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Management of Neuropathic Pain Using Natural Products in Different Animal Models: A Review

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ABSTRACT: The focus of this review is on how natural products and their bioactive ingredients can treat neuropathic pain disorders by acting as neuroprotective agents. which includes information about neuropathic pain and their types, namely central neuropathy and peripheral neuropathy with their mechanistic involvement of various pathways may contribute to the development of neuropathic pain. It also includes information about treatment modalities for peripheral neuropathy i.e., first-line therapy includes, tricyclic antidepressant, antiepileptic, anticonvulsants and serotonin- noradrenaline reuptake inhibitors (SNRIs) and second-line therapy (opioids, topical capsaicin, lidocaine patch). Several alternative remedies exist, includes non-pharmacological treatments that play a key part in the reduction of neuropathic pain. Bioactive ingredients, provide great efficacy with minimal side effects correlated with synthetic compounds. The main focus is on animal models utilised for the evaluation of neuropathic pain, Which include several animal models such as, Streptozotocin Induced diabetic neuropathy in rats and mice is a widely used animal model for assessment of neuropathic pain. Other animal models include, Alloxan-Induced Diabetic Neuropathy, the Spinal Cord Injury (SCI) model, the Chronic Construction Injury model (CCI), the Partial sciatic Nerve Injury model (PNI), Anticancer agents induced neuropathy (vincristine and paclitaxel and Oxaliplatin-induced Neuropathic pain and spinal nerve ligation (SNL) model of neuropathic pain.

1. INTRODUCTION

Neuropathic pain (NP) is frequently defined as a persistent scorching or shooting pain brought on by nerve breakdown or damage in the somatosensory nervous system, which affects peripheral nerve fibers such as Aβ, Aδ and C fibers and central neurons (Colloca et al., 2017). According to (Tripathi & Verma, 2016), NP is defined by the International Association for the Study of Pain (IASP) as "pain caused by damage or disease affecting the somatosensory nervous system." This occurs due to certain conditions such as metabolic disorders, infection, cancer, trauma, medicines, and toxins.

NP is marked by spontaneous greater pain reaction to stimuli that are painful or innocuous. The somatosensory nervous system is involved with the conscious awareness of sensations that come from the muscles, joints, skin, and fascia, such as touch, pressure, pain, warmth, position, movement, and vibration. Amputation, alcoholism, chemotherapy, diabetes, facial nerve problems, HIV infection, multiple myeloma, multiple sclerosis, arthritis in the spine, spine surgery, syphilis, thyroid issues, vitamin B12 deficiency, Charcot-Marie-tooth, post-herpetic neuralgia, post-sternotomy, post-mastectomy, post-thoracotomy, and post-herniorrhaphy are some common causes of NP. Lesions in the somatosensory nervous system brings undesirable change in the transmission of sensory signal to an electric signal in the nervous system. NP shows gloves and stockings pattern of distribution, it mainly affects feet, calves, hands and forearms. NP brings changes or modulation, or alteration in pain signaling, pain transmission neurons, inhibitory interneurons and descending modulatory control systems, Ion channel, second-order nociceptive neurons and pain mechanisms (Kumar et al., 2018).

The NP broadly divides in two types central neuropathy and peripheral neuropathy.

1.1. Central neuropathy

According to the IASP, central pain is pain that originates from or is brought on by a primary CNS injury or dysfunction (Finnerup, 2008). A group of persistent NP disorders known as central pain syndrome are brought on by CNS injury. Central pain may arise after a traumatic brain injury and spinal cord injury (Colloca et al., 2017), like syringomyelia, multiple sclerosis, stroke (infarction or hemorrhage), Parkinson's disease,

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tumors, and epilepsy (Boivie, 2006). The characteristics of central pain are it is chronic, disabling, and resistant to treatment due to which it has a major influence on mood and lifestyle quality of the patients suffering from it. The clear diagnostic criteria for central pain are not established, which makes the diagnosis difficult (Finnerup, 2008). In recent times the NP scale (NPS) is the only validated tool for assessment of central neuropathic pain. The available treatments are only effective in reducing pain to some extent (Finnerup et al., 2005). Approximately 8% of stroke patients and 25% of multiple sclerosis individuals experience central pain (Finnerup, 2008) and 50% of spinal cord injury patients. Example of Central NP includes harm to the spine or brain, a stroke, or multiple sclerosis.

1.2. Peripheral neuropathy

Peripheral neuropathy is a condition developed due to damage to the peripheral nerves. Peripheral nerves are located outside the brain and carry signals to and from the brain and spinal cord. It is the common, chronic, disabling sometimes mortal condition that causes sufferings to the patient. Peripheral neuropathy has heterogenicity in etiopathogenesis, manifold pathology, and diversified severity. Glove and stocking sensory loss, absence of tendon reflexes, distal wasting and weakness, and progressive polyneuropathy are the hallmarks of this condition (Hughes, 2002; Martyn & H, 1997). Chronic NP can develop as a result of peripheral nerve injury in several ways (Kuner & H, 2016). It is evident that hyperglycemia is crucial for the onset and development of diabetic neuropathy and other microvascular consequences of diabetes. which are mainly driven by (S. Khan et al., 2015). Trigeminal or postherpetic neuralgia, peripheral nerve damage, uncomfortable polyneuropathies, or radiculopathies are examples of peripheral neuropathy.

