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A REVIEW ON NEUROPATHIC PAIN: NEUROPROTECTIVE AGENT

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Abstract:
Neuropathic pain may be spontaneous or evoked in response to physical stimuli that may manifest as increased sensitivity to pain hyperalgesia or as a pain evoked by a nonpainful stimuli allodyania. Chronic neuropathic pain is a common significant and depilating and problem that present challenge to health-care. Despite the multi-target of available drugs, there are no curative conventional treatments for neuropathic pain. A literature investigation was carried out by analyzing classical peer reviewed papers and textbooks, taking into consideration worldwide well established scientific databases mainly PUBMED and SCOPUS to retrieve accessible published literature. The selection of physiotherapies was based upon their potential in reliving NP in pre-clinical model. Diabetic mellitus is a metallic associated with structural and functional alteration of various organ system. The tissue injury is attributed to chronic hyperglycemia. Additionally, neuro-inflammation is a known factor in the development and maintenances of neuropathic pain. During neuropathic pain development, the c-c motif chemokine receptor 2|(CCR2)acts as an important signaling mediators.

Key Words: *Neuropathic pain, Diabeic neuropathy, model of neuropathic pain, Neuroprotective agent.*

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INTRODUCTION:

Pain is one of the most important health problems worldwide, and it remains an important challenge of modern medicine. Chronic pain is a public health problem that causes personal and social afflictions. Depending on its origin, chronic pain can be classified as inflammatory or neuropathic. Neuropathic pain can arise from a disease or injury to the central nervous system (CNS) or the peripheral nervous system (PNS). Millions of people worldwide are suffering from this chronic condition that could compromise their engaging in daily activities.This definition of neuropathic pain distinguishes it from other types of pain, including musculoskeletal pain, restricting its extent to the somatosensory nervous system. Pain, an unpleasant sensation and emotional experiences that in our daily life, is an alert of tissue injury to prevent further or impending tissue damage. Acute pain is a useful biologic purpose and self-limiting in nature that arises in response to a specific injury. Chronic pain, in contrast, may be considered as a disease state. It may outlast the usual duration of recovery, if accompanied with a disease or injury [1].

Neuropathic pain is associated with increased drug

Despite the increases of placebo responses that result in the failure of multiple new drugs in clinical trials. This Primer presents the current descriptions of the presentation, causes, diagnosis and treatment of neuropathic pain, with a focus on peripheral neuropathic pain given that our knowledge is greater than that of central neuropathic pain [2].

In this context, natural products (NPs) or secondary metabolites which present fewer side effects emerge as interesting therapeutic resources for the development of new drugs for the management of certain chronic pain states. In fact, NPs traditionally have played an important role in drug discovery and were the basis of most early medicines [3]. Despite its importance, there are no systematic reviews on the analgesic potential of NPs for neuropathic pain. Accordingly, we conducted a systematic review of the literature to examine and synthesize the literature on NPs and then identify those that assess antinociceptive effects in neuropathic pain models [4].

The four criteria for grading NP diagnosis are follows:

1. Neuro-anatomical related pain.
2. There is a related lesion or disease in the history of nervous system.
3. The existence of positive or negative neurologic manifestation with the abundance of pain in neurologic in neurological assessment or in the more objective confirmatory tests.
4. The existences of related disease or lesion by no less than a single confirmatory test [5].

Epidemiology:

The estimation of the incidence and prevalence of neuropathic pain has been difficult because of the lack of simple diagnostic criteria for large epidemiological surveys in the general population. Thus, the prevalence of neuropathic pain in the chronic pain population has mainly been estimated on the basis of studies8 conducted by specialized centres with a focus on specific conditions, such as postherpetic neuralgia, painful diabetic polyneuropathy, postsurgery neuropathic pain, multiple sclerosis, spinal cord injury, stroke and cancer [6].

