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Role of Phytoconstituents and Molecular Docking Simulation Based Screening of Naturally Active Potent Components to Combat Neuropathy

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Abstract: Background: Neuropathic pain is a widespread debilitating problem and addressing the same remains a major challenge in healthcare. It indicates a general and enduring pain invoked by physical injury or an underlying disease involving the somato-sensory machinery. Globally, approximately 10% of the population suffers from neuropathic pain as a result of various disease conditions. The incidence of neuropathic pain is approximately 10% which strikes the general population awfully. The key pharmacological mechanisms that work in the reduction of pain are yet to be explored completely and mainly encompass nociceptive transduction blockade, neurogenic inflammation reduction through deceleration of neurotransmitters, and deterrence of peripheral and central sensitization. The pharmacotherapy includes neuronal desensitizers, antidepressants, serotonin-noradrenaline reuptake inhibitors, anticonvulsants, and opioid analgesics. Nevertheless, in suppressing neuropathic pain, the usage of these drugs is restricted by side effects like drowsiness, ataxia, constipation, arthralgia, cognitive dysfunction adverse effects like tolerance and physical dependence. Numerous drugs available for the treatment of neuropathic pain none of them can restore the pre-disease status. Therefore, finding more effective drugs to alleviate neuropathic pain is imperative.

Method: A thorough literature survey was performed from 2000 -2022 using scientific databases, like Google, PubMed, Science Direct, Scopus, and Web of Science, for determining the design of the study, and each article was checked for in vitro, in vivo, in silico evaluation of phytocomponents and plant extracts to combat neuropathic pain and inflammation.

Result: The utilization of bioactive compounds and alternative treatment approaches has garnered more attention due to the lack of existing synthetic remedial therapy. Emerging scientific reports and findings propose that phytochemicals contribute to the deterrence and treatment of neurodegenerative and inflammatory diseases without having any side effects and drug resistance.

Conclusion: The promising effect of these bioactive phyto-molecules is owing to their antioxidant and anti-inflammatory potential. Hence, alternative natural components have been screened through the structure-based docking simulation. The present article is an extensive review of medicinal plants and natural compounds along with their docking-based screening to demonstrate beneficial effects against neuropathic pain and inflammation.

Keywords: Neuropathy, medicinal plants extracts, phytocompounds, nutraceuticals, docking-based screening, beneficial effects

1. INTRODUCTION

Pain described as a distressing feeling and an emotional response that serves as a warning of potential or ongoing tissue damage, aiming to prevent further harm. [1]. The presence of neuropathic pain seems to have a direct impact on the somatosensory system due to an underlying injury or medical condition. [2]. Neuropathic pain is defined by its origin in the central or peripheral nervous system, which can stem from a variety of causes such as nerve damage, infections, alcoholism, multiple sclerosis, and diabetes, among others. One of the most commonly reported types of neuropathic pain is chronic neuropathic pain, which is typically associated with underlying medical conditions, particularly cancer, and diabetes. [3].

1.1. ***Pathological pathway of Neuropathic Pain***

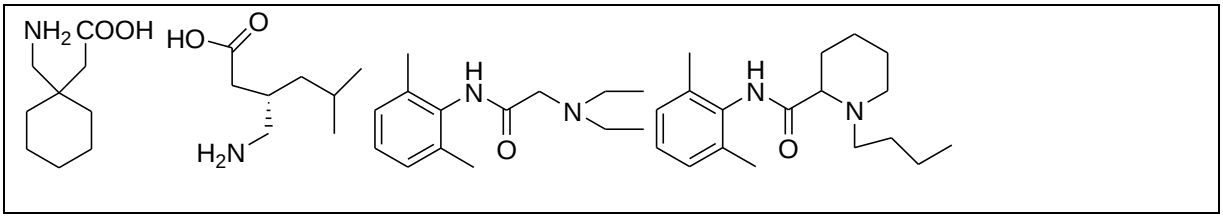
The somatosensory system involved in neuropathic pain is comprised of marginal fibers, namely Aδ, Aβ and C fibers, as well as central neurons. It is estimated that around 7-10% of patients are significantly affected by neuronal damage [4]. An impairment of the somatosensory nervous system can result in a disruption of the transmission of sensory signals between the spinal cord and the brain. Neuropathic pain caused by a voluminous factors, including central and peripheral nerve damage, radiculopathy, nerve amputation, postherpetic neuralgia, and comorbidities such as diabetic neuropathy. Painful stimuli are detected through the activation of nociceptors located in sensory afferent neurons [5].

Upon stimulation, first-order sensory neurons are initially activated, resulting in an influx of sodium ions and a subsequent efflux of potassium and chloride ions. This process triggers a rush of calcium ions due to the activation of voltage-dependent calcium channels. The neurons then pass through the posterior horn of the spinal cord and travel to the brainstem. Second-order neurons are activated when an excitatory neurotransmitter, glutamate fastens with NMDA (N-Methyl D-Aspartate) receptors. These neurons cross at the thalamus and communicate with third-order neurons, which are involved in communication within the limbic system and cerebral cortex. Additionally, the release of norepinephrine and serotonin from the brainstem to the spinal cord can provide anti-nociceptive stimulation at the dorsal horn. [6].

Neuropathic pain is primarily mediated by specific receptors known as TRP (Transient Receptor Potential) family receptors. However, normal pain mediators also play a parallel role in neuropathic pain. Pain facilitators such as IL-6 (Interleukin-6), IL-1 (Interleukin-1) and TNF-α (Tumor Necrosis Factor- Alpha), NO (Nitric Oxide), MAO-A & B (Mono Amine Oxide-A & B), PPAR- Alpha (Peroxisomes Proliferator- Activating Receptor- Alpha), and Cox-1 & 2 (CycloOxygenase-1 & 2) are also involved in neuropathic pain. In addition to TRPV (Transient Receptor Potential Cation Channel Subfamily V) and TRPA (Transient Receptor Potential Cation Channel Subfamily A) receptors, the excitatory neurotransmitter Glutamate and its receptors, including NMDA, are also related to neuropathic pain. Inhibition of any of these factors can result in a reduction of nociceptive pain.

2. MANAGEMENT OF NEUROPATHIC PAIN

The transmission of pain occurs through synaptic connections between first and second-order neurons, which results in the suppression of inhibitory synaptic connections. While non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used to treat pain, they remain ineffective in treating neuropathic pain. Currently, treatment of neuropathic pain is limited to medications such as Gabapentin, Pregabalin, Lidocaine, Bupivacaine, Lacosamide, Carbamazepine, Eslicarbazepine, Lamotrigine, Morphine, Hydromorphone, Oxycodone, and Bupropion. Fig. **1** [7].