1.3. Pathways Involved in neuropathic pain

1.3.1 Diabetic Neuropathy and the Polyol Pathway

Extremely high intracellular glucose levels result from hyperglycemia in nerve cells, which also results in the glycolytic pathway being saturated. The enzymes aldose reductase and sorbitol dehydrogenase convert extra glucose into sorbitol and fructose (Vinik et al., 2013).
Myoinositol is decreased as sorbitol and fructose buildup, which in turn affects the activity of the membrane Na^+/K^+ATPase, impairs axonal transport, and damages the structural integrity of neurons. According to Brownlee (2005) the aldose reductase (AR)-mediated conversion of glucose to sorbitol depletes the antioxidant nicotinamide-adenine dinucleotide phosphate (NADPH), which is necessary for the renewal of reduced glutathione (GSH). Nitric oxide synthase requires NADPH as a cofactor; when NADPH levels are low, nitric oxide synthase produces less nitric oxide, which results in less vasodilation, which lowers blood flow to the nerve. Galactosaemic animals peripheral nerve ATPase causes myoinositol levels to drop (Edwards et al., 2008). It triggers a chain of events that includes decreased membrane Na^+/K^+ATPase activity, intra-axonal sodium accumulation, and structural breakdown of the neuron as a result.

1.3.2 Protein Kinase-C (PKC Activity in Diabetic Neuropathy

PKC pathway is another way by which hyperglycemia damages the tissue. Diacylglycerol (DAG) concentration is stimulated by high glucose levels, and this triggers the PKC pathway. Increased PKC-ß-isoform production has been linked to the vascular endothelial growth factor (VEGF), PAI-1, NF-B, and TGF-ß are angiogenic proteins that are overexpressed along with diabetic complications.

1.3.3 Hexosamine Pathway in Diabetic Neuropathy

Considered an important mediator in the pathophysiology of diabetes induced oxidative stress and its consequences. Fructose -6 phosphate is a metabolic intermediate step in glycolsis. Some fructose -6-phosphate is diverted from the glycolytic pathway to the hexosamine pathway during the breakdown of glucose. The hexosamine pathway experiences increased flux under hyperglycemic circumstances, which leads to an excess of GlcNAc and abnormal gene expression changes (Brownlee, 2005).

1.3.4 Advanced Glycation End Products (AGE in Diabetic Neuropathy)

AGE, which is produced as a consequence of nonenzymatic glycation of proteins, nucleotides, and lipids in hyperglycemia, may interfere with integrity and mechanisms for neuronal repair (Edwards et al., 2008).

Table 1
Non-Pharmacological remedies for the Prevention of Peripheral Neuropathy (Pattan et al., 2010)

Non-Pharmacological remedies	Examples
Hypnosis	Altered state of consciousness
Relaxation	Deep breathing and stretching
Comfort therapy	Exercise, applying heat or cold, massage therapy, theatre therapy, music therapy
Physical and occupational therapy	Aqua therapy, Tone and strengthening and Desensitization
Neurostimulation	Acupuncture and TENS (transcutaneous electrical nerve stimulation)
Others	Healthy diet, Avoid Alcohol intake and Avoid Cigarette smoking

2. IMPORTANCE OF NATURAL PRODUCTS AND BIOACTIVE COMPOUNDS

Natural products and bioactive compounds there have been extensively utilized in ages to cure a variety of illnesses. Usage of plants, bioactive substances and natural products in advancing and advanced countries has been escalated nowadays because of

their healing properties, biological activities, nutritional values and fewer side effects (Ekor, 2014). In contradiction a number of ailments such as cardiac, diabetes, reproductive, melanoma, and neurodegenerative diseases have shown that natural ingredients have a protective impact and their bioactive compound and have been reported within the ancient eras (Sairazi et al., 2020). For the treatment of neurological conditions Natural compounds are now being used as neuroprotectants (Lim & Kim, 2016). Table 1 shows non-pharmacological remedies with their examples for the prevention of peripheral neuropathy.

3. ANIMAL MODELS FOR ASSESSMENT OF NEUROPATHIC PAIN

Animal models play a crucial role in studying neuropathic pain, as they provide valuable insights into the underlying mechanisms and aid in evaluating potential therapies. NP is a complex state that arises from dysfunction of the neurological system, resulting in persistent pain signals and abnormal sensory processing. By utilizing animal models, researchers can investigate various aspects of neuropathic pain, including its etiology, pathophysiology, and treatment options. One of the primary advantages of animal models is their ability to replicate certain features of human neuropathic pain. These models are designed to mimic specific neuropathic conditions by inducing nerve injury or disease-like symptoms, allowing researchers to study the associated pain behaviours and physiological changes. By observing animals responses to pain stimuli and analyzing their neurobiological alterations, scientists can gain insights into the mechanisms involved in neuropathic pain. Animal models also enable researchers to explore the effects of potential therapies for neuropathic pain. They provide a controlled experimental setting where interventions can be tested and their efficacy assessed. This includes pharmacological interventions, such as administering analgesic drugs or investigating novel compounds, as well as non-pharmacological approaches like physical therapy or neuromodulation techniques. Animal models allow for the evaluation of treatment outcomes, dose-response relationships, and potential adverse effects, providing valuable information to guide clinical studies in humans. There are various animal studies available for the screening of NP and research has shown the effectiveness of each model and the excellent effects of natural products on neuropathic pain. The various screening models are listed in Figure 1. Here are some typical animal models for NP research include:

3.1. Diabetic Neuropathy Models

Animals with experimentally induced diabetes, such as streptozotocin (STZ)-treated rodents, can develop peripheral neuropathy resembling diabetic neuropathy observed in humans. These models are utilised to study the underlying diabetic NP.

3.2. Spinal Cord Injury (SCI) Models

SCI models involve contusion, compression, or transection of the spinal cord. These models not only mimic the sensory and motor deficits observed in human spinal cord injury but also lead to the evolution of NP symptoms.

3.3. Spinal Nerve Ligation (SNL) Model

In this model, a specific spinal nerve is surgically ligated, leading to the evolution of NP symptoms in the corresponding dermatomes. It mimics certain aspects of nerve damage-related NP observed in humans.

3.4. Chronic Constriction Injury Model (CCI)

This model involves the placement of a ligature around a peripheral nerve, resulting in sustained compression and chronic constriction. It induces neuropathic pain-like behaviors and is particularly useful for studying peripheral nerve injury-induced pain.

3.5. Spared Nerve Injury (SNI) Model

In this model, some of the major branches of a peripheral nerve are carefully spared, while others are injured. It produces robust and long-lasting behavioral changes, allowing researchers to study mechanisms of both allodynia (pain from non-painful stimuli) and hyperalgesia (increased sensitivity to painful stimuli).

3.6. Chemotherapy-Induced Neuropathy Models

Various chemotherapeutic agents, such as paclitaxel or vincristine, can be used to induce peripheral neuropathy in animals. These models are relevant for studying NP associated with chemotherapy treatment.

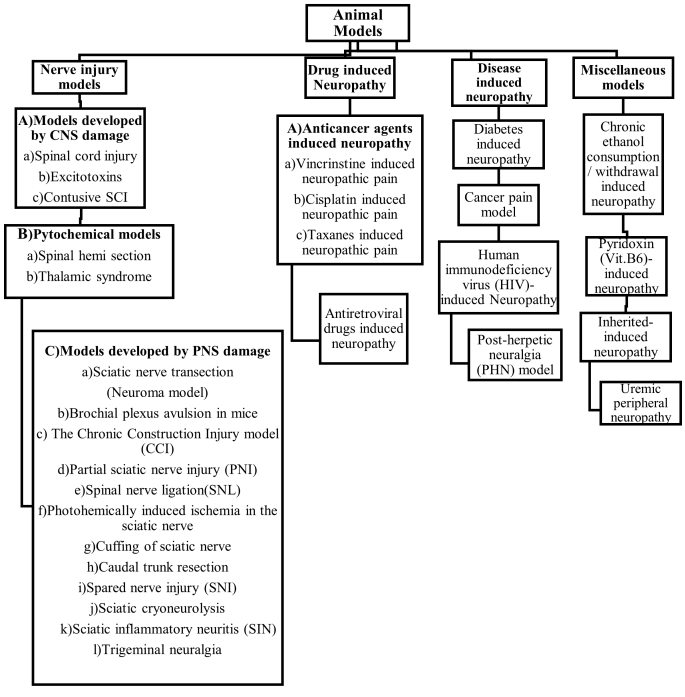

Figure 1. Classification ofAnimal Models (Hoke, 2012)

3.7. Streptozotocin-Induced Diabetic Neuropathy in Rats and Mice

The classic model was developed by Jakobsen and Lundbeck and the classic model was developed by Filho and Fazan for phrenic nerve neuropathy in rats. The toxicity produced by Streptozotocin is due to presence of nitrosoamide moiety, it damages the DNA of insulin secreting beta cells present in pancreas and produces toxicity (Islam, 2013). The level of damage to beta-cells is dose dependent. Due to the similarity with glucose STZ get easily transported through glucose transporter GLUT2.The diabetes is developed in animals by giving a single injection of STZ through an intraperitoneal or intravenous route. Different factors such as age, strain, and species are responsible for the sensitivity of animals to STZ. The development of Diabetic neuropathy using STZ reduces diameters of the myelin sheath, axon, and nerve fiber, shows impairment in motor performance and significantly decreases the myelination of the phrenic nerves and the right and left fascicular regions (Islam, 2013). As STZ increases AR activity, oxidative-nitrosative stress, toll-like receptor 4, protein kinase C, PARP and ACE activations, C-peptide deficiency, impaired neurotropism and proinflammatory response streptozotocin induced diabetic animal models are extensively used to understand diabetic NP (Gao & Zheng, 2014). Table 2 and Table 3 shows the list of natural products used in the screening of diabetic neuropathy along with the parameters assessed by the researcher.

3.8. Alloxan Induced Diabetic Neuropathy

Alloxan is very unstable weak barbituric acid derivative which is first isolated by Brugnatelli in 1818 (Ighodaro et al., 2017; Szkudelski, 2001). Alloxan is selectively up taken by the beta cells of pancreas due to the similarity with glucose in molecular shape and hydrophilicity, it gets accumulated in the cells and produces diabetogenicity (Szkudelski, 2001). Alloxan produces diabetes through a partial degeneracy of the beta (β) cells present in islets of pancreas and brings a considerable change in insulin production by β-cells both qualitatively and quantitatively (Szkudelski, 2001). It is First time used as McLetchie. It produces type 1-DM by a) b)hrs of administration of single dose by intraperitoneal route (Szkudelski, 2001). Table 4 shows the list of natural products used in the NP with the parameters assessed by the researcher.

3.9. Spinal Cord Injury (SCI)

NPmodel by SCI is developed by using one the following technique-Contusion or weight dropping

i. Spinal cord compression
ii. Excitatory neurotoxins
iii. Photochemical-induced ischemia
iv. Spinal cord transaction
v. Crushing of the spinal cord
vi. Clip Compression Injury
vii. Spinal Cord Displacement
viii. Canal Stenosis
ix. Spinothalamic Tract Lesion

Spinal cord injury by any of the above techniques damages the nerves that transport the motor and sensory signals from and to spinal cord and brain which leads to the NPcharacterized by hyperalgesia and various mechanisms of SCI are studied. The mechanism of spinal cord injury includes Peripheral mechanism, Spinal mechanism and Supraspinal mechanism. Table 5 shows the list of natural products used in the management of SCI neuropathy with the parameters assessed by the researcher.

3.10. The Chronic Construction Injury model (CCI) model

This model was developed in rats by Bennett and Xie in 1988 and in mice by Sommer in 1997, model was designed in such a way that it mimics the peripheral nerve damage in patients of NP. This model is produced under anesthesia by the constriction of the nerve most commonly sciatic nerve and in some cases infraorbital nerve and the median nerve (Sommer, 2007), in which the nerve is tied using several ligatures resulting in incomplete nerve injury involves epineural inflammation, intraneural edoema, and Wallerian degeneration (Kumar et al., 2018). After 1 from the injury, the allodynia and hyperalgesia develops as described in Table 4. Pain hypersensitivity testing is done by measuring the mechanical and thermal withdrawal threshold & latency (Kumar et al., 2018). In Table 6, a list of natural products used in the management of CCI Neuropathy with the parameters assessed by the researcher.

3.11. Partial Sciatic Nerve Injury Model (PNI)

In this model the peripheral neuropathy is developed by tight ligation of peroneal nerve or tibial nerve. Unlike STZ-induced diabetic animals, PNI induced neuropathic animals were not chronically ill, growth rate is not reduced, polyuria is not observed, diarrhea, and enlarged and distended bladders is not found. Signs and symptoms of neuropathy develop after 1 week of surgery. This model initiates long-lasting mechanical hyperalgesia but thermal hyperalgesia is not produced by this model. PNI is evaluated by, Morphine and L-Baclofen. The major limitation of PNI is that the major pathogenesis was not characterized (Islam, 2013). Table 7 shows the list of natural products used in the management of PNI Neuropathy with the parameters assessed by the researcher.

3.12. Anticancer agents induced neuropathy

Chemotherapy have many side effects, from which peripheral neuropathy is the usual side effect. Chemotherapy damages somatosensory nervous system which may be the reason for development of peripheral neuropathy. The antineoplastic agents used in chemotherapy damages the healthy cells including nerves that affect feeling and movement in the hands and feet (Islam, 2013).

Table 2
Natural products used in the screening of diabetic neuropathy induced by STZ

Sr. No	Herbal Drug	Plant part used /Type of extract	Animal	Parameters	References
1.	Artemisia Dracunculus	Ethanolic extract	Mice	Thermal hyperalgesia, Mechanical hyperalgesia, Mechanical allodynia, Nitrated protein expression, MNCV and SNCV,HETE concentration, Glucose, Fructose and Sorbitol conc.	Watcho et al. (2011)
2.	Adenanthea pavonina	Aq. extract Of Seeds	Male wistar rats	Thermal hyperalgesia, Motor co-ordination, Spontaneous locomotor activity, SOD, Total calcium, Histopathological evaluation	Pandhare et al. (2012)
3.	Ficus racemosa	Aq. extract of stem bark	Wistar rats	Thermal Hyperalgesia, Motor coordination activity, Locomotion activity, Blood glucose, HBA1C, Serum protein, CRP, CAT, SOD, NO, MDA	Solanki and Bhavsar (2015)
4.	Pterocarpus marsupium Roxb	Aq. extract of whole plant	Male Wistar rats	Thermal hyperalgesia, Mechanical hyperalgesia, Formalin test, Inflammatory Cytokines (TIL-1β, IL-6, TNF-α) Histological examination	Gunasekaran et al. (2017)
5.	Phoenix dactylifera L.	Aq. extract of fruit	Male wistar rats	MNCV, Morphological observations and Analysis of Sciatic Nerve	Zangiabadi et al. (2011)
6.	Gymnema sylvestre	Ethanolic extract leaves	Male Wistar albino rats	Mechanical hyperalgesia,Thermal hyperalgesia, Levels of Glucose& insulin, TBA, GSH, SOD, CAT, GPx ,GR,IL‑1β, IL‑6, TNF‑α, NO, NGF, IGF, NGF protein expression, Histopathology	Fatani et al. (2015)
7.	Operculina turpethum	Aq. extract of root	Wistar rats	Thermal hyperalgesia, Serum glucose, NO, MNCV, ECG Profile, HR, R-R interval, R wave amplitude changes, Cardiac Hypertrophy Index	Professor et al. (2016)
8.	Olea Europaea	Ethanolic extract of leaf	Male wistar rats	Thermal hyperalgesia Immunoblot analysis	Kaeidi et al. (2011)
9.	Dioscorea Bulbifera	Ethanolic extract of rhizome	Male Sprague dawly rats	Tactile Allodynia and Hyperalgesia, Thermal Hyperalgesia, Levels of IL‑6, TNF‑α, NGF, Morphologic and morphometric assessment.	Lee et al. (2013)

Continued on next page

Table 2 continued

10.	Thepsia Populnea	Ehanolic extract of bark	Albino mice	Thermal hyperalgesia, NO	Phanse (2010)
11.	Rubus Fruticosus	Hydroethanolic extract of whole plant	Male Wistar rats	Tail-flick latency time, Glucose level	Gomar et al. (2015)
12.	Z. Jujuba and A, reticulata	Methanolic extract of Root bark and bark	Adult male Wistar rats	Heat hyperalgesia, Cold allodynia, Mechanical hyperalgesia	Kandimalla et al. (2017)
13.	Swietenia mahagoni	Aq. Extract of leaf	Adult Wistar rats	Serum SOD, CAT, GSH, TBARS, Urine analysis, Histological exam.	Urooj (2015)
14.	Allium cepa Lam.	Methanolic extract of A. cepa leaves	Sprague Dawley rats	Mechanical allodynia, Mechanical hyperalgesia, HBA1C, SOD, GSH, Histopathology	D. Khan et al. (2020)
15.	Ficus carica Lam.	Methanolic extract of leaves	Sprague Dawley rats	Mechanical allodynia, mechanical hyperalgesia ,blood urea nitrogen, Serum creatinine	Dureshahwar and U (2019)
16.	Lagerstroemia speciosa L.	Alcoholic Extract of leaves	Male wistar rats	Mechanical hyperalgesia, cold allodynia, Thermal hyperalgesia, LPO,GSH,NO	Bhokare and Upaganlawa (2016)
17.	Phyllanthus amarus & Esculetin	Hydro-ethanolic PAE	Male wistar rats	Motor coordination test, Maze learning test, HbA1c,Estimation of nitrite, MPO, Estimation of Calcium, Protein estimation, Na^+/K^+ ATPase, MNCV, Ach estimation, TEM	Srilatha and Reddy (2019)
18	Tanacetum parthenium	Hydro alcoholic extract of flower	Male SprageDawley albino rats	Paw-pressure test, Motor Coordination test, Parthenolide content , fingerprint profile	Galeotti et al. (2014)
19	Hypercum perforatum L.	Hydro alcoholic extract of seed	Male SprageDawley albino rats	Paw-pressure test, Motor Coordination Test	Galeotti et al. (2014)
20.	Agaricus brasiliensis	Aqueous extract of mushroom	Male adult Wistar rats	Thermal hyperalgesia,Mechanical hyperalgesia, Thermal allodynia, SOD, LPO, NO, Na^+/K^+ ATPases, TNF-α, IL-1β	Ji et al. (2014)

Table 3
Bioactive compounds used in the screening of diabetic neuropathy induced by STZ induced by STZ

Sr. No.	Chemical constituent	Animal	Parameters	References
22.	Protocate-chuic Acid	Male wistar rats	Mechanical hyperalgesia, Cold allodynia, Thermal Hyperalgesia, Grip strength using rotarod test, LPO, GSH	Dhanshree et al. (2017)
23.	Corosolic acid	Male SD rats	Mechanical Allodynia, Mechanical hyperalgesia, cold Allodynia, LPO, GSH, SOD, CAT, NO, Na+/K+ ATPase	Bhokare and Upaganlawa (2016)
24.	Curcumin	Male albino Wistar rats	Thermal Hyperalgesia, Mechanical Allodynia,	Banafshe et al. (2014)
25.	Geraniol	Male albino Wistar rats	Thermal hyperalgesia, Cold allodynia, Narrow beam test, ROS Generation, Hydroperoxides, LPO, NO, GSH, SOD, CAT, Protein Carbonyls, Thioredoxin reductase (TRR) activity, Acetylcholinesterase, Protein, Succinate dehydrogenase (SDH) activity, Protein carbonyl (PC) levels, Citrate synthase (CS) activity	Prasad and Muralidhara (2014)
26.	Lycopene	Male albino mice of Laca strain	Thermal hyperalgesia, NO estimation, Estimation of TNF-α	Kuhad et al. (2008)
27.	α-Lipoic acid + Ferulic acid	Male Wistar rats	Mechanical allodynia, Cold allodynia, Mechanical hyperalgesia, Randall-Selitto Analgesiometer, Thermal allodynia hyperalgesia, GSH, NO, LPO, Na+ /K+ ATPase	Gupta et al. (2020)
28.	Resveratrol	Male albino mice of Laka strain	Thermal hyperalgesia, NO, TNF-α	Sharma et al. (2007)
29.	Morine	Male Wistar albino rat	Mechanical hyperalgesia, NGF, IGF-1, Inflammatory cytokines, TBARS, GSH, SOD CAT	Alsharari et al. (2014)
30.	Crocin & Safranal	Male Wistar rat	Cold allodynia, LPO, Histopathological evaluation	Abbas et al. (2015)
31.	Lycopene	Male Wistar rats	SFI, Hot plate test, Randall sellitto, Von frey hair test, GSH, LPO, NO, CAT, NO	Kasar and Rasal (2023)

Table 4
Natural products in the treatment of Alloxan induced Neuropathy

Sr. No.	Herbal Drug	Plant part used/Type of extract	Animal	Parameters	References
1.	Ficus Benghalensis	Methanolic extract of leaf	Male Wistar rats	Heat- hyperalgesia, Mechanical hyperalgesia, Cold allodynia, Motor coordination, Spontaneous Locomotor (Exploratory) Test	Stalin et al. (2016)
2.	H. Spinosa (HSME)	Methanolic extract of aerial parts	Adult Wistar albino rats	Thermal hyperalgesia,Mechanical hyperalgesia, Thermal allodynia, • Protein content, MDA, GSH, GPx, CAT, GST, GR	Thorve et al. (2012)
3.	Enicostemma littorle Blume	Methanolic extract	Male Charles Foster rats	• Aldose reductase activity, Protein Estimation, Na^+/K^+ ATPases, LPO, GSH, SOD, GPox	Bhatt et al. (2009)
4.	Hericium erinaceus	Ethanolic extract of fruits	Male adult Wistar rats	• Thermal hyperalgesia, Mechanical allodynia, LDH, GSH, LPO, GPx, GR, CAT, Na^+/K^+ ATPase, GST, • Total antioxidant status	Yi et al. (2015)

Table 5
Natural products in the management of Spinal Cord Injury (SCI) Neuropathy Models

Sr. No.	Herbal Drug	Plant part used Type of extract	Animal	Parameters	References
1.	Harpagophy-tum procumbens	Aqueous extract of whole plant	Male Sprague-Dawley rats	• Mechanical Allodynia, Motor Function, Locomotor • Activity, NO, ROS • Production, Western Blot Analysis, LC–MS Analysis of 4‑HNE and 4‑HHE	Ungerer et al. (2020)
2.	Thymo-quinone		Female adult Wistar albino rats	• Mechanical allodynia, • Heat–cold allodynia, • Serum paraoxonase, Total antioxidant status, Tumor necrosis factor, Total oxidant status,IL-1β, MDA • NO	Celik et al. (2014)

Table 6
Natural products in the management The Chronic Construction Injury model (CCI) Neuropathy Models

Sr. No.	Herbal Drug	Plant part used /Type of extract	Animal	Parameters	
1.	Acorus calamus	Hydroethanolic extract of rhizomes	Wistar rats of either sex	Heat hyperalgesia and allodynia, Radiant heat hyperalgesic, Cold allodynia, Static mechanical hyperalgesic test, Tactile mechanical hyperalgesia, Mechanical allodynia, Motor co-ordination, Total protein content, SOD, MPO, Calcium ions, Histopathological evaluation	Muthuraman and Singh (2011)
2.	Alstonia scholaris	Methanolic & chloroform extract of Leaves	Wistar rats	Mechanical hyperalgesia, Thermal hyperalgesia, Cold allodynia, Estimation of TNF-α, TBARS, GSH, total calcium, MPO, Chromatographic analysis	Singh et al. (2017)
3.	Aloe Vera	Ethanolic extract of leaf	Adult female albino rats of Wistar strain	Thermal hyperalgesia, Cold allodynia, Mechanical allodynia, Total protein content, NO, MPO, Total calcium, Histopathological evaluation	Kanyadhara et al. (2014)
4.	Salvia officinalis, Rosmarinic and Caffeic Acids	Ethanolic extract of leaves	Swiss male mice	Mechanical allodynia, Cold allodynia, thermal hyperalgesia, Walking track Test, CRP, Urea, Creatinine, AST,ALT, Histopathological Study	Gabbas et al. (2019)
5.	Lippia Citriodora	Ethanolic extract of fine powder of leaves	Male Wister rats	Mechanical allodynia, Cold allodynia, Heat hyperalgesia Western blot assay proteins	Amin et al. (2018)
6.	Zingiber officinale and Zea mays	Hydroalcoholic extract of dried seeds	Male Wistar rats	Mechanical allodynia, Thermal Hyperalgesia, MNCV, Blood Glucose Level, MDA, SOD, CAT, GPx, Aldose Reductase, Histopathology, Axonal Density	Wattanathorn et al. (2015)
7.	Allium cepa Lam.	Methanolic extract of A. cepa leaves	Sprague Dawley rats	Mechanical allodynia, Mechanical hyperalgesia, HbA1c, SOD, GSH, Histopathological evaluation	D. Khan et al. (2020)
8.	Banaba	Alcoholic Extract of leaves	Wistar rats of either sex	Mechanical hyperalgesia, Cold allodynia, Thermal hyperalgesia, LPO, GSH	Bhokare et al. (2015)
9	Mangifera indica L.	Aq. extract of stem bark	Male Sprague-Dawley rats	Mechanical hyperalgesia, Histopathology	Garrido-Suárez et al. (2014)
10.	Syringic acid and Sinapic acid	Phenolic acid	Wistar rats	Heat and Mechanical hyperalgesia, Cold and Mechanical Allodynia, MNCV, GSH, MDA, CRP, Insulin assay, Serum electrolytes, TNF-α, IL-6, INF-γ	Pawar et al. (2021)

Table 7
Natural products in the management of Partial Sciatic Nerve Injury Models (PNI)

Sr.No.	Chemical constituent	Animal	Parameters	References
1.	Euphol	Male Swiss mice	• Mechanical Hyperalgesia, Mechanical • Allodynia, Locomotor activity, Catalepsy, Cytokine levels, RT-PCR, MPO	Dutra et al. (2012)
2.	Hesperetin	Wistar rats	• Radiant heat hyperalgesia test, Cold allodynia test, Randall Selitto, Von-Frey hair, pinprick test, Rota-rod, Spontaneous locomotor (exploratory) test, MNCV, Total protein content • LPO, NO, Interleukin-1β and Interleukin-6 by ELISA, RT-PCR	Aswar et al. (2014)
3.	Cassine	Male Swiss mice	• Mechanical hyperalgesia, heat hyperalgesia, MPO, IL-1b, IL-6 and KC levels, Immunohistochemical analysis, Hypothermia, Catalepsy, • Locomotor activity	Silva et al. (2012)
4.	Myricitrin/flavonoid (genus Eugenia)	Adult female Swiss mice	• Von Frey test, Algesimeter, Behavioral tests, Mechanical hyperalgesia, Thermal hyperalgesia	Hage-nacker et al. (2010)
5.	Tormentic acid/triterpene (Vochysia. divergens)	Male and female Swiss mice	• von frey tests, Open-field test, • Behavioral tests	Bortalanza et al. (2002)
6.	Linalool/monoterpene	Adult female Swiss mice	• Mechanical and Cold hypersensitivity, Proinflammatory Cytokines	Batista et al. (2010)

Table 8
Natural products in the management of Vincristine-Induced NP Models

Sr. No.	Herbal Drug	Plant part used /Type of extract	Animal	Parameters	References
1.	Palisota hirsuta K. Schum	Hydroalcoholic extract of leaves	Male Sprague Dawley rats	Tactile Allodynia and Hyperalgesia , Mechanical Hyperalgesia, Thermal Hyperalgesia, Assessment of Cold Allodynia	Boakye-Gyasi (2014)
2.	Burkea Africana	Ethanolic extract of stem bark	Sprague Dawley rats	Tactile Allodynia, Mechanical Hyperalgesia, Cold Allodynia, Thermal Hyperalgesia, Total Protein Content, SOD, GSH, CAT, LPO,MPO	Jibira et al. (2020)
3.	Xylopia aethiopica	Ethanolic extract of fruits	Sprague Dawley rats	Tactile allodynia, intermediate and mechanical hyperalgesia, Cold allodynia, Mechanical hyperalgesia	Ameyaw et al. (2014)
4.	Ocimum sanctum	Hydro-methanolic extract of fresh leaves	Wistar albino rats	Thermal hyperalgesia, Cold allodynia, Cold Hyperalgesia, Mechanical hyperalgesia, LPO, Reduced nitroblue tetrazolium (NBT), Total calcium	Kaur et al. (2010)
5.	Capsaicin		Female Egyptian rats	Electrophysiological study, Histology	Masry et al. (2013)

Table 9
Paclitaxel-Induced NP Models

Animal	Dose of paclitaxel	Route of administration	Dosing Time	Sign and symptoms developed (Kumar et al., 2018)
Rat	1 or 2 mg/kg	i.p.	Four alternate days	Endoneural edema and Allodynia
Rat	16 mg/kg	i.p.	Once a week for 5 weeks	Motor impairment or systemic toxicity Electrophysiological, Morphological, and degenerative changes
Mice	10 mg/kg	i.p.	Single dose	Peripheral neuropathy

Table 10
Paclitaxel-Induced NP Models

Sr.No.	Herbal Drug	Plant part used /Type of extract	Animal	Parameters	References
1.	Rubia cordifolia	Ethanolic extract of root & rhizomes	Adult albino Wistar rats	Cold allodynia, Thermal hyperalgesia	Diwane et al. (2015)
2.	Syringic acid and Sinapic acid	Phenolic acid	Wistar rats	Heat hyperalgesia, Cold and Mechanical Allodynia	Pawar et al. (2021)

Table 11
Oxaliplatin -Induced NP Models

Sr.No.	Chemical constituent	Animal	Parameters	References
1.	Mitragynin	Male Sprague-Dawley rats	Mechanical allodynia Locomotor activity	Foss et al. (2020)
2.	Cinnamic acid	Male Sprague Dawley (SD) rats	Cold Allodynia Mechanical allodynia	Chae et al. (2019)

Table 12
SpinalNerve Ligation (SNL) Model of Neuropathic Pain

Sr.No.	Chemical constituent	Animal	Parameters	References
1.	Iridoid glycosides (Paederia scandens)	Adult male SPF SD rats	Electronic von Frey filaments, Nitric oxide synthase (NOS) activity, NO, cGMP	Liu et al. (2012)
2.	Koumine/alkaloid (Gelsemium elegans Benth)	Male mice and SD rats	Acetic acid-induced pain, formalin-induced pain, thermal hyperalgesia, Electronic von Frey apparatus, LC–MS	Xu et al. (2012)

In chemotherapy the chances of development of peripheral neuropathy is 80- 90 % (Hoke, 2012). Various Antineoplastic agents are used by researchers to develop the CIPN model such as paclitaxel, cisplatin, carboplatin, and oxaliplatin and others such as vincristine, thalidomide, suramin, and bortezomib (Hoke, 2012).

3.13. Vincristine-Induced Neuropathic Pain

Vincristine is used as antineoplastic agent. It belongs to the vinca alkaloid family. It is used in treatment of malignant tumors (Higuera & Luo, 2004), lymphoma and leukemia (Kumar et al., 2018). Use of vincristine causes peripheral neuropathy which limits its use. Vincristine develops neuropathy by altering microtubular structures of intracellular tubulin and damages peripheral axons results in dysfunction in primary afferent fibers like Aβ-, Aδ-, and C-caliber, which results in dose-dependent neuropathy. The early signs of neuropathy by vincristine administration is paranesthesia, which progresses to hyperesthesia. This model developed by giving IV injection or by continuous intravenous infusion of vincristine (Higuera & Luo, 2004). The sufficient dose for development of neuropathy by vincristine is as low as 50 μg/kg. It induced consistent and long-lasting signs and symptoms of neuropathy like Allodynia, hyperalgesia(mechanical) and hypoalgesia (thermal) similar to the vincristine treated cancer patients, which makes it a potential study tool for studying the pharmacological mechanisms of vincristine induced NP (Kumar et al., 2018). Table 8 shows a list of natural products used in the therapy of Vincristine induced Neuropathy with the parameters assessed by the researcher.

3.14. Paclitaxel-Induced Neuropathic Pain

Paclitaxel, a vinca alkaloid is a potential antineoplastic agent as a treatment for breast cancer, head and neck cancer, melanoma and ovarian cancer. By inhibiting the polymerization of microtubules and binding to tubulin, paclitaxel causes sensory neuropathy and myelosuppression and interferes with mitosis. In models receiving low doses of paclitaxel, loss of pain perception, morphological abnormalities, neurophysiologic problems, and changes to motor function are rare. So it is better to study these changes with the model of higher doses (Kumar et al., 2018; Sousa et al., 2016). The Paclitaxel-Induced NP model proved that, they produced slightest effects on the rats health and mimics the conditions developed in patients treated with taxens , which makes it a potential study tool for studying the pharmacological mechanisms (Kumar et al., 2018). Tables 9 and 10 shows the list of natural products used shows the list of sign and symptoms of Paclitaxel-Induced neuropathy with the parameters assessed by the researcher.

3.15. Oxaliplatin-Induced Neuropathic Pain

It is a third-generation antineoplastic drug based on platinum that is used to treat colorectal cancer that has progressed. Oxaliplatin develops neuropathy by inhibiting DNA synthesis and the replication of DNA, damages the neuronal cell bodies, decreases SNCV and axons in peripheral nerves are deteriorating (Toyama et al., 2014). Development of neuropathy at combined dosages (36 and 48 mg/kg i.p.) (Kumar et al., 2018). Table 11 shows the list of natural products used in the management of Oxaliplatin -Induced Neuropathy with the parameters assessed by the researcher.

3.16. Spinal Nerve Ligation (SNL Model of Neuropathic Pain

The SNL framework serves as a technique for researching medication for neuropathic pain that is chronic. The experimental drugs with analgesic qualities that are utilised as remedies for persistent neuropathic pain are found using this model. In order to produce peripheral pain, the L5 and L6 spinal nerves are surgically ligated. Table 12 shows the list of natural products used in the management of SNL neuropathy with the parameters assessed by the researcher.

4. CONCLUSION

Natural products including plant extracts as well as bioactive components are having potential due to the presence of various active biomolecules. Due to this they possess various medicinal values. From the present review it is has been concluded that natural products have potential to prevent neuropathy and further studies are required at molecular as well as cellular level to confirmed there potential.

CONFLICTS OF INTEREST

None.

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