The recent development of simple screening tools in the form of questionnaires has helped conduct several large epidemiological surveys in different countries (the United Kingdom, the United States, France and Brazil) and provided valuable new information on the general prevalence of neuropathic pain4. In using screening tools, such as the Douleur Neuropathique questions (DN4)or the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale23 (BOX 2), the prevalence of chronic pain with neuropathic characteristics has been estimated to be in the range of 7–10%. Chronic neuropathic pain is more frequent in women (8% versus 5.7% in men) and in patients >50 years of age (8.9% versus 5.6% in those <49 years of age), and most commonly affects the lower back and lower limbs, neck and upper limbs. Lumbar and cervical painful radiculo pathies are probably the most frequent cause of chronic neuropathic pain [7,8].

Pathomechanisms:

Pathomechanisms causing the development of NP are divided into 3 group: first, electro physiologcal properties of the cellular membrane of the first sensory neuron changes in nociceptor excitability, gene expression changes in neuronal cell body and in the release of neurotransmitter. Second the alteration in impulse-processing in the spinal-cord dorsal-horns. Third, disorder in the CNS such as distributed balances between the activity of ascending excitatory systems and descending inhibitory system. Moreover, the autonomic nervous system dysfunction might also entangled with the NP development [9].

Screening:

The screening scales can be used indentified NP or the presence of a clear neuropathic factor in the pain syndrome. They may be used if medical history or

physical examination reveals signs of neuropathic pain [10].

Diagnosis and Current Therapies of Neuropathic Pain:

Postherpetic Neuralgia (PHN):

Diagnosis of PHN may be in patients complaining of severe unilateral pain in dermatomes where herpes zoster virus has caused lesions. This diagnosis is possible after the lesions have completely healed [11]. The agent are using (Opioids, amitriptyline, 5% lidocaine, gabapentin, pregabalin, and 8% capsaicin) are the most efficatious first-line agents in treatment of PHN. Recommendations suggest that monotherapy should be started. Switching to a combination is only recommended in case of failure of monotherapy [12].

Diabetic Polyneuropathy:

Diabetic polyneuropathy is caused by both types of diabetes mellitus (DM). Prevention of neuropathy in DM patients is achieved through maintaining a proper level of glucose in blood [13]. As for treatment, gabapentin, pregabalin, TCAs, venlafaxine ER and duloxetine are the first-line agents to treat diabetic neuropathy, while opioids and tramadol are the second-line agents. Primarily patients are given a single first-line drug. Switching to a different drug from an alternate therapeutic group is done in case of failure of the first-line agent. Knowing that alleviation of pain is not achieved, we consider one of the following approaches: choose a secondline drug; choose a synthetic or natural drug having other mechanism of actions; or use drug combinations [14].

Neuropathic Pain:

Cancer patients- pain may have different causes and mechanisms. Treatment choice depends on NP intensity where tramadol is administered in case of moderate intensity NP, while a strong opioid is given in cases of high intensity pain. Combination of the previous drugs with gabapentin and pregabalin helps in increasing effectiveness and reducing opioid doses. Venlofaxine and duloxetine are administered in treatment of neuropathy after chemotherapy [15].

Nerve Injury and Neuropathic Pain:

The appearance of peripheral nerve injury on somato sensory processing and pain is directly related to age at which damage took place. The mechanical hypersensitivity of the patients does occur but only late in life. This delay hypersensitivity could be observed by cold stimulation and weight bearing tests. This pain could be attenuated by pre-treatment with, an inhibitor of pro-inflammatory polarized by microglia, mino-cyclne [16].

Trigeminal Neuralgia (Tn):

TN is diagnosed in patients who experience chronic NP in the trigeminal nerve area. The first-line agent for treatment of TN is carbamazepine. However, if carbamazepine is contraindicated, then the use of clonazepm, baclofen, or antiepileptics (gabapentin, lamotrigine or pregabalin) is indicated. Surgery is recommended in case of failure of pharmacotherapy, yet treatment with botulin toxin is advisable prior to a surgery.an inhibitor of pro-inflammatory polarised microglia, minocycline [17].