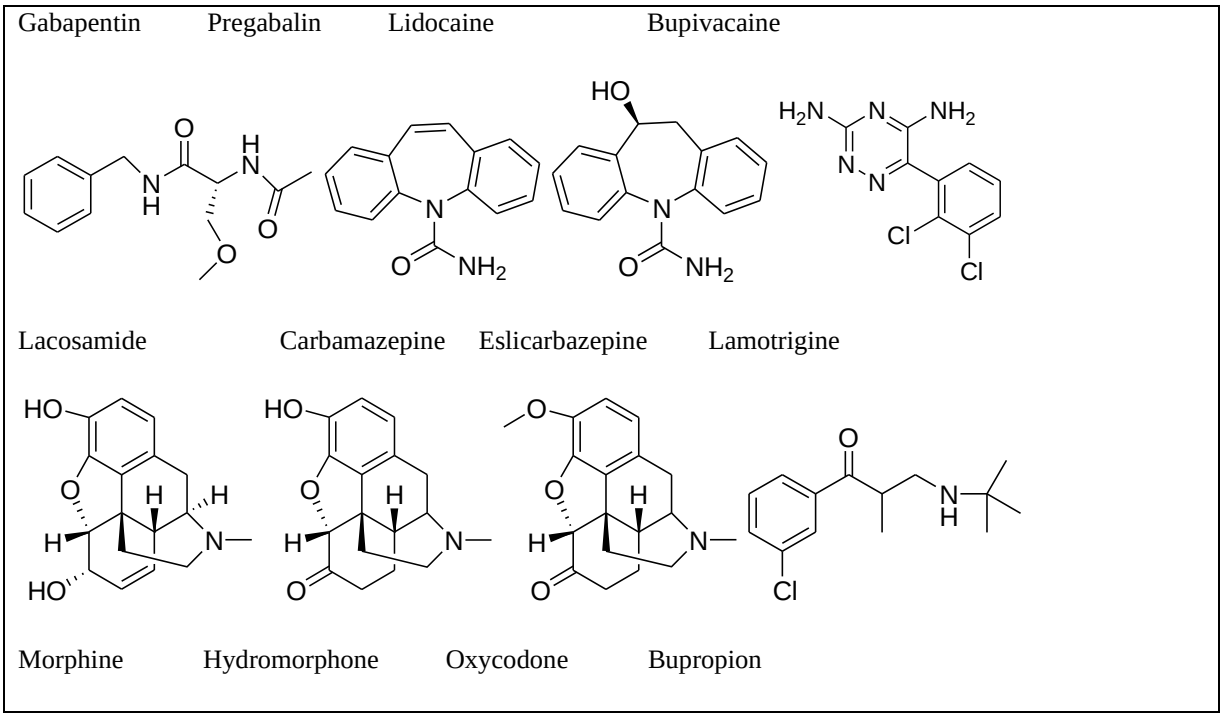


Figure. (**1).** Pharmacotherapy for the Neuropathic Pain

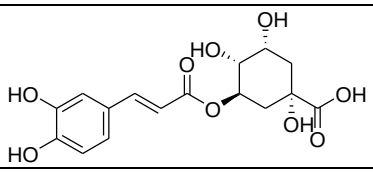
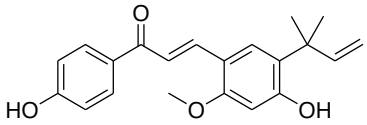
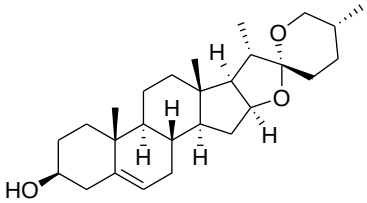
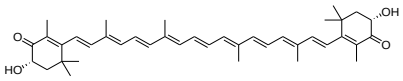
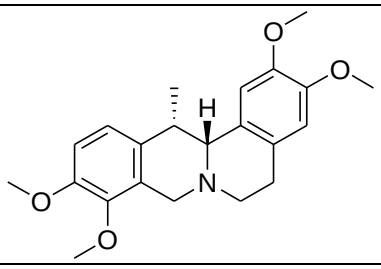
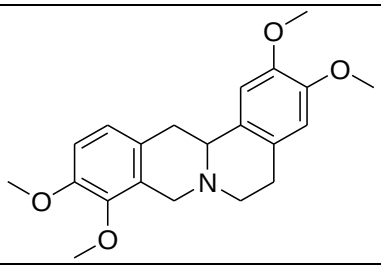
Pregabalin and gabapentin, derivatives of gamma-aminobutyric acid (GABA) truss with alpha-2/delta-1 subunit of voltage-gated calcium channels in the brain and spinal cord indicated for analgesic, anxiolytic and anticonvulsant activity. Lidocaine and Bupivacaine, which are voltage-gated sodium channel blockers, are exploited as local anesthetics for treating post-herpetic neuralgia and allodynia either alone or in combination with neuropathic pain. Lacosamide, another sodium channel blocker, is an anticonvulsant medication used for neuropathic pain management and is presently undergoing clinical trials. Carbamazepine, eslicarbazepine, and lamotrigine are other anticonvulsant medications that work by blocking voltage-gated sodium channels. Opioids like morphine, oxymorphone, and hydrocodone bind to the kappa, delta and mu opioid receptors found in the brain, spinal cord, and other nerve endings, resulting in agonistic effects that alleviate pain. Bupropion, an antidepressant, is a norepinephrine and dopamine reuptake inhibitor employed in neuropathic pain medication. [7].

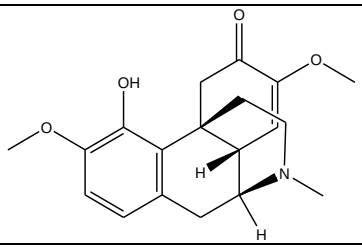
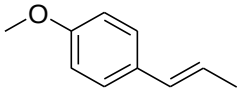
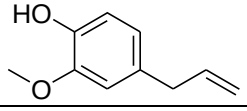
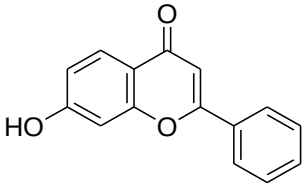
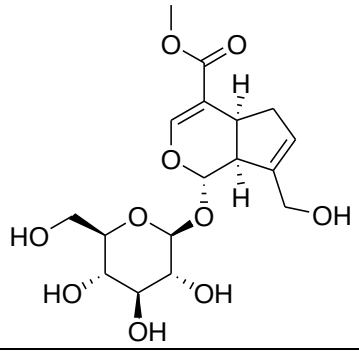
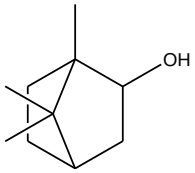
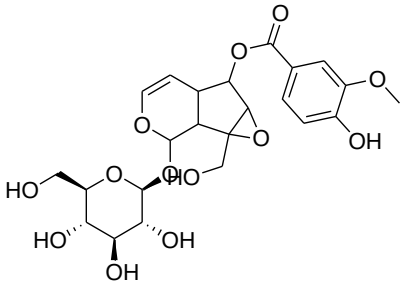
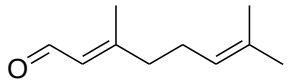
The primary hurdle in utilizing synthetic drugs to alleviate neuropathic pain lies in their potential for eliciting withdrawal symptoms that present as complex manifestations of restlessness, headaches, hyperhidrosis, nausea, anxiety, and diarrhea [8]. As such, research efforts are actively exploring alternative therapeutic strategies that offer improved safety and efficacy. Medicinal plants have emerged as a promising avenue for addressing neuropathic pain, as they have exhibited minimal adverse effects. The current review underscores the use of plant extracts and isolated compounds, as substantiated by their efficacy in treating neuropathic pain as demonstrated through various screening models.

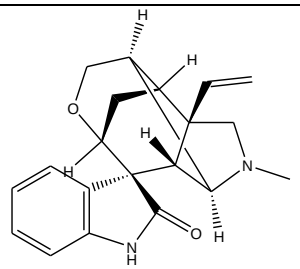
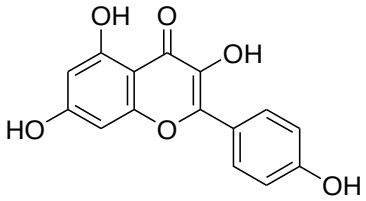
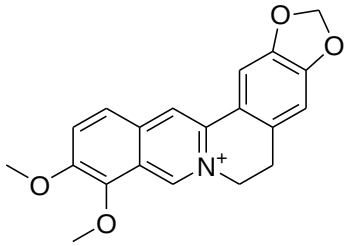
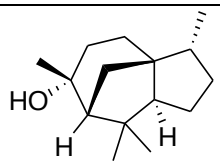
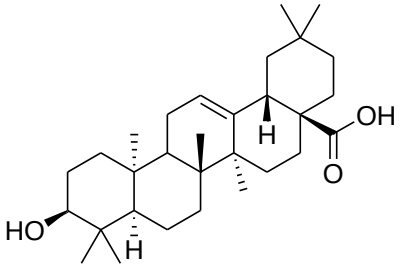
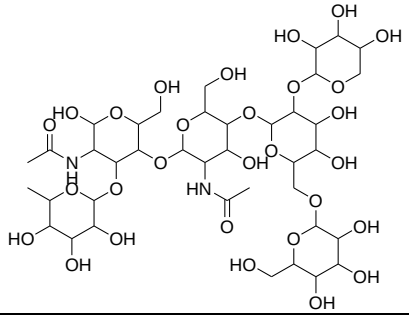
2.1. ***Isolated Phytocomponents to Combat the Neuropathic Pain***

The unparalleled chemical diversity of natural compounds has rendered them a promising source for screening various pharmacological activities, leading to positive outcomes. Analytical phytochemical screening facilitates the isolation of specific molecules, yielding screening results that are more precise, accurate, and efficacious, with superior potency [9]. Table 1 depicts the isolated molecules, their corresponding chemical structures, the model utilized to assess their anti-neuropathic pain properties, and the mechanism of action of the phytoconstituents (Fig. 2).

Table: **1:** List of phyto-constituents with potential role in neuropathic pain**.**

Sl. No.	Name of compound	Structure of the compound	Screening model used	Mechanism of action	References
1.	Chloregenic acid		CCI injury to sciatic nerve	Antioxidant	[7-11]
2.	Licochalcone A		CCI injury to sciatic nerve	Suppressed p53 gene and reversed the expression of TNF-α, IL-1, and IL-6.	[12-13]
3.	Diosgenin		CCI injury to sciatic nerve	Inhibition of MAPK and NF-κB expression.	[14-15]
4.	Astaxanthin		Spinal nerve ligation	Inhibiting the activation of ERK1/2, NF-κB , p38 MAPK, p65 and activation of inflammatory response.	[16-17]
5.	Levocorydalmine (l-CDL)		Spontaneous pain, latency and paw withdrawal threshold	Inhibition of expression of TNF-α, CCR2, CCL2 and IL-1β	[18]
6.	Tetrahydropalmatine		Spared nerve injury model	inhibit inducible nitric oxide synthase (iNOS), p65 and pro-nociceptive mediators, phosphorylated MAPKs	[19-20]

7.	Sinomenine		Formalin-induced paw oedema	Inhibition of voltage gated sodium channel	[21-22]
8.	Anethole		CCI induced paw oedema	Suppression of tumor necrosis factor alpha (TNF-α), interleukin (IL-6, and IL-1β), and up-regulated the anti-inflammatory cytokine (IL-10)	[23]
9.	Eugenol		Acrylamide neuropathy model	Inhibition of ROS, malondialdehyde and NO	[24-25]
10.	7-Hydroxyflavone		Carrageenan-induced paw	IL-1β , TNF-α, IL-6 and NF-κB, COX-2 and 5-LOX	[26-27]
11.	Geniposide		Chronic constriction injury (CCI) model	Inhibiting EGRF/PI3K/AKT pathway and also mainly Calcium signaling pathway	[28-29]
12.	Borneol		Xenopus oocytes and neurons cultured from trigeminal ganglia	Inhibits TRPA1 mediated cationic currents	[30-31]
13.	Picroside II		CCI induced model	Suppression of IL-1β, TNF-α, IL-6 and suppressed the NF-κB pathway	[32-33]
14.	Citral		Mechanical allodynia and partial ligation of sciatic nerve models	Suppression of cytokines and tumor necrosis factor	[34-35]

15.	Gelsemine		Mechanical allodynia	Suppression of interleukin-1β (IL-1β & 6), and Tumor necrosis factor-α (TNF-α)	[36-37]
16.	Kaempferol		CCI injury	Suppression of proinflammatory cytokines	[38-39]
17.	Berberine		Nociceptive inflammatory pain response induced by cisplatin	Decreased expression of NF-κB, NGF, IL-and TNF-α	[40-41]
18.	Cedrol		CCI of sciatic nerve	Decrease levels of TNF-α and IL-6	[42-43]
19.	Oleonolic acid		Peripheral nerve injury model	Activation of TLR4-NF-κB pathway	[44]
20.	Bromelain		Thermal hyperalgesic and mechanical allodynia and nerve ligation	Decrease in enzyme GSH and SOD, also decrease in NrF-1 and NrF-2	[45-46]

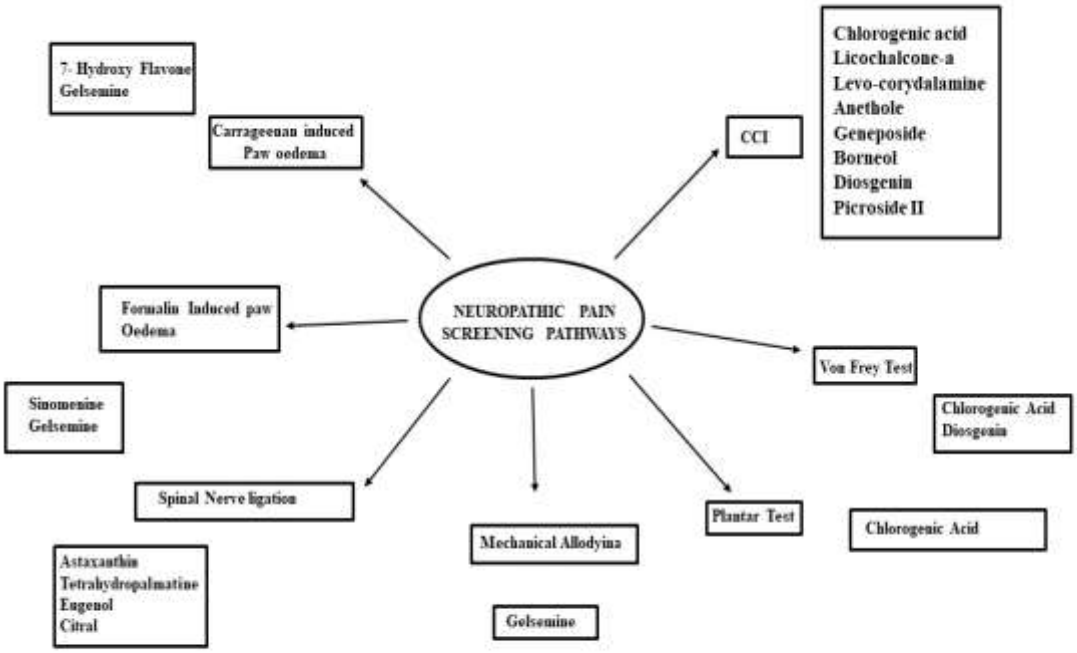


Figure **(2).** Screening models of neuropathic pain inclusive of phytocomponents.

2.1.1. ***Chlorogenic Acid***

Chlorogenic acid, a polyphenol compound derived from plants such as apples and pears, is also present in vegetables like tomatoes, carrots, and sweet potatoes. Additionally, variable amounts of this acid are found in wine, olive oil, and coffee [7,8]. Chlorogenic acid has exhibited a wide range of activities, including neuroprotective, antioxidant, anti-inflammatory, antibacterial, analgesic, anticancer, hepatoprotective and antihistaminic effects. Polyphenol-rich diets have been established to possess antinociceptive properties, with a moderate impact on inflammatory pain. To evaluate its potential as a neuropathic pain treatment, chronic constriction injury (CCI) was induced in male Sprague Dawley rats by occluding the sciatic nerve [9]. Chlorogenic acid demonstrated pain relief in CCI by exerting its antioxidant and anti-inflammatory activities. In the cold plate test, plantar test and electronic von Frey test a preliminary nociceptive activity was observed at intrathecal doses ranging from 0.5 to 2mg/kg [10]. The study suggests that chlorogenic acid may be useful initially in mitigating mechanical and cold hyperalgesia, and higher doses may impact motor performance via the activation of GABAergic transmission in the spinal cord [11].

2.1.2. ***Licochalcone****-A*

Chalcones, which contain polyphenols, have demonstrated their potential as lead compounds for treating various diseases. Licochalcone-A, a by-product isolated from the roots of *Glycyrrhiza inflata*, has shown efficacy in treating numerous conditions such as tumors, angiogenesis, parasitic infections, antioxidant activity, bacterial infections, and more [12]. The nerve pain assessment was impersonated in rats using the chronic constriction injury model. The screening was performed twice daily at 1.25, 2.5, and 5.0 mg/kg i.p., and the mechanical withdrawal threshold and thermal withdrawal latency was measured. To evaluate its effectiveness against neuropathic pain, ELISA, Western blot, and Immunofluorescence analytical methods were utilized to assess lumbar spinal cord enlargement. Dose-dependent inhibition and reduction of p53, interleukin-6 ,tumor necrosis factor-α and interleukin-1 were also observed, which supports its usage in ameliorating neuropathic pain [13].

2.1.3. *Diosgenin*

Diosgenin, a derivative of hydrolyzed acids and bases, and steroidal saponin, have been extensively isolated from the tubers of Dioscorea and Solanum species [14]. Diosgenin has demonstrated efficacy in treating cancer, diabetes, inflammation, and atherosclerosis, as well as neuropathic pain and neuroprotection. Neuropathic pain activity was assessed in Sprague Dawley rats exhibiting allodynia by quantifying the levels of inflammatory mediators associated with chronic constriction injury. The rats were treated with graded doses of 10mg/kg, 20mg/kg and 40mg/kg, i.p. daily for two weeks. Mechanically induced pain was measured exploiting von frey filament by ascertaining paw volume . Western blotting and ELISA techniques were exercised to assess IL-2, TNF-α and IL-1β. Diosgenin was found to reduce the quantity of inflammatory markers that amplified due to chronic constriction injury via activation of nuclear factor (NF-κB) and phosphorylated-p38 mitogen-activated protein kinase (MAPK) [15].

2.1.4. *Astaxanthin*

Astaxanthin is a carotenoid pigment that is naturally found in plants such as *Haematococcus pluvialis, Chlorella zofingiensis, Chlorococcum, and Phaffiarhodozyma*. It can also be commercially produced by cultivating microalgae and fungi from crustaceans, salmonids, and birds, as well as from seafood industry waste [16]. Astaxanthin has demonstrated various beneficial effects, including antioxidant, antitumor, neuroprotective, anti-aging, atherosclerotic, and pain-relieving activities for neuropathic pain.

In vivo assessment of neuropathic pain was performed on BV2 microglial and PC12 cell lines. These cells were pretreated with Astaxanthin and sub cultured in media and nutrients. Subsequently, spinal nerve ligation was induced at L5 spinal nerve using silk thread. Before the surgical procedure, behavioral testing was conducted to evaluate mechanical allodynia and paw withdrawal response. Western blotting was utilized to assess the levels of various inflammatory intermediaries, such as IL-1β, IL-4, IL-10, TNF-α, IL-6, and IL-17. It was found that Astaxanthin reduced the levels of these intermediaries. Moreover, Astaxanthin also inhibited the phosphorylation of

p38 mitogen-activated protein kinase (p38 MAPK), extracellular signal-regulated kinase (ERK) and nuclear factor-κB (NF-κB) P65, which play crucial roles in the neuropathic pain pathway [17].

2.1.5. *Levo-Corydalmine*

l-CDL, a compound derived from *Corydalis yanhusuo* and commonly consumed as Chinese medicine traditionally for cancer-related pain, has been shown to possess analgesic properties for treating neuropathy-associated pain. The activity of l-CDL on neuropathic pain was assessed by measuring the pain withdrawal threshold. In vivo and in vitro evaluation of the expression of TNF-α, IL-1β, CCL-2, and CCR2 was performed using RT-PCR, Western blotting, and ELISA techniques. The down-regulation of the CCL-2 and CCR-2 genes by l-CDL resulted in the inhibition of TNF-α and IL-1β, thus providing pain relief. These findings suggest that l-CDL could be a promising therapeutic option for managing neuropathic pain. [18].

2.1.6. *Tetrahydropalmatine*

Tetrahydro palmatine is a tetrahydroproberineisoquinoline alkaloid that is extracted from plants such as *Stephania Epigaea, Corydalis yanhusuo, and Phellodendron chinense* [19]. In order to study its effects on neuropathic pain, researchers used the spared nerve injury model. The drug was found to reduce mechanical hyperalgesia and cold allodynia, both of which are associated with nerve injury. The administration of tetrahydro palmatine through intraperitoneal injection decreased the activity of the nitric oxide synthase enzyme and subsequently reduced the expression of intermediate molecules like IL-1β. Further exploration using Western blotting and immunofluorescence techniques revealed that the drug also controlled the expression of iNOS, p65, IL-1β and phosphorylated MAPKs, all of which contribute to the development of neuropathic pain [20].

2.1.7. *Sinomenine*

Sinomenine is an alkaloid obtained from the plant *Sinomenium acutum*, which has lengthy use as medicine traditionally in treating rheumatic arthritis, neuralgia, and analgesia [21]. To assess its effects on neuropathic pain, researchers used the formalin-induced paw edema model. They observed a decrease in licking behavior at a dose of 50mg/kg administered intraperitoneally, and the drug was found to increase the pain threshold. Additionally, dose-dependent inhibition of voltage-gated sodium channels was observed. The outcome suggest that sinomenine, potential as peripheral analgesic but may have limited use in other forms of pain management [22].

2.1.8. *Anethole*

Anethole is an aromatic compound with a phenylpropene nucleus that is commonly used as a flavoring agent and is extracted from plants such as anise, fennel, liquorice, magnolia blossoms, and star anise. The isolated component has been found to exhibit anticancer, analgesic, anti-inflammatory, antifungal, genotoxic, antimicrobial, and hepatotoxic activity. To assess its effects on neuropathic pain, researchers used a chronic constriction injury model in mice. The drug was administered intra-gastrically at doses of 125, 250, and 500 mg/kg continuously for seven days, followed by a surgical procedure. Behavioral symptoms were measured for 0, 7, 8, 10, 12, and 14 days after

surgery, and the expression of inflammatory cytokines was examined using Western blot and immunofluorescence methods [23].

2.1.9. *Eugenol*

Eugenol, commonly known as clove oil, is an aromatic oil extracted from cloves, as well as in small amounts from other plants such as basil, cinnamon, lemon balm, and nutmeg [24]. It has a yellow color and a strong odor. Eugenol has been extensively studied for its therapeutic properties, including its ability to treat bacterial infections, exhibit antioxidant and antiaflatoxigenic activity, induce apoptosis, display antiproliferative properties, act as an antipyretic and antianaphylactic agent, exhibit anti-inflammatory and anthelminthic activity, and more. Researchers used the acrylamide neuropathy model to evaluate eugenol's effects on neuropathic pain. Acrylamide was instilled intraperitoneally at dose 50mg/kg for five weeks to induce neuropathic pain. Reactive oxygen species (ROS), nitric oxide and monoaldehyde levels were measured in both the sciatic nerve and brain. The drug also inhibited calcium rise and acetylcholinesterase activity caused by acrylamide. The expression of enzymes was found to be reduced by estimating the biomarkers [25].

2.1.10. *7-Hydroxy Flavone*

7-hydroxy flavones were extracted from the leaves of *Avicennia officinalis* using methanol [26]. These flavones possess antioxidant, anticancer, and anti-nociceptive properties. The anti-nociceptive activity was evaluated by inducing thermal and chemical nociception through carrageenan-induced paw edema. The mediators involved were assessed using RT-PCR, and in vitro cyclooxygenase and lipoxygenase inhibitory assays were conducted. Hydroxy flavone showed a dose reliant inhibition of cyclooxygenase (COX) and lipoxygenase (LOX) and demonstrated efficacy in inhibiting neuropathic pain caused by carrageenan-induced paw edema. Additionally, it reduced the expression of TNF-α, COX-2, IL-6 &1β, NF-κB, and 5-Lipoxygenase, pro-inflammatory mediators which are typically upregulated following drug administration. Thus, it has the potential as a treatment for chemically-induced allodynia [27].

2.1.11. *Geniposide*

Geniposide, a bioactive compound present in around 40 varieties of natural herbal plants, exhibits several pharmacological effects such as analgesic, anti-inflammatory, anti-Alzheimer's, antithrombotic, hepatoprotective, and neurotrophic properties [28]. In the study, the potential of geniposide to alleviate neuropathic pain was investigated using CCI (chronic constriction injury). The mechanism of action was found to be mediated through the inhibition of the EGRF/PI3K/AKT pathway, primarily by targeting the calcium signaling pathway [29].

2.1.12. *Borneol*

Borneol is a terpenoid alcohol extracted from Artemisia, Blumea, and Kaempferia, which have been traditionally used in medicine [30]. The extract has demonstrated efficacy in treating various conditions such as algesia, nociceptive pain, fungal and bacterial infections, thrombolysis, anticoagulation, and anti-cerebral ischemia. In the study, the potential of borneol to alleviate neuropathic pain was evaluated by targeting transient receptor potential

A1 (TRPA1). Borneol was found to inhibit mustard oil-induced selective activation of TRPA1 receptors, and the inhibition was dose-dependent. The compound was able to inhibit TRPA1-linked cationic currents at millimolar concentrations (IC50 0.3 mM) in heterologous systems such as Xenopus oocytes and cultured trigeminal ganglia nerves [31].

2.1.13. *Picroside II*

Picroside is an economically important compound obtained from the perennial plant *Picrorhiza scrophulariiflora* Pennell [32]. As an iridoid glycoside, this plant possessing antioxidant, anti-inflammatory, hepatoprotective, anti-metastatic and anti-angiogenic activities. Nociceptive pain assessment was performed using thermal hyperalgesia and chronic constriction injury (CCI)-induced mechanical allodynia along with the expression of inflammatory mediators NF-κB, IL-1β & 6 and TNF-α. Intraperitoneal administration of Picroside II was found to reduce the expression of these mediators, indicating its efficacy in treating neuropathic pain. Moreover, the drug also inhibits the phosphorylation of NF-κB in astrocytes [33].

2.1.14. *Citral*

Citral is an acyclic monoterpenoid composed of two isoprene units and is commonly extracted from various plant oils due to its strong aroma. It is widely used in the synthesis of vitamin A, lycopene, ionone, and methyl ionone [34]. The isolated molecule has proven antibacterial, antifungal, anti-inflammatory, anticancer and anti-nociceptive activities. In this study, the efficacy of citral in alleviating neuropathic pain was evaluated using mechanical allodynia and partial sciatic nerve injury models. The drug was found to act on TRPV1 and 5-HT2 (5-Hydroxy Tryptamine) serotonin receptors, leading to the inhibition of cytokines and TNF-α[35].

2.1.15. *Gelsemine*

Gelsemine is a monoterpenoid type of indole alkaloid isolated from *Gelsemine sempervirens* extracts [36]. Although its activity is not well established, it has been shown to possess neuroprotective, anxiolytic, neuropathic pain-alleviating, and nephroprotective properties. In this study, the efficacy of gelsemine in alleviating neuropathic pain was evaluated using mechanically induced allodynia. Western blotting technique is employed in evaluating the mediators like TNF- α, IL-6 & 1β. Gelsemine was found to reduce the expression of these mediators, and there was also a decrease in the phosphorylation of tau protein (Tubulin-associated protein) in brain cells [37].

2.1.16. *Kaempferol*

Kaempferol is a natural flavone and polyphenolic compound that is found in fruits and vegetables and has a yellow color [38]. The evidenced activities include anticancer, anti-inflammatory, osteoprotective, antiatherogenic, antitumor, antioxidant, antimicrobial, and hypoglycemic properties. The compound's neuropathic pain-relieving properties were appraised using the chronic constriction injury (CCI) model. The levels of certain mediators were analyzed using immunofluorescence and western blotting techniques. The findings disclosed that kaempferol inhibits the activation of TLR4/NF-κB pathways in neuropathic pain and diminishes the levels of IL-1β & 6, TNF-α,

LPS and PGE2 which are mediators. In addition kaempferol also proved its efficiency in inhibiting p38 MAPK, JNK and ERK that play a pivot role in synthesis of inflammatory intermediaries[39].

2.1.17. *Berberine*

Berberine, a benzylisoquinoline alkaloid extracted from plants of the Berberidaceae family, possesses medicinal properties widely used to manage various conditions such as cardiovascular diseases, type-2 diabetes, anti-microbial and anti-cancer effects, Alzheimer's disease, antiviral and giardiasis treatments and hypertension [40]. Its neuropathic property is screened using chemotherapy-induced chronic constriction injury focusing on TRPV1 receptors. The parameters released were estimated using western blotting, immunofluorescence, and ELISA. The study found that Berberine exhibited a dose-dependent decline in NF-κB, NGF (Nuclear Growth factor), IL-1β& 6, and TNF-α. Additionally, Berberine was observed to inhibit the pro-activation of JNK/p38 MAPK/ERK phosphorylation. [41].

2.1.18. *Cedrol*

Cedrol is a sesquiterpene alcohol commonly found in Cupressus plants of the Cupressaceae family. The drug exhibits a variety of activities, including immunomodulatory, fungistatic, analgesic, anti-inflammatory, sedative, hair growth-promoting, antiarthritic, and antinociceptive properties [42]. Neuropathic pain is assessed using the chronic constriction injury model. Mechanical and thermal hypersensitivity tests are performed using von Frey filaments, radiant heat, and acetone drops. Inflammatory mediators such as IL-6 & TNF- α are identified and quantified in the L4-L6 region. A dose-reliant decline in the mediator expression is observed. [43]

2.1.19. *Oleanolic acid*

Oleanolic acid, a naturally occurring pentacyclic compound present in edible plants, possesses multiple pharmacological properties such as anti-inflammatory, antiviral, antidiabetic, antiglycative, hepatotoxic, antioxidant, and antinociceptive effects. Its potential to alleviate neuropathic pain is evaluated using mechanical and chemical-induced allodynia and spinal nerve ligation models. ELISA and western blotting techniques are used to measure the quantities of cytokines namely IL-6 & 1β, and TNF-α, at L-4 and L-6 vertebrae. Administration of oleanolic acid is observed to downregulate the TLR4-NF-κB process in microglia, ensuing a reduction in the activation of proinflammatory mediators [44].

2.1.20. *Bromelain*

Bromelain is a proteolytic enzyme derived from pineapples that has been traditionally used as a medicinal remedy. It is frequently employed in cosmetic and topical applications [45]. Bromelain has various therapeutic properties, including anti-inflammatory, analgesic, neuropathic pain-relieving, anticancer, antiulcerogenic, proteolytic, and immunogenic effects. The neuropathic pain-alleviating property of bromelain is evaluated using mechanical and thermal allodynia tests, as well as a sciatic nerve ligation model. Bromelain has been shown to activate the expression of nuclear transcription factors (NrF-1 &2), that intensify the antioxidant defense mechanism and

decrease stress. The levels of enzymes such as GSH (y-l-Glutamyl-l-Cysteinyl-Glycine) and SOD (Superoxide Dismutase) are estimated to assess the efficacy of bromelain in alleviating neuropathic pain [46].

3. PLANT EXTRACTS FOR NEUROPATHIC PAIN

A range of plant extracts have exhibited efficacy in the treatment of neuropathic pain by virtue of their diverse range of constituents that are capable of inhibiting multiple mediators of this type of pain. The presence of multiple bioactive components in these extracts is the primary factor behind their ability to treat various illnesses. To achieve more specific and targeted effects, it is necessary to isolate and screen all of the active elements present.

3.1. *Gastrodia elata*

Gastrodia elata Blume, popular as Tianma belonging to the Orchidaceae family, is a habitual Chinese herb, mentioned in Shen Nong's Herbal Classic for many years. It is widely used as a remedy for various conditions, including headaches, neuralgia, epilepsy, rheumatism, cramps, dizziness, and neurological diseases [47]. The primary bioactive compounds found in *G. elata* are β-sitosterol, gastrodin, parishin, 4-hydroxybenzyl alcohol, and polysaccharides. The phytoconstituents are evidenced for analgesic, antihypertensive, antiepileptic, and neuroprotective activities. *G. elata* polysaccharides also evidenced for anticancer, immunomodulatory, antivirus, antioxidant, anti-osteoporotic activities [48].

Studies have shown that *G. elata* polysaccharides exhibit a neuroprotective effect against corticosterone-induced apoptosis in PC12 cells. The polysaccharides inhibit instigation of X-box binding protein 1, caspase 12 & 9, glucose-regulated protein and and DNA damage-inducible gene 153. [49]. Additionally, the therapeutic potential of *G. elata* polysaccharides was investigated in experimental rats with chemotherapy-induced peripheral neuropathy. The results indicate that the treatment increased the paw withdrawal threshold, restored sciatic nerve injury, and attenuated the cytokines namely IL-6,1β& 8, NF-κB, and TNF-α. Furthermore, the treatment down-regulated the mRNA levels of TNF-α and IL-6& 8, in the spinal cord, sciatic nerve, and dorsal root ganglion. The study concluded that *G. elata* polysaccharides evidenced nociceptive pain induced by chemotherapy inhibiting neuroinflammation. [50]

3.2. *Petersianthus macrocarpus*

Petersianthus macrocarpus (Lecythidaceae), commonly referred to as “Abing” in Cameroonian conventional medicine, with prolonged history of usage in West and Central Africa for treating various conditions such as malaria, hemorrhoids, headache, ulcer wounds, venereal diseases, and pain [51]. Studies on animal models have shown that extracts from *P.macrocarpusstem* bark can provide analgesic effects by impeding with opioid, capsaicin, and excitant amino acid pathways [52]. In addition, the bark extract from stem of *P. macrocarpus* exhibit antihyperalgesic and antioxidant activities on the complete Freund's adjuvant- stimulated chronic inflammatory pain model [53]. The ellagic acid and triterpenoid saponins Peter saponins III and IV insulated from the bark have been established for their analgesic activity. Moreover, the extract proven its efficiency in reducing spontaneous pain, tactile allodynia, cold allodynia and mechanical hyperalgesia in a rat model with chronic constriction injury (CCI)-

induced neuropathic pain [54,55]. The extracts also demonstrated a significant reduction in the nitric oxide and of TNF-α and NF-κB gene expression in the brain. The occlusion of peripheral calcium and sodium channels may be the mechanism behind the therapeutic effect of the extracts, since voltage-gated calcium and sodium channels play a trivial role in the generation of spontaneous pain [56].

3.3. *Lawsonia inermis*

Lawsonia inermis, universally acknowledged as henna from the family Lythraceae , has been used popularly in treating varied conditions such as fever, pain, wounds, hair and skin problems, and hemi-cranial headaches [57]. Henna is well-known for its diverse biological activities, including anti-fungal, anti-oxidant, antibacterial, anti-inflammatory, antipyretic, analgesic, and immunomodulatory effects, as well as other pharmacological activities such as virucidal, antiparasitic, anticancer, hepatoprotective, anthelminthic, and anti-oxidant effects. Numerous phytoconstituents from different classes have been identified from *Lawsonia inermis*, with coumarins, flavonoids, and naphthoquinones being the most common compounds, along with gallic acid, tannic acid, alpha- and beta-ionone. Among these, the major phytoconstituent is Lawsone (2-hydroxy-1,4 naphthoquinone) [58].

Extracts from *Lawsonia inermis* leaves and bark have been shown to exhibit analgesic effects in acetic acid-induced pain and anti-arthritic activity in animal models. The anti-inflammatory molecules obtained from the leaves and stems include luteolin, Lawsochylin A, 4-hydroxy-α-tetralone, 2-butoxysuccinic acid, apigenin, and lawsonaphthoate A. The antinociceptive effect of *Lawsonia inermis* on a chronic constriction injury (CCI)-induced neuropathic pain model revealed that a 14-day intraperitoneal administration improved behavioral changes in rats and suppressed the expression of inflammatory cytokines (IL-1β & TNF-α). Additionally, it enhanced oxidative markers (Malandialdehyde) and overall thiol levels in the medulla spinalis [59].

3.4. *Sedum Lineare Thunb*

Sedum lineare, a member of the Crassulaceae family commonly known as Chinese parsley, used conventionally in Chinese medication to remedy liver-related ailments such as jaundice, hepatitis, and liver injury. Extracts of the plant were prepared using alcohol as a solvent with phytoconstituents namely oleanene triterpenes δ-amyrone, Olean-13(18)-ene-3,12,19-trione and δ-amyrine acetate. These compounds were shown to inhibit the release of NO and TNF-α, which are responsible for causing macrophage inflammation [60]. The plant extract was evaluated for its analgesic effects using the spared nerve injury model, and improvements in mechanical hypersensitivity and a reduction in TRAF6, TNF-α, HMGB1, TRL4, and IL-1β levels were observed. The plant extract also significantly reduced IKK phosphorylation and NF-κB p65 expression, while apparently increasing IκB and IL-10 protein expression in the spinal cord. The work prooved that the extracts potentially suppress the NF-κB/TLR4 spinal signaling pathway, activate microglia by regulating the balance between pro- and anti-inflammatory factors in spinal cord [61].

3.5. *Thymus* species

Thymus algeriensis and *Thymus fontanesii*, members from family Lamiaceae, allocated extensively in the Mediterranean region. *T. algeriensis* has been utilized in traditional medication to treat benign prostate hypertrophy, respiratory problems, gastrointestinal disorders, and to prevent miscarriage. *T. fontanesii* is used as a stabilizer in food to treat various gastrointestinal diseases. The extracts from these plants possess analgesic, anti-inflammatory, antioxidant, and antipyretic properties. The extracts contain several secondary metabolites, such as flavones, flavanols, luteolin, quercetin, apigenin, and phenolic acids like caffeic, rosmarinic, and phloretic acids [62]. Interestingly, studies have shown that Thymus species, including *T. algeriensis*, have acetylcholinesterase inhibitory activity, and possess antioxidant properties that protect against oxidative stress induced by UVA radiation in HaCaT cells. In addition, the extracts from these plants protect against chronic constriction injury in rats by activating the Nrf-2 pathway, and inhibiting NOX-1, inducible NOS, inflammatory mediators, lipoxygenase, COX-2, Nuclear Factor-κB, PGE2, and TNF-α. These extracts also improve detrimental operational changes in the sciatic nerve and brainstem. The experimental results suggest that the protective effects of these extracts are mediated partially through the lessening of oxidative stress and the inhibition of inflammation and nerve apoptosis [63].

3. 6. *Symplocos chinensis*

Symplocos chinensis is a widely used herb for treating malaria, nephritis, tumefaction, oleanolic acid and botulin [64]. Leaves and roots extracts of the plant contain three ursane-type triterpenes namely corosolic acid, 2α,3α,19α,23-tetrahydroxyurs-12-en-28-oic acid and ursolic acid. They found to inhibit protein tyrosine phosphatase, which can be useful in managing diabetes type 2, including obesity. oxo-19α,23,24-trihydroxyurs-12-en-28-oic acid and 2β,3 β,19α,24-tetrahydroxy-23-norurs-12-en-28-oic acid were also isolated from the roots of *Symplocos chinensis* and exhibited toxicity with B16 and BGC-823 cells [65]. The hypolipidemic activity of the leaves was investigated against hyperlipidemic rats and the extracts were found to reduce total cholesterol, triglycerides, and lipoproteins [66]. The aqueous extract and semi-synthesized compounds from the leaves showed antinociceptive effects against surgical injury to the nerve in a chronic manner and also exhibited antinociception against the vincristine-induced pain model. The isolated 5-hydroxymethylfurfural was recognized as an effective compound, and among the various derivatives synthesized, 5-succinoxy methylfurfural showed the best results in screening neuropathic pain [67].

3.7. *Lueheadivaricata* Mart

Luehea divaricata, a shrub from family Malvaceae and commonly identified as “açoita-cavalo”, has been traditionally used by various indigenous communities in Brazil to treat various conditions including dysentery, rheumatism, skin lesions, leukorrhea, tumors, and bronchitis [68]. Recent studies have shown that the leaf extracts of this plant contain numerous antioxidant compounds, while exhibiting no mutagenic potential or acute toxicity in animals [69]. Furthermore, the hydroalcoholic extract derived from the bark of the plant has been found to alleviate inflammatory pain in mice. The aqueous leaf extract has been found to possess antinociceptive properties against sciatic nerve injury in a chronic manner, with gabapentin being used as a standard. The extract also exhibits a high phenol content and excellent reducing capacity based on various assays. In animal models with chronic constriction injury, the extract increases the threshold of thermal and mechanical allodynia. Moreover, investigations conducted

to estimate the lipid hydroperoxide levels and antioxidant capacity in lumbosacral spinal cord and the wounded sciatic nerve segment tissues, hydrogen peroxide levels, superoxide anion levels and total thiol content in the spinal cord tissues have shown that the extract reduces the level of these antioxidant markers, indicating a correlation between the antioxidant capacity and the management of neuropathic pain [70].

3.8. *Crocus Sativus* L

Saffron, also known as *Crocus Sativus* of the Liliaceae family, is a perennial plant found all over the world. It has been used as an ancient medicine for various ailments such as depression, pain, asthma, sleep disorders, and cardiovascular diseases [71]. The leaf and flower parts of saffron contain numerous compounds including safranal, crocin, picrocrocin, crocetin, beta-carotene, lycopene, zaxatin, and vitamins like riboflavin and thiamine [72]. These compounds exhibit various pharmacological actions such as anti-inflammatory, antiepileptic, analgesic, anticancer, antioxidant, neuroprotective, anti-depressant, anti-microbial, sedative, and memory-enhancing effects [71].

Saffron has been proven effective in treating neuropathic pain, with safranal being the main active component, extracted using alcohol and water as solvents. The apical and lateral buds of saffron are reported to be prominent for the management of nociceptive pain and inflammation [73]. The efficiency of saffron in neutralizing allodynia-induced pain has been demonstrated using formalin, acetic acid, and carrageenan-induced paw edema, as well as neuropathic pain induced by sciatic chronic constriction [74,75,76]. The effectiveness of the tested compounds in diminishing neuropathic pain was dose-dependent, as assessed through von Frey filaments, acetone drop, and heat produced by radiant source methods at different time intervals post-surgery [71,77].

3.9. *Cassia artemisiodes*

Cassia plants are commonly found in tropical countries, including India. One of these plants is *Cassia artemisiodes* (Leguminosea), and its root bark contains several antioxidant compounds such as 1,1'-dihydroxy-3,3'-dimethyl-8,8'-dimethoxy-6,6'-O-bianthraquinone, 1-hydroxy-8-methoxy-3-ethylanthraquinone, 1,6-dihydroxy-8-methoxy-3-methylanthraquinone, 1,6,8-trihydroxy-3-methylanthraquinones and 1,8-dihydroxy-6-methoxy-3-methylanthraquinone [78]. Recently, research has focused on the potential of this plant in treating neuropathic pain. Screening for neuropathic pain involves inducing chemically-induced allodynia using carrageenan, histamine, and serotonin. Additionally, in silico screening has been performed, leading to the inhibition of COX-2 and 5-LOX. RT-PCR has also been used to confirm the activity of the extracts in inhibiting the activation of intermediaries like iNOS, TNF-α, IL-1β& 6 and COX-2. The extract has demonstrated significant potential in inhibiting the expression of mediators, particularly in the case of diabetes-induced neuropathic pain [79].

3.10. *Bauhinia brachycarpa*

Bauhinia brachycarpa, a flowering orchid of the subfamily Cercidoideae, is a Chinese ethnic plant known as Gui-Ding-Ba and Pi-Mi-Li, and is widely distributed across the globe. This plant is commonly used for managing bone-related pain and myalgia and has been studied for its antinociceptive and anticancer properties [80]. In animal models, the ethanolic extract of the plant's leaves demonstrated antinociceptive effects against both acetic acid-

induced peripheral inflammatory pain and central pain induced by a hot plate. The extract was also found to be effective against trigeminal neuralgia triggered by infraorbital nerve ligation. Mechanical and thermal-induced allodynia and ligation of the sciatic nerve were used to induce the nociceptive model in mice treated with standard pregabalin and doses of 250, 500, and 1000 mg/kg of the plant extract. ELISA and qPCR techniques were exercised to quantify the levels of IL-10, TNF-α, Iba-1, CD-16, CD206, Arg-1, IL-1β, and iNOS at the spinal cord. Results disclosed a considerable reduction in the levels of inflammatory mediators [81].

3.11. *Centella asiatica* L

Centella asiatica, a plant belonging to the Apiaceae family, has been used as a remedy for various ailments for thousands of years in Ayurveda. It is known for its ability to revitalize nerves and brain cells and to treat skin infections and wounds. The plant has been found effective in treating conditions such as syphilitic lesions, dysentery, and gastric ulcers. It is also used in the treatment of leprosy, lupus, varicose ulcers, eczema, psoriasis, fever, amenorrhea, and more. *Centella asiatica* has prooven antioxidant, anti-inflammatory and neuroprotective effects. The plant's primary active compounds are madecassoside and asiaticoside, while other compounds include brahmoside, brahminoside, isothankuniside, centelloside, phytosterols, flavonoids such as quercetin and kaempferol, and an alkaloid called hydrochotine [82]. The plant extract has been shown to work through established mechanisms such as 5-HT1A/1B receptors for migraine and dopaminergic neurons for neuroprotection. The extract has also been found to have a neurogenic effect mediated via ERK1/2 and Akt signaling pathways. The plant extract has demonstrated antioxidant properties by restraining peroxidation of lipids with simultaneous increase in catalase and superoxide dismutase in rats treated with rotenone. The extract has been shown to inhibit chronic infra-orbital nerve injury-induced allodynia by downregulating calcitonin gene-related peptides in a dose related manner. Additionally, the extract has been found to attenuate common carotid arteries occlusion-induced memory deficits [83].

3.12. *Thymus persicus*

Thymus persicus, a plant species endemic to Iran and belonging to the Lamiaceae family, is a highly aromatic herb used for cough , skin and intestinal diseases. It possesses various pharmacological properties, including bactericidal and insecticidal activities, anti-cancer effects, repellent and fumigant properties, antioxidant, anti-diabetic, anti-Alzheimer, and nociceptive activities. Thymol, limonene, carvacrol, 1-borneol, gamma-terpinene, alpha, and beta-pinene are the major constituents of T. persicus, along with pentacyclic triterpenoids such as betulinic acid, ursolic acid and oleanolic acid isolated from its aerial parts [84]. The plant extract was obtained using the hydro-distillation method and has been tested in formalin-induced paw edema model, with a focus on L-arginine/NO/cGMP/KATP channel signaling pathways and has been found to possess nociceptive properties by reducing pain signaling [85].

3.13. *Boesenbergia rotunda*

Boesenbergia rotunda is a curative herb, also known as “Chinese ginger and finger root”, belonging to the family Zingiberaceae. It is an annual crop that is primarily grown in China and West Malaysia and is used extensively as a condiment. In addition, the rhizomes of the plant are used as vegetables. The plant has proven its proficiency for anticancer, anti-inflammatory, cytotoxic, antioxidant, anti-ulcerogenic, colorectal cancer, hepatoprotective,

antibacterial, vasorelaxant and ameliorative properties. The plant's bioactive compounds include chalcone derivatives such as pinostrobin and pinocembrin, cardamonin, 2',6'-dihydroxy-4'-methoxychalcone, and (±) boesenbergin, as well as flavonoid derivatives such as 5,7,3′,4′-tetramethoxyflavone, 5-Hydroxy-7-methoxyflavanone, 5,7-dimethoxyflavanone, 5-hydroxy-3,7-dimethoxyflavone and 5,7,4′-trimethoxyflavone [86].

To evaluate the plant's potential in treating diabetic peripheral neuropathy, male SD rats were induced with the condition using streptozotocin (40mg/kg) and 30% fructose solution. The rats were then subjected to neuropathic pain assessments using hot plate, tail flick, and von frey apparatus to evaluate hyperalgesia in varied conditions with diabetes. The study also focused on pain associated with myelinated C fibers in diabetic animals, which was also evaluated through formalin and acetic acid-induced neuropathic pain models. The study observed a reduction in inflammatory mediators TNF-α and IL-1β during the nociceptive response [87].

3.14. *Ageratum conyzoides*

Ageratum conyzoides a herb belonging to the family Asteraceae , commonly known as “billy goat weed, chickweed, goat weed, white weed, and mentrasto”. The plant is rich in polyoxygenated flavonoids and has been proven for a wide range of beneficial activities namely anticoccidial, antihyperglycemic, antiaflatoxigenic, antioxidant, antiprotozoal, anti-inflammatory, antibacterial, anticancer, antifungal, antigonadotropic, and antiulcerogenic activities. The extract has terpenoids, alkaloids, chromenes, benzofurans, and flavonoids. The essential oils in plant extract include terpinene-4-ol, E-caryophyllene, bornyl acetate, γ-muroleno, α-muroleno, δ-cadinene, caryophyllene oxide, α-humulene, longifolene, and precocene I and II [88].

The plant's ability to alleviate neuropathic pain was evaluated using models that induce thermal and mechanical allodynia and chronic constriction injury. Extracts containing the essential oil components were found to be more effective in reducing neuropathic pain than extracts without these components. The anti-nociceptive properties of the plant extract were found to be similar to those of the standard drug pregabalin. Caryophyllene and longifolene, which are present in the plant's essential oil, are thought to act through opioid receptors to alleviate neuropathic pain. Caryophyllene is also believed to increase GABA levels in the spinal cord [89].

3.15. *Nauclea pobeguinii*

Genus Nauclea, which is from the family Rubiaceae and is innate to Africa, comprises seven species with a history of traditional medicinal use. These plants contain indoloquinolizidine alkaloids and have been shown to possess various properties such as anti-malarial, anti-bacterial, antiplasmodial, analgesic, anti-inflammatory, anti-arthritic, neuroprotective, genotoxic, antidiabetic, antitrypanosomal, and neuropathic pain properties. In vitro studies have demonstrated a reduction in COX and 5-LOX inflammatory mediators [90]. Formalin and Freund's adjuvant-induced inflammation models were used for *invitro* screening of analgesic effects. The aqueous and methanolic extracts at drench of 150 and 300 mg/kg were tested for neuropathic pain in diabetic rats induced by streptozotocin (200 mg/kg). The parameters evaluated included glucose levels in blood, animal weight, proinflammatory mediators, and sciatic nerve growth factors. The extracts demonstrated antinociceptive properties against various types of

allodynia. Prolonged administration of the extracts showed neuropathic pain properties by reducing levels of inflaming mediators such as NGF, TNF-α IGF and IL-1β & 6 [91].

4. NUTRACEUTICALS IN NEUROPATHIC PAIN

Neuropathic pain has gained widespread attention in recent years due to the adverse effects on neuronal function and comorbidities that accompany it. Reactive oxidative species has a crucial part in neuropathic pain. The majority of drugs work by neutralizing chemical mediators and oxidative radicals that contribute to the condition. However, oxidative radicals can also activate TRP receptors, which are key players in neuropathic pain.

A combination of nutraceuticals has demonstrated efficacy against neuropathic pain through various mechanisms. Curcumin, chlorogenic acid, hesperidin, linalool, naringenin, and papain function as antioxidants to neutralize neuropathic pain. Diosmin, dehydrocorybulbine, naringin, and alpha-terpineol, on the other hand, deactivate microglial cells to neutralize neuropathic pain.

Beta-caryophyllene, cannabidiol, alpha-terpineol, and zerumbone act by inhibiting calcium channel receptors in dorsal neurons. Dehydrocorybulbine and diosmin act by inhibiting dopamine D2 receptors. Hesperidin acts by inhibiting GABA receptors to neutralize neuropathic pain. Diosmin and hesperidin also inhibit opioid receptors in neutralizing neuropathic pain. Capsaicin, hecogenin acetate, naringin, and zerumbone inhibit TRP receptors to neutralize neuropathic pain. [92].

5. DOCKING BASED SCREENING OF PROMISING PHYTOCHEMICALS COMBATING NEUROPATHIC PAIN

Neuropathic pain is a significant concern in modern times, as existing synthetic drugs may have issues with resistance or toxicity. Therefore, people are increasingly relying on natural medicines in combination with synthetic drugs to address these complex problems. To identify phytocomponents that have a high affinity for pain mediator multitargets, structure-based docking simulations have been conducted. In silico high-throughput screening is a promising research area for screening drug molecules, as pharmacoinformatic software can be used to perform docking and calculate the binding energy of the ligand to specific targets. Docking simulations have been employed to screen various phyto components that have an affinity for neuropathic pain mediator targets, and the results are presented in Figure 3 and Table 2, which list the phyto ligands and their corresponding docking scores.

Table **2:** Table inclusive of *Insilico* Docking molecules with Binding Energies:

S.No	Molecule	Target	Binding Affinity (Kcal/mol)	Type of Interaction	Binding site Residues	Screening Model	Reference
1.	Chlorogenic Acid	Glutamate Receptor	-6.80	Vanderwaals, Electrostatic interaction	Val32, Glu33, Ala36, Glu37, Leu48	*Invitro, Insilico*	[93]
2.	Astaxanthin	NMDA	-5.332	Inhibitory	Fit into NR2B active	*Invitro,*	[94, 95]

		receptor			site	*Insilico, Invivo*	
3.	Zerumbone	Cannabinoid Receptor CB1	-7.80	H-Bond, Pi-Pi Bond,	Phe170, Phe174, His178, Phe189, Leu193, Val196,Pro269	*Insilico, Invivo*	[96]
		CB2	-9.40	H-Bond, Vander waals forces, Pi Interactions	Phe87, Phe91, Phe94, His95, Phe106, Val113, Phe183		
		PPAR α	-5.10	H-Bond, Pi-alkyl Interactions	Leu247, Leu254, Ile272, Cys275, Cys276, Val332, Ala333, Ile339		
		PPAR γ	-6.10	H-Bond, Pi-Pi bond, Pi-alkyl interactions	Cys285, Arg288, Ile326, Leu330, Leu333, Val339, Ile341, Met364		
4.	Aegeline	MAO-A	-10.06	H-Bond	Tyr407	*Insilico, Invivo*	[97]
		MAO-B	-10.09	H-Bond Π-π stacking	Gln206 Tyr398 Trp119		
5.	Icariin	NMDA	-12.646	H-Bond, Π- Π bond	Gln110, Ser132, Glu236, Phe114, Arg115, Phe176	*Insilico, Invivo*	[98]
		TRPV1	-4.892	H-Bond, Π-π bond	Arg114, Arg115, Asp150, Leu163,Arg211, Tyr199		
		N-type Ca Channel	-2.974	H-Bond	Lys57, Lys97, Glu115, Gln 315, Pro 412		
6.	C-Glycosyl Flavanoids	GABA	-7.10	Affinity prediction in terms of best fit	GABA P2X4	*Insilico*	[99]
7.	Papain	NMDA	9.80	H-Bond, Π- Π bond	GLn110,Ser132, Phe176. Tyr109, Arg115 and Glu106	*Insilico*	[100]
8.	Myricetin	Cox-1 A chain	-8.10	H-Bond	His388, Gln203, Thr212, Thr206, Phe210	*Insilico, Invivo*	[101]
		Cox-1 B chain	-9.83	H-Bond	Thr212, Glu454, His383, His207		

		Cox-2 A chain	-5.72	H-Bond	Gln289, Asn382, His468		
		Cox-2 B chain	-7.46	H-Bond	Thr212, Gln454, Asn382		
9.	Rutin	TNF-α	-5.31	H Bond Π- amide and π-alkyl interaction	Gly121, Gly122, Leu57, Leu94 Phe124	*Insilico*	[102]
10.	6-Methoxy Flavone	Cox-1	-6.8487	H-Bond, Arena-arena and Hydrophobin interaction	Ala199, Thr206, His207, Gln203, Met391, His388, His386, Asn382, Phe210	*Insilico, Invivo*	[103]
		Cox-2	-6.7441	Polar and H-Arena interaction	His214, Thr212, His388, His207, Lys211		
12.	Piperine	PPARG	-4.01	H-Bond	Lys367	*Invitro, Insilico,*	[104]
		NF-kB1	-3.72	H-Bond	Phe298	*Invivo*	

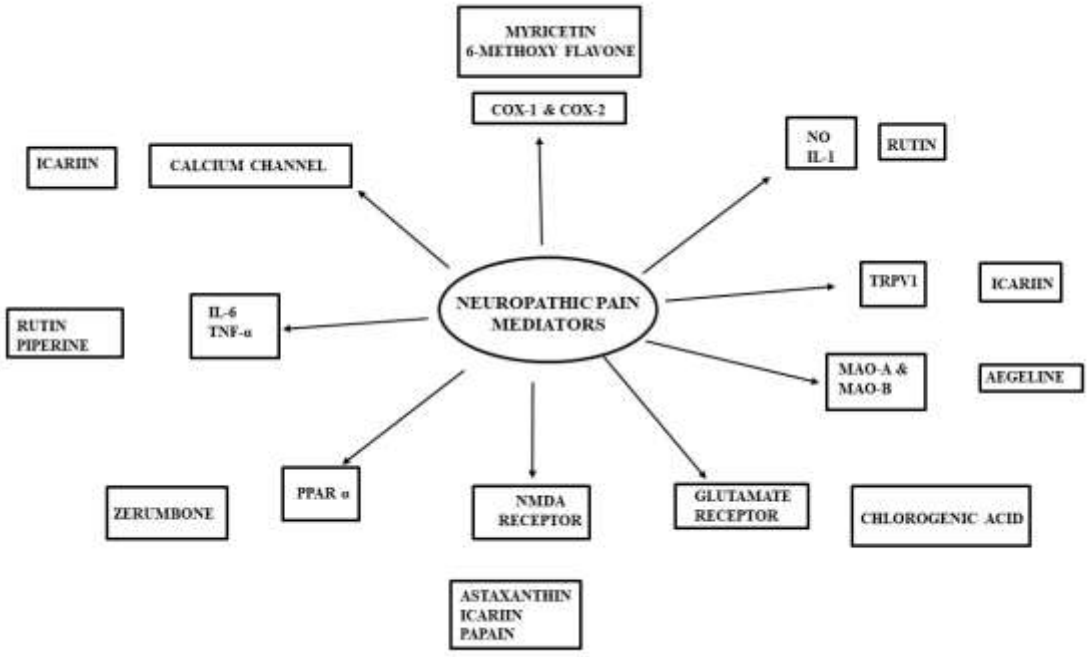


Figure (**3).** Screening of various phyto component having affinity towards neuropathic pain mediator targets utilizing docking simulation.

5.1. *Chlorogenic acid*

Essential phytometabolite, chlorogenic acid has been validated for antinociceptive activity by interacting with the AMPAR receptor, that controls excitatory synaptic signaling via GluA1. Surface plasmon resonance (SPR) research by Zhu et al. revealed that the component has a dissociation constant (KD) value of 496 M and direct binding affinity to GluA1. Using AutoDoc Tools v1.5.6 at central coordinates (13.746-x, 4.621-y, and 14.997-z). *In silico* docking was also performed to examine the expected binding score of the ligand chlorogenic acid towards the GluA1 active site. Numerous conformers have been produced and the binding complex's lowest binding affinity score obtained was -6.8 Kcal/mol. A hydrogen bonding interaction between the ligand and the protein was witnessed at Glu28 (glutamate), Gly29 (glycine), and Glu33. GROMACS v2019.3 was employed for molecular dynamics (MD) simulation for 90 ns. The simulation was set up with antagonistic ions present in complicated water molecules totaling 68,471 atoms. Root Mean Square Deviation (RMSD) simulations witnessed with a small fluctuation at 0.45 nm. RMSF (Root Mean Square Fluctuation) values at segments 15–23, 60–77, 115–130, and 144–182 demonstrated significant flexibility. The Rg (Radius of Gyration) number divulged the dynamic behavior of the receptor. The value was subpar for the first 10 nits before improving to 78 nits and then stabilizing. The simulation revealed that the hydrogen-bond interactions steadily increased. [93]

5.2. *Astaxanthin*

A marine medication entitled astaxanthin is examined for neuritis in *In vitro*, *In vivo* and *In silico*. *In vitro* examination was enacted by computing the diminution of lipopolysaccharides in C6 glial cells. Astaxanthin at dose of 5 and 10 micromoles downgraded inflammation by declining instigation of astrocytes. *In vivo* screening was accomplished by chronic constriction injury through mechanical and thermal hyperalgia devoting von frey anesthesiometer and Hargreave's apparatus. At 5mg/kg diminution and at dose 10mg/kg attenuation of thermal and mechanical hyperalgia was percieved.

In silico studies of Astaxanthin were accomplished with "Automated docking software Glide 5.0(Schrodinger-Maestro)" through X-ray crystallographic structure (PDB ID: 5EWJ) NMDA receptor. NMDA receptors in the dorsal horn is a key target for neuropathic pain. Docking interaction was observed at NR2B receptor protein. The G-Score and D-Scorefor Astaxanthin at NR2B receptor was -5.332 with an Epik state penalty of 0.00. [94,95]

5.3. *Zerumbone*

Zerumbone, a major constituent of *Zingiber zerumbet* was proved its proficiency against anticancer, immunomodulator, anti-inflammatory, antimutagenic, antibacterial, and so on. *Invivo* confirmation of activity is performed in chronic constriction injured mice employing vonfrey filament test and Hargreaves plantar test by pretreating the animal groups with CB1, CB2, PPARα and PPARγ receptor antagonists. Zerumbone at 10mg/kg showed efficient neuropathic pain activity with antagonist of CB1 receptor compared with CB2 receptor by activating potassium ion channel and suppressing N,P/Q-type calcium currents. The reasons behind the involvement of PPARα rather PPARγ in neuropathic pain may be due to its location at metabolic tissues and reticence of inflammatory mediators expression. Inspite of location of PPARγ receptor in adipocytes due to its rapid negative

feedback control in nociceptive pain transmission via CNS , its anatagonist they are employed as antihyperalgesic effects but less in compared with PPARα. The *Insilico* studies of zerumbone were premeditated with cannabinoid receptors and PPAR ALPHA are vital in neuropathic pain employing AutoDoc Veena. The binding energy obtained for cannabinoid CB1 receptor is -7.8 kcal/mol and for cannabinoid CB2 receptor is -9.4 kcal/mol. The binding energies obtained for binding with PPAR ALPHA is −5.1 Kcal/mol and for PPAR GAMMA is −6.1 Kcal/mol. Zumberone coordinates with CB1 receptor at Phe170, Phe174, His178, Phe189, Leu193, Val196, Pro269, with CB2 receptor at Phe87, Phe91, Phe94, His95, Phe106, Val113, Phe183, with PPAR α at Leu247, Leu254, Ile272, Cys275, Cys 276, Val332, Ala333, Ile339 and with PPAR γ at Cys285, Arg288, Ile326, Leu330, Leu333, Val339, Ile341, Met364. The molecule was evidenced Insilco and *Invivo* in treating neuropathic pain via cannabinoid and PPAR receptors [96].

5.4. *Aegeline*

Aegeline, a major constituent quarantined from leaves and fruits of the medicinal valued plant Aegle marmelos from south Asia origin. The plant has been exploited for hypoglycemic, anti-fungal, anti-pyretic, anti-proliferative, anti-bacterial, and anti-inflammatory activities. Aegeline has proven its efficiency *In silico* and *In vivo* by inhibiting the enzyme monoamine oxidase. *Invivo* neuropathic activity was compared with *Aegle marmelos* fruit extract and isolated compound aegeline. *Invivo* activity is performed in reserpinized (0.5mg/kg, s.c) mice measuring paw withdrawal threshold using Pressure application measurement, mechanical allodynia using Von-Frey apparatus and Forced swim test. The fruit extract at 200mg/kg dose and isolated aegeline at 10mg/kg elicited reserpine induced pain depression. *Insilico* docking performed with MAO-A, MAO-B and iNOS. Binding energy of a molecule with MAOA is -10.06 Kcal/mol, for MAO-B is -10.09 Kcal/mol and for iNOS is -31.54 Kcal/mol. Aegeline interacts with MAO-A with H-bond at Tyr407, with MAO-B H-bond at Glu206 and pi -pi interaction at Try398 and Trp119. It showed an efficient H-bond interaction with iNOS at Leu264 with Hydrogen bond. [97]

5.5. *Icariin*

A natural prenylated flavanol glycoside extracted from species Epimedium, a popular Chinese medicine extensively reputed as goat weed. *In vivo* pharmacological activity was exploited employing partial sciatic nerve injury model. Post ligation the groups are treated with 50 and 100mg/kg for 21 days followed by evaluation of inflammatory mediators. Dose dependent suppression of inflammatory mediators release is notified. *In silico* screening was executed at Dell precision T7610 Workstation employing Schrodinger suit 9.8. The interaction was done with TRP family receptor TRPV1, glutamate, an excitatory receptor NMDA and on calcium channel receptors. The binding targets used are TRPV1, NMDA, and N-Type Calcium channels. The docking score obtained for NMDA, TRPV1, and N-type Calcium Channel receptors is -12.646 Kcal/mol, -4.892 Kcal/mol, and -2.974 Kcal/mol. The drug exactly locks at Asp136, Ile133, and Ser132 with a Pie interaction at Try109. The binding sites match with the standard drugs . [98]

5.6. *C- Glycosyl Flavanoids*

C-glycosyl flavonoids from *Mimosa pudica*is endured with computational docking utilizing Autodoc Veena. The ligands are isoorientin, isovitexin, vitexin, and orientin. The ligands are bound with the receptor GABA (Gamma Amino Butyric Acid) and P2X4. Pharmacokinetic and toxicity studies were performed online employing swiss ADME and PROTOX to evaluate Lipinski rule of 5. The binding affinities towards GABA obtained for isoorientin, isovitexin, vitexin and orientin were -7.1, -7.1, -6.7 and -6.5 Kcal/mol. respectively whereas same predictions were made on active site of P2X4 and predicted affinities were shown as -6.1, -5.9, -6.3, -6.3 and -4.1 Kcal/mol. respectively. The isoorientin and isovitexin were predicted as efficient components with respect to other flavonoids binding.[99].

5.8. *Papain*

Papain is a protease isolated from *Carica papaya*. It is well-proven antioxidant acting against neuropathic pain in silico by inhibiting NMDA, a glutamate receptor. Docking studies are exercised using Schrödinger suite 9.8. The ligand had a hydrogen bond interaction at GLn110 and Ser132 and also ∏-∏ interaction with Phe176.The residues such as Tyr109, Arg115 and Glu106 produce hydrogen bond with papain component [100].

5.9. *Myricetin*

Rhizophora apiculate, is a traditional mangrove located on the southeast coast of India. The flavonoid in this plant has medicinal value. Neuropathic pain property was evaluated *Invivo* utilizing leaf extract of *R.apiculata* with "acetic acid induced writhing test and Hot plate method". Dose reliant inhibition of responses was observed. At dose frequency with 200 mg/kg 79.51% inhibition of writhing response was noticed with maximum pain latency time in eddy's hot plate method. *In silico* effects of Myricetin from Rhizophora were performed using AutoDoc software. The *In silico* studies accomplished employing COX-1& 2, the biological catalyst responsible for release of mediators. The binding energy for COX-1 with A chain was -8.1 Kcal/mol, and with B chain was -9.83 Kcal/mol. The binding energy for COX-2 A chain was -5.72 Kcal/mol and for B chain is -7.46 Kcal/mol. The drug was more facilitating inhibiting COX-1 than COX-2. The amino acids that had an interaction with drug and protein are Glutamine, Alanine, Glutamic acid, Asparginine, Histidine, Glycine, Isoleucine, Methionine, Phenylalanine, Lysine, Tryptophan, Serine, Threonine, Tyrosine, and Valine. [101]

5.10. *Rutin*

Rutin, a plant pigment widely popular as rutoside a combo of flavanol and glycoside extracted widely from plants and vegetables. It has been established in treating various diseases. The *insilico* pharmacological activity for neuropathic pain was proven by AutoDoc 4.2. A brief focus on the effect of neuropathic pain mediators is focused, especially on tumor necrosis factor-alpha, Interleukin-6 & 1β and Nitric oxide synthase. The binding energy obtained for tumor necrosis factor-alpha for 100 runs was -5.13 Kcal/mol. TNF-α has specific H-bond interaction at chain-A: Gly121 and Chain-B: Gly121, Gly122. A π-amide interaction at chain-B: Gly121, Gly122 and π-alkyl interaction at chain-B: Leu57, Leu94 and Phe124 showing inhibitory constant at 25.62 µM. IL-1β was visualized with H- bond interaction with Arg4, Phe46, Gln48 and Lys103 with a π anion interaction at Glu42 visualizing inhibitory constant at 61.42 µM . a multiple Hydrogen bond interactions were noticed with IL-6 at Asp35, Ser37,

Lys171, Gln175 with π-σ interaction at Leu33, Arg30 and π-cationic interaction at Asp 30 and π- alkyl interaction at Leu 178 with inhibitory constant at 12.35 µM. Similarly, with iNOSa H-bond interaction was observed at Ser339, Trp683, Val685, Asp601, Hem801, π-π bond at Trp683 and π-alkyl interaction at Met341 [102].

5.11. *6-Methoxy Flavone*

6-methoxy flavone and allosteric facilitator of GABA A receptor was evaluated *Invivo, Invitro* and *Insilico* for neuropathic pain. *Invivo* activity was assayed with dynamic and static allodynia developed by giving cisplatin followed evaluation utilizing Von Frey filaments with dose mediated inhibition. *Invitro* activity was accomplished with COX colorimetric assay. 6- methoxy flavone showed IC_{50} value with COX-1 at 2.94 µg/ml and for COX-2 at 1.87 µg/ml. The *in silico* pharmacological screening of 6-methoxy flavone was screened against drug-induced neuropathic pain. Flavonoids are well established in treating neuropathic pain. The *In silico* activity was performed using the MOE-Dock program. The docking was done using COX-1 and COX-2. The binding energy with cox-1 was -6.8487 with three hydrogen bond interactions, five polar interactions, and π-π interactions. The binding energy attained with cox-2 was -6.7441 with five hydrogen bonds and two polar interactions. The methoxy group was found more interactive with the proteins. [103]

5.12. *Piperine*

Active component from Piper longum has proven its efficiency in treating inflammation, immunomodulator and many other activities. *Invitro* animal screening was inspected by surgical model of sciatic nerve at L4 and L5 lamina. The animals are given with drugs followed by identifying mechanical threshold. The group treated with piperine holds back more threshold compared with standard group. After 15 days the animals are sacrificed estimating the serum levels of IL-1β &-10, TNF-α &-β1 by ELISA. The group of animals receiving piperine showed a decline in IL-1 β and TNF-α and simultaneous increase in IL-10 and TNF-β1 compared with control group indicating inflammatory activity. *In vivo* analysis was performed by cell line culture of Human sciatic nerve cells in RPM1640 medium. The analysis was done by HE staining. In comparison with sham groups there is a drastic decline in number of vacuoles indicating piperine has a role in nerve remodeling. *In silico* docking was performed with PPARG and NF-kB1 with binding energy of -4.01 and -3.72 Kcal/mol which is more with respect to standard drug celecoxib. In silico binding of piperine with PPARG was observed at Lys367 and with NF-kB1 at Phe298. [104]

6. CONCLUSION

The major motive behind focusing on neuropathic pain is to focus light on natural compounds with good therapeutic efficiency and minimal side effects with respect to synthetic drugs. Potent chronic and deep-seated pain neutralizers like opiates are employed; despite their addiction, the consumption is minimal due to side effects. To meet the demand of fostering exigency for painkillers novel, safe and cheap therapeutic agents are obligated. Phyto extracts and components are increasingly consumed to reduce the complicacy and tolerability of synthetic drugs and opioids. Phytoextracts are consumed along with synthetic drugs. Neuropathy is chronic pain mechanisms which disrupt body's normal homeostasis through abnormal bioactivation of cells via inflammatory responses. Potential

alternatives to conventional drugs for treating neuropathic pain and inflammation are engrossed. The prescribed synthetic drugs along with naturopathy including nutraceuticals are greatly highlighted in the present research which potentiates the screening of potent phytocompounds as alternatives to conventional drugs to fight neuropathic pain and inflammation.

List of Abbreviations:

- ADME Absorption, Distribution, Metabolism and Distribution.
- CNS Central nervous System
- CCI Chronic constriction injury
- Cox-1 CycloOxygenase-1
- Cox- 2 CycloOxygenase – 2
- cGMP cyclic Guanyl mono phosphate
- DNA Deoxyribo nucleic acid
- ERK extracellular signal-regulated kinase
- ELISA Enzyme Linked Immunosorbent Assay
- GABA Gamma-aminobutyric acid
- GSH y-l-Glutamyl-l-Cysteinyl-Glycine
- HMGB1 High mobility group box 1 protein
- HE staining Hematoxylin and eosin staining
- H-bond Hydrogen bond
- IL-1 Interleukin-1
- IL-1β Interleukin-1β
- IL-4 Interleukin-4
- IL-6 Interleukin-6
- IL-10 Interleukin-10
- IL-17 Interleukin-17
- i.p. Intra Peritoneal
- iNOS induicable nitric oxide synthase
- IKK Nuclear factor-κB (IκB) kinase
- KATP channel ATP sensitive potassium channel
- KD Dissociation constant
- LPS Lipopolysaccharide
- MAO-A Mono amine oxidase A
- MAO-B Mono amine oxidase B
- MD Molecular dynamics
- MAO-A & B Mono Amine Oxide-A & B
- MAPK Mitogen-activated protein kinase
- NMDA - N-Methyl D-Aspartate
- NSAIDS Non-steroidal anti-inflammatory drugs
- NO Nitric Oxide
- NF-κB Nuclear factor-κB
- NGF Nuclear growth factor
- NrF-1 Nuclear transcription factors-1
- NrF-2 Nuclear transcription factors-2
- NGF Nuclear growth factor
- PPAR- Alpha Peroxisomes Proliferator- Activating Receptor- Alpha
- PGE2 Prostaglandin E2

- p38 MAPK p38 mitogen-activated protein kinase
- ROS Reactive oxygen species
- RT-PCR Reverse Transcriptase Polymerase Chain reaction.
- RMSD Root Mean Square Deviation
- Rg Radius of Gyration
- SOD Superoxide Dismutase
- SPR Surface plasmon resonance
- TRL4 Toll-like receptor 4
- TRP - Transient Receptor Potential
- TNF-Alpha - Tumor Necrosis Factor- Alpha
- TRPA Transient Receptor Potential Cation Channel Subfamily A
- TRPV Transient Receptor Potential Cation Channel Subfamily V
- TRPA1 Transient receptor potential A1
- TRAF6 Tumor necrosis factor receptor (TNFR)-associated factor 6
- 5-LOX 5-Lipoxygenase

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Conflict of Interest

The conflict of interest for this exertion is null.

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