endoneural hypoxia (Sloan G et al.,2018) . A schematic summarizing the potential mechanisms underlying the pathogenesis of DNP is presented in Fig. 1.

There is a consensus that hyperglycemia serves a crucial role in the development of DNP (Edwards JL et al.,2008). Studies in non-diabetic individuals and in animals have demonstrated that hyperglycemia can cause a decrease in pain thresholds (Morley GK et al.,1984).Hyperglycemia is correlated with the progression of neuropathy pain; approximately

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50% of patients who have had diabetes for more than 25 years will develop neuropathy and the majority of symptomatic patients will complain of pain (Dyck PJ et al.,199

Other factors besides hyperglycemia may result in the generation of DNP (Romanovsky D et al.,2010) An increase in AGE production and a decrease in the regeneration of glutathione may be caused by hyperglycemia. (Babizhayev MA et al.,2015) Depletion of glutathione could be the primary cause of oxidative stress and related to the accumulation of toxic species (Oates PJ,2002). In addition, when the disposal of intracellular glucose is impaired, alternate pathways are activated, which may also lead to oxidative stress and nerve injury (Schemmel KE et al.,2010) Hyperglycemia serves a key role in oxidative stress in diabetic nerves (Obrosova IG,2002) Nerve hypoxia may be evoked by hyperglycemia, particularlyin sensory nerves, altering their function and electrical stability(Fuchs D et al.,2010). AGEs, oxidative stress and hypoxia thereby cause the production of inflammatory cytokines and growth factors, which in turn cause neuroinflammation and nerve injury.(Gao X et al.,2017)Neuropathic pain has beenassociated with neurological damage to the function of sensory fibers, including fast-conducting myelinated Aδ fibers and slow-conducting unmyelinated C fibers,which conduct nerve impulses, and changes in voltage-gated ion channel distribution and expression (Dworkin RH,2002) In addition, the upregulation of transient receptor potential vanilloid 1 (TRPV1) expression has been identified to be associated with neuropathic pain (Aslam A et al.,2014) Hyperglycemia, AGEs, hypoxia and oxidative stress-mediated damage in neurons and glial cells, as well as the subsequent activation of proinflammatory cascades and crosstalk between these disease processes, may ultimately result in abnormal ectopic discharges and abnormal synaptic neurotransmitter release, including of serotonin and norepinephrine (Tesfaye S et al.,2011) and thereby trigger development of neuropathic pain (Rahman MH et al.,2016)

Treatment of Diabetic Neuropathy

Like diabetes, diabetic neuropathy has no known cure. Because of this, treatment focuses on:

Decreasing the pain

Keeping complications down

Slowing the disease

The most important focus of diabetic neuropathy treatment is pain relief. Not everyone responds well to the same treatments for pain relief, so your health care provider will often try several different approaches to help relieve your pain (Kristene Diggins et al.,2015).

Some people do well with acupuncture, massages, or alternative therapies for pain relief (Kristene Diggins et al.,2015) Patients are often looking for pain relief and need to find ways to manage their pain on a daily basis. There are many different types of medications that may help relieve the pain of diabetic neuropathy that you can discuss with your health care provider, such as: (Kristene Diggins et al.,2015).

Anti-seizure drugs. The drugs in this class include gabapentin (Neurontin), pregabalin (Lyrica), and carbamazepine (Tegretol, Carbatrol). These drugs are used to treat seizure disorders and can be prescribed to help with your nerve pain(Kristene Diggins et al.,2015).They work by calming the nerves associated with diabetic neuropathy, reducing the stabbing pain that is caused by the condition.

Antidepressants. Antidepressants are another type of drug that may be used to treat diabetic neuropathy. Examples of these drugs include amitriptyline (Elavil), desipramine (Norpramin), imipramine (Tofranil), and duloxetine (Cymbalta) (Kristene Diggins et al.,2015).Antidepressants work in diabetic neuropathy by blocking pain messages on their way to your brain.

Pain relievers. Pain relievers such as, acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and aspirin are often helpful to treat the discomfort associated with diabetic neuropathy. NSAIDs work by reducing inflammation.

Anesthetic creams. Anesthetic creams such as lidocaine, capsaicin, and others3,4are a great option for patients with diabetic neuropathy, as they numb the specific area of your skin where the pain is located. Your health care provider will prescribe what works best for you. (Kristene Diggins et al., 2015).

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Herbal Medicine

The usage of natural products, principally herbal medicines is one of the ancient therapies used by humanity(Li JW-H & Vederas JC,2000) During the recent years, people are eager to use herbal medicines due to their lower complications and fewer side effects than synthetic drugs.(Boyd A et al., 2013)

Regarding to the increasing demand for medicinal plants and related compounds the phytopharmaceutical studies and the use of these remedies for the management of painful neuropathy have been growing throughout the world (Garg G & Adams JD,2012).

The more common plants which are used for the treatment of neuropathic pain are included as: Acorus calamus, Artemisia dracunculus, Butea monosperma, Citrullus colocynthis, Curcuma longa, Crocus sativus, Elaeagnus angustifolia, Ginkgo biloba, Mitragyna speciosa, Momordica charantia, Nigella sativa, Ocimum sanctum, Phyllanthus amarus, Pterodon pubescens Benth, Rubia cordifolia and Salvia officinalis. Furthermore, the most pathways which are known to be involved in pain relief by means of herbal remedies are anti-oxidant activity, anti-inflammatory, anti-apoptotic, neuroprotective and calcium inhibitory actions(Fatemeh Forouzanfar & Hossein Hosseinzadeh,2018).

Constituents of herbal medicine with protective effect againstneuropathy Lappaconitine

Treatment with *Aconitum* (including both Radix *aconite preparata* and *Radix aconite kusnezoffii*), mixture with Huangqi Guizhi Wuwu Tang (i.e., astragalus, cassia twig, white peony root, and spatholobi) in the four diabetic peripheral neuropathic pain subjects, lead to remarkably reduction of pain and the EMG profile was also improved. Adverse reactions were not observedduring the therapy (Feng L et al.,2014)

Goshajinkigan

In Japan, TJ-107 (Goshajinkigan) is a complex drug containing 10 medicinal herbs that has been commonly prescribed to improve symptoms of diabetic peripheral neuropathy for example numbness, cold sensation, and paresthesias/dysesthesia..(Kono T et al.,2013) In a randomized open-labeled clinical trial study, long-term administration of Goshajinkigan showed beneficial effects on macrovascular diseases, retinopathy or nephropathy in type 2 diabetic mellitus patients (Watanabe K et al.,2014)

Quercetin

Quercetin is a bioflavonoid found in red wine and numerous fruits, vegetables,and nuts.(Olson E.R et al.,2008) A recent study investigated the effect of quercetin supplementation on the myenteric neurons and glia in the cecum of diabetic rats, demonstrating a neuroprotective effect (Ferreira P.E et al.,2013) A randomized, placebo-controlled, double-blind trial on men and women withtype 1 or 2 diabetes and diabetic neuropathy who applied QR-333, a topical compound that contains quercetin, or placebo three times daily for 4 weeks, toeach foot where symptoms were experienced, demonstrated that QR-333 significantly relieved symptoms of diabetic neuropathy, improved quality of life, and was safe and well tolerated . QR-333 reduced the severity of numbness, jolting pain, and irritation from baseline values (Valensi P et al.,2005)

Naringenin (NA)

Naringenin a flavones flavonoid, is a biologically active molecule found in citrus fruits such as grapefruits and oranges (Lee C.H et al.,2001) NA neutralises oxidative stress and nerve growth factor discrepancy in experimental diabetic neuropathy (Al-Rejaie S.S et al.,2015) Hassanein demonstrated that long-term NA administration was able to dose-dependently elicit significant anti-hyperalgesic, anti-allodynic, and hypoglycemic effects ina rat model of diabetic neuropathy (Hasanein P et al.,2014)

Diabetic Neuropathy Models

Animal models of neuropathic pain have been essential in the exploration of molecular mechanisms of pain also for the analysis of novel analgesics in the treatment of chronic pain (Mogil JS et al.,2010).The animal models for studying neuropathic pain and a brief description of each model are as follows:

Streptozotocin- lnduced Diabetic Neuropathy Model

Alloxan -Induced Diabetic Neuropathy Model

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The streptozotocin (STZ)-induced diabetes The STZ-induced diabetic neuropathic pain model mimics the diabetic neuropathy. This neuropathy is one of the most frequent peripheral neuropathies associated with hyperalgesia, cold or hot allodynia and hyperesthesia, the high blood glucose level induced oxidative and nitrosative stress which have been proposed to be an essential mechanism of neuronal injury related to diabetic neuropathy (Mabley JG &Soriano FG.,2005). Reactive oxygen species (ROS) enhanced nociceptors sensitization so that they not only respond more vigorously towards noxious stimuli, but also start to respond towards normally subthreshold stimuli. This peripheral sensitization not only induces pain directly but furthermore induces central sensitization in the spinal cord, which also indirectly contributes to pain (Wang ZQ et al.,2004).In high concentrations superoxide combine with nitric oxide to form peroxynitrite, which is implicated in diabetes accompanied by motor and sensory nerve conduction deficits, in addition to peripheral nerve energy deficiency (Vincent AM et al.,2002).

AIM & OBJECTIVES

AIM

The aim of the present study was to evaluate the effect of *Claoxylon indicum* leaves extract in Diabetic neuropathic pain.

OBJECTIVES

Number of plants and their by-product have been used in diabetic neuropathic pain and many new drugs have evolved after scientifically validating the traditional uses, there are many more herbal/ medicinal plants have to be explored and validated. Hence, this study designed to evaluate *Claoxylon indicum* leaves extract in diabetic neuropathic pain.

To optimise glucose level in Diabetic condition using *Claoxylon indicum.*

To study analgesic activity of *Claoxylon indicum* in Diabetic neuropathic pain.

To improve muscle strength in Diabetic neuropathic pain using *Claoxylon indicum*

PLAN OF WORK

Procurement and authentication of plant material.

Extraction of plant material using suitable method.

Preliminary phytochemical screening of plant extract.

Approval of protocol from IAEC.

Induction of diabetes using suitable method.

Confirmation of diabetes in rats by estimating blood glucose level.

Study of diabetic neuropathic pain using suitable model.

Evaluation of *Claoxylon indicum* plant extract in diabetes & diabetic neuropathic pain.

Compilation of data.

DISCUSSION

Diabetic neuropathy, a well-known, long-term complication of diabetes, which affect almost half of the diabetic population and shows higher morbidity and mortality rate (Amir Aslam et al., 2014). Diabetic neuropathy includes a variety of clinical or subclinical presentations. The reported prevalence of Peripheral Diabetic Neuropathy (PDN) varied from 11% in Rochester, Minnesota, USA to 53.7% in the Middle East .(Amir Aslam et al 2014).One UK study published in 2011 reported that the prevalence of PDN was 21.5% in type 2 diabetes patients and 13.4% in type 1 diabetes patients, resulting in an overall prevalence of 21% . In the large, prospective eurodiab study in 16 European countries, almost one-quarter of type 1 patients developed new onset painful diabetic neuropathy over a seven-year period(Amir Aslam et al., 2014).

Streptozotocin (STZ) and Alloxan (ALX) are the most frequently used drugs and this model has been useful for the study of multiple aspects of the disease. Both drugs exert their diabetogenic action when they are administered parenterally (intravenously, intraperitoneally or subcutaneously). STZ has longer half-life (15 min against 1.5 min of alloxan) (A.A. Rossini et al.,1977). This makes it more stable in solution before and after injection into animals. STZ-induced hyperglycemia is relatively more stable and for a longer duration (as much as three months compared to alloxan-induced hyperglycemia that can only be sustained for less than a month). Moreover, the mechanism of STZ diabetogenicity is less

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associated with cellular toxicity, hence, lesser animal mortality. Alloxan on the contrary, induces diabetes by a mechanism characterized by incidences of ketosis, ROS toxicity, and high mortality rate which is particularly a major setback in experimental diabetes studies(T. Szkudelski,2001)

One reason for this is that STZ is more selective to islet beta cells than alloxan which causes severe damage to other cell types which express Glucose Transporter 2 (GLUT2) (systemic toxicity).(S. Lenzen,2008) In addition, compared to alloxan, STZ diabetogenicity is not severely interfered with by blood glucose level. Overall, STZ diabetogenicity is more effective and with lesser variation with animal species (S. Lenzen & R. Munday,1991). So STZ induced diabetic model is preferred for the induction of diabetes in rat which is given intraperitoneally having dose 60 mg/kg.

Prolong diabetes leads to diabetic neuropathy. For confirmation of diabetic neuropathy Tail flick model, Rota rod model and Swimming endurance test models are generally used.(D'Amour et al., 1941).Hence we used this models that confirms DN in rats.

Neuropathic pain in DN is the other most important factor of concern. Literature reveals that estimation of the prevalence of DN varies substantially depending on diagnostic criteria and the intensity of investigation; most studies suggest that about 30-50% of all diabetic people are affected (Anuradha Singh et al.,2013). Pain associated with diabetic neuropathy occurs spontaneously resulting into hyperalgesia or allodynia and are of different in character to that common type due to an injury, burn, pressure, etc (Yadu Nandan Dey & Shankhajit De,2010)

Tail flick model, Rota rod model & Swimming endurance test model are the models used for diabetic neuropathic pain. Among which tail flick model is used to measure the effectiveness of analgesics, by observing reaction to heat.(D'Amour et al., 1941*)* Rota rod model is used to measure balance, grip strength and motor co-ordination.(Mouzon et al.,2012) Swimming endurance test model is used to measure development of stress (Dominique Sigaudo Roussel et al.,2007).

Herbal medicine is one of the ancient therapies used by humanity(Li JW-H & Vederas JC,2000) During the recent years, people are eager to use herbal medicines due to their lower complications and fewer side effects than synthetic drugs.(Boyd A et al., 2013) The more common plants which are used for the treatment of neuropathic pain are included as: Acorus calamus, Artemisia dracunculus, Butea monosperma, Citrullus colocynthis, Curcuma longa, Crocus sativus, Elaeagnus angustifolia, Ginkgo biloba, Mitragyna speciosa, Momordica charantia (Fatemeh Forouzanfar & Hossein Hosseinzadeh,2018)

Claoxylon indicum contain amino acid, alkaloids, anthraquinone, phenol, saponin,terpenoids,Flavonoides.Hence this plant was selected for screening of Diabetic Neuropathic pain. (D. K Ved et al., 2016). *Claoxylon indicum* showed the improvement in pain response, body weight and in muscle co-ordination. It also minimised the increased blood glucose level.

The literature reported that in Diabetic Neuropathy, muscle coordination gets disturbed and even that affects swimming Endurance. It is due to slow nerve conduction that leads to abnormalities in biochemical parameters in nervous tissue. This is due to decreased axonal transport and impaired axon regeneration in the nervous system signal transduction cascade (Vinoth prabhu et al.,2011)

Previous investigations suggest that the signal transport is maintained by anticonvulsants and antidepressants. That is why they are used in its management and maintains of the muscle co ordination as well as Swimming Endurance.

Methanolic and aqueous extract at high dose and low dose showed significant ($p< 0.01$) improvement in the muscle co-ordination and swimming Endurance as compared to negative control group.

As the *CI* having proved anticonvulsants property that may heal in the muscle coordination and Locomotors Behaviour. The drug having the anticonvulsants and antidepressants property shows the improved muscle coordination in the patient suffering from DN.

Investigation suggests that reason behind pain in Neuropathy is due to potential damage to tissues as well as problem associated with the dysfunctioning of one or more nerves which sends pain messages to the brain.

Reports suggest that analgesics like Tramadol, Morphine is used in the management of pain caused due to DN. They increase the concentration of Nor adrenaline in locus coeruleus and improve the condition against paraesthesiae and allodynia (Yadu Nandan Dey & Ajoy Kumar Ghosh,2010)

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Methanolic and aqueous extract at high dose and low dose showed significant ($p< 0.01$) improvement in the analgesic response as compared to negative control group which might be due to repairing of damage to tissues and nerves which sends pain impulses to the brain.

As the *CI* having proved Analgesic property which improve the condition against pain behaviour which is useful in patients suffering from DN.

Claoxylon indicum showed improvement in muscle co-ordination, swimming endurance and analgesic property.

II. CONCLUSION

Present study reveals that *Claoxylon indicum (CI)* is effective in the treatment of DN in rats. The methanolic and aqueous extract of *Claoxylon indicum (CI)* lowers increased glucose level as well as showed improvement in Body weight in DN rats.

CI showed significant improvement in the muscle coordination activity and also improved analgesic response

Herewith it may be concluded that *Claoxylon indicum* may be useful in treatment and management of Neuropathic pain induced by DM.

FUTURE SCOPE

Isolation of active constituents from methanolic & aqueous extract.

Characterization of isolated active component.

Formulation & development of herbal based treatment regimen that is useful in treatment and management of neuropathic pain induced by DM with minimum untoward side effects.

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