Post-Amputation:

Pain Phantom pain was incident in amputated patients with extremity and stump pain located surrounding the post-surgical stump scar. Due to the fact that strong opiods, tramadol, gabapentin, lidocaine infusions, calcitonin, pregabalin or amitriptyline are recommended, evidence of effectiveness of these therapeutic agents is lacking. Other types of treatment have emerged, such as psycotherapy and physiotherapy. In phantom pain, spinal cord thermo lesion and stimulations of the peripheral nerves are effective, while neuro destruction is possible in stump pain [18].

Neuropathic Pain in Osteoarthritis:

The most common disorder of the muscle skeleton is osteoarthritis (OA), characterized by joint pain due to the central pain pathways and peripheral joint sensitization and the local joint inflammation done by nociceptive mechanism and changes in the bones [19]. Thus, medicines acting centrally can relieve osteoarthritic pain, although osteoarthritic pain causes are not completely understood. OA apparent mechanism of NP is due to increase in sodium channels, secondary hyperalgesia resulting from dorsal-horn sensitization of the NP modulation central point, and windup owing to the increase of calcium influx when NMDA receptors are activated [20]. However, non-pharmaceutical treatment, as physiotherapy, hydrotherapy, and most important the use of electrical stimulation of nerves and cold or heat packs are essentially equal. Consequently, the centrally acting medications might be used together with anti-inflammatory and analgesic drugs for some patients in the future. Additional options like strontium ranelate/bisphosphonates for methotrexate are still under investigation [21].

Diabetes and Nervous System:

It is now generally accepted that diabetes can alter central nervous system [CNS] function. Even in the absence of overt cerebrovascular accidents or repeated

hypoglycemic reactions, uncontrolled hyperglycemia is associated with cognitive changes. These changes are documented both in patients with diabetes as well as in animal models of experimental diabetes. The contributory causes of CNS dysfunction in diabetes include the presence of hypertension, uremia, peripheral and autonomic neuropathy and multiple drug use [22].

Relation between Diabetes and Neurodegeneration:

Diabetes dramatically increases risk of neurodegenerative diseases. Diabetes has been shown to have a specific and detrimental effect on the hippocampus, the area of the brain involved in memory processing, is the area that is at risk in Alzheimer's disease. Research has revealed that the hippocampus is damaged by glucose. Therefore, we have another advanced glycosylated end product of importance which is beta-amyloid. Beta-amyloid can be modified by glucose, and this enhances its inflammatory predisposition in the brain. Beta - amyloid is one of the hallmarks of Alzheimer's disease. Alzheimer's plaques and neuro fibrillary tangles have glycosylated proteins. Animal models of 'induced diabetes' suggest a direct neurodegenerative effect of diabetes. The issues like, vascular disease, glycation protein, and beta-amyloid has directly link diabetes with an increased risk for Alzheimer's disease. Fundamentally, these are all inflammatory issues [23]. People with diabetes are at increased risk for stroke, still less information is available about the effect of diabetes on neuro degeneration. Recent work involving more than 1000 people has shown that those with diabetes have greater cortical atrophy, independent of hypertension, total cholesterol, smoking, BMI, coronary heart disease and socio-demographics than people without the condition. Evidence emerged recently that obesity is in fact a risk factor for dementia and Alzheimer's disease. The prevalence of obesity is increasing rapidly and it has never been timelier to focus on a healthy weight, especially for people with diabetes [24].

Alzheimer's disease, Dementia and Diabetes:

Alzheimer's disease the most common type of dementia. Over half of all dementia is due to Alzheimer's – a neurodegenerative disease that is characterized by memory loss, cognitive decline and ultimately, severe behavioral changes and complete loss of the ability to care for oneself. The usual first noticeable symptom is short term memory loss, which progresses from simple forgetfulness to a consistent loss of short-term memory, and finally, the most devastating part of the disease, the loss of well-known skills and inability to recognize familiar people. Alzheimer's involves changes in the brain, part of the progression of the disease. People with Alzheimer's loss neurons and develop atrophy, a sign of neuro degeneration. People with the disease also have amyloid (protein) plaques and neurofibrillary tangles (protein aggregates found in neurons) in their brain – the pathological hallmarks of Alzheimer's [25].

Many population-based studies have found an association between Alzheimer' disease, vascular dementia and type 2 diabetes. In one study, the risk was stronger for people with type 2 diabetes who used insulin compared with those who used oral blood glucose-lowering medications; both groups had a higher risk of Alzheimer's compared to people without diabetes [26]. Although initially, the association between type 2 diabetes and vascular dementia appeared to be more consistent than the relationship between type 2 diabetes and Alzheimer's [27], recent work has shown more consistent evidence for diabetes and 'pure' Alzheimer's [28]. Vascular dementia is the second most common type of dementiain elderly people with age between 60 and 75. It refers to a number of syndromes which result in vascular lesions in the brain [29].

Relation between Diabetes and Neuropathy:

Diabetic neuropathy is characterized by diffuse or focal damage to peripheral somatic or autonomic nerve fibers resulting from diabetes mellitus. The syndromes may be grouped under two general headings: diffuse and focal neuropathies. The diffuse neuropathies, i.e., distal symmetrical sensor motor polyneuropathy (DPN) and diabetic autonomic neuropathy (DAN) are common, usually chronic, and often progressive [30]. The focal forms of diabetic neuropathy reflect damage to single (mononeuropathy) or multiple peripheral nerves (mononeuropathy multiplex), cranial nerves, regions of the brachial or lumbosacral plexuses (plexopathy), or the nerve roots (radiculopathy). The most common peripheral nerve mononeuropathies, medial and ulnar neuropathy, are essentially in distinguishable from entrapment neuropathies in non diabetic subjects, suggesting that the diabetic nerve has increased susceptibility to compression. The most common cranial neuropathy affects the third nerve, producing unilateral headache, diplopia, and ptosis with papillary sparing (diabetic ophthalmoplegia) [31].

Signs and Symptoms:

Diabetic Neuropathies are Affects All Peripheral Nerves: The pain fibers, motor neurons, autonomic nerves. It is necessarily can affect all organs and

systems since all are innervated. There are several distinct a syndromes based on the organ systems and members affected, but these are by a no means exclusive. A patient can have sensory motor and autonomic neuropathy or any other combination. Symptoms vary depending on the nerve. Affected and may include symptoms can other than those listed. Symptoms usually develop gradually the over years [32].

Symptoms May Include [33]:
- Numbness and tingling of extremities
- Dysesthesia [abnormal sensation to a body part]
- Diarrhea
- Erectile dysfunction
- Urinary incontinence [loss of bladder control]
- Facial, mouth and eyelid drooping
- Vision changes
- Dizziness
- Muscle weakness
- Difficulty swallowing
- Speech impairment
- Fasciculation [muscle contractions]
- Anorgasmia
- Burning or electric pain

Examples of Neuropathic Pain

Origin of pain	**Structure**	**Example**
Peripheral nervous system	Nerve	Diabetic painful neuropathy Neuroma Phantom limb pain Trigeminal neuralgia Lumbosacral plexopathy
	Dorsal root	Postherpetic neuralgia Brachial plexus avulsion
	Spinal cord	Spinal cord injury Spinal cord infarction
Central nervous system		Multiple sclerosis
	Thalamus	Infarct Tumour Parkinson's disease.

Pathophysiology Of Diabetic Neuropathy:
There may be multiple etiologies which account for the various neuropathic syndromes seen in patients with diabetes. Hyperglycemia clearly plays a key role in the development and progression of diabetic neuropathy as well as the other micro vascular complications of diabetes. All of these pathways are related to the metabolic and/or redox state of the cell. Pathways which are mainly driven by metabolism are: glucose flux through the polyol pathway; the hexosamine pathway; excessin appropriate activation of protein kinase C (PKC) is of forms; accumulation of advanced glycation end products. While each pathway may be injurious alone, collectively they cause an imbalance in the mitochondrial redox state of the cell and lead to excess formation of reactive oxygen species (ROS) [34]. Increased oxidative stress within a cell leads to activation of the Poly [ADP-ribose], polymerase [PARP] pathway, which regulates the expression of genes are involved in promoting inflammatory reactions and neuronal dysfunction. This section will discuss each of these mechanisms and the central role of ROS.Diabetic neuropathy is thought to occur from the both hyperglycemia-induced a damages to nerve cells and from the neuronal ischemia caused by hyperglycemia-induced decreases in neurovascular flow [35].

Important Pathways/Mechanism involved in the pathophysiology of DN are listed as followings:
a] Polyol Pathways
b] Hexosamine Pathways
c] Protein Kinase C pathways
d] Advanced glycation end product pathways
e] Poly [ADP-ribose] polymerase pathway
f] Mechanism of Oxidative stress and Apoptosis
g] Role of Inflammation
h] Role of Growth factors

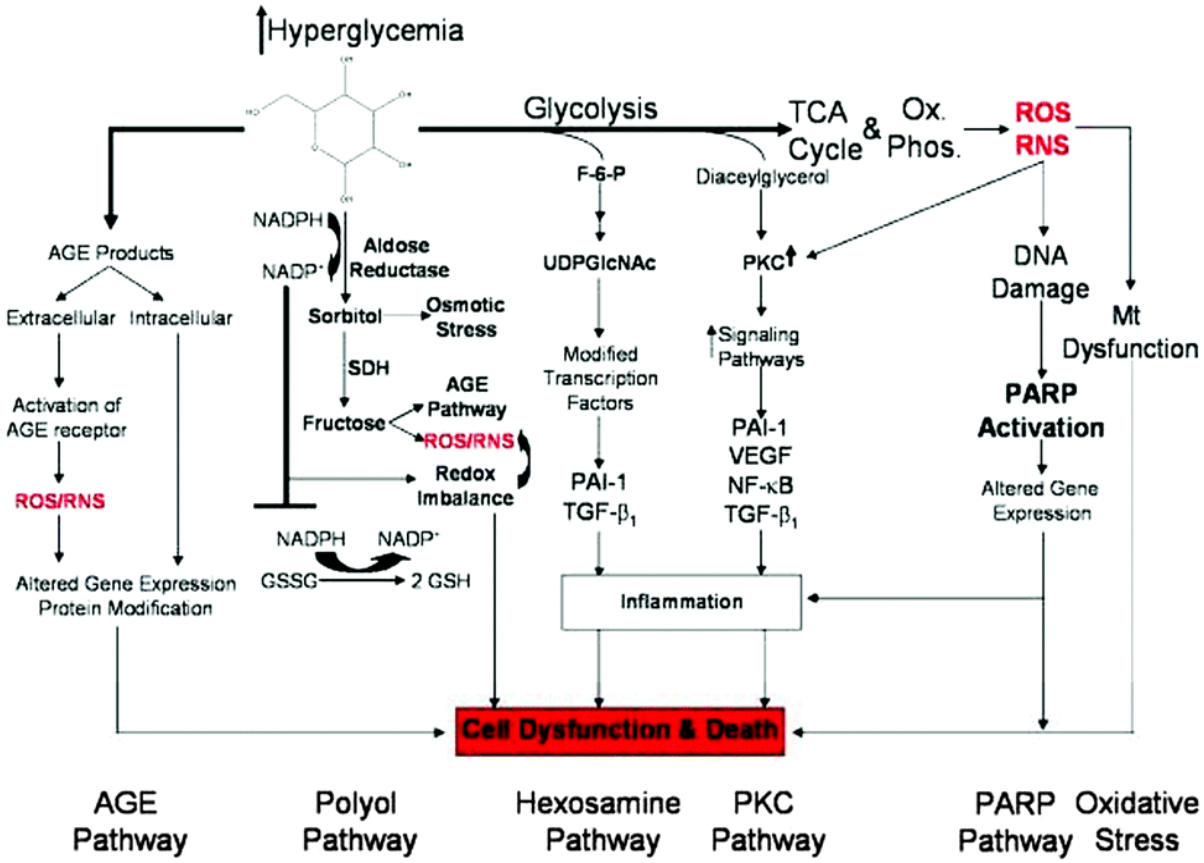

Figure: 1 Schematic of hyperglycemic effects on biochemical pathways in diabetic neuropathy.

Excessive glucose metabolism generates excess NADH and leads to overload of the electron transport chain causing oxidative stress, damage to Mt, activation of PARP. PARP activation by ROS acts in conjunction with the hexosamine and PKC pathway to induce inflammation and neuronal dysfunction. A combination of oxidative stress and hyperglycemia activate the detrimental pathways of AGE, polyol, hexosamine and PKC pathways which lead to redox imbalance, gene expression disturbances, and further oxidative stress [36].

These pathways also induce inflammation and neuronal dysfunction. NF-κB: Nuclear factor kappa B; PARP: Poly [ADP-ribose] polymerase; PKC: Protein kinase C; AGE: Advanced glycation end products; RNS: Reactive nitrogen species; ROS: Reactive oxygen species, GSH: glutathione; GSSG: oxidized glutathione; UDPGlcNAc: UDP-N-Acetyl glucosamine; VEGF: Vascular endothelial growth factor [37].

Regulation of Peripheral Nerve Excitability:

Nerve injury increases expression of sodium channels in the DRG and around the terminal injury site of injured axons. Nav1.7 and Nav1.8 double-knockout mice normally develop neuropathic pain in PSNL animal model. Nav1.7 is not required for oxaliplatin-induced neuropathic pain but is essential in CCI mice, suggesting that the neuropathic pain trigger affects the mechanism by which pain develops [38]. In addition, knockdown of Nav1.8 by means of siRNA alleviates mechanical allodynia in CCI rats [39].

Antagonists of transient receptor potential vanilloid member 1(TRPV1) are both effective in neuropathic pain alleviation. TRPV1agonistsreleasetransmittersandinducecationinflux in to the nerve, as well as receptor desensitization [40]. Topical formulations of high-dose capsaicin have been shown to be efficacious in a number of neuropathic pain conditions, including Phase 3 studies in post herpetic neuralgia patients [41]. It has been reported that antagonists that block TRPV1 signal transduction can reverse heat-related hyperalgesia in sciatic nerve ligation in mice [42]. After chronic compression of the DRG, mechanical allodynia was enhanced by injection of a TRPV4 agonist but reversed by its antagonist [43]. Antagonists of NMDA receptors, which are subtypes of the glutamate

receptor, are third-line treatments for neuropathic pain and can reduce pain in animal models but have many side effects, including sedation, confusion, and motor in coordination[44].

G Protein-Coupled Receptors (GPCRs):

G protein-coupled receptors (GPCRs) comprise the largest super family of trans membrane receptors and transduce extracellular stimuli into intracellular responses. Targeting GPCRs is highly successful, so that 30% of drugs target GPCRs for conditions including allergies, hypertension, migraine, asthma, stroke, and pain [45]. GPCRs and their ligands play a number of important roles in them modulation of acute and chronic pain, including neuropathic pain [46].

GABA Receptors:

Gamma-amino butyric acid (GABA) is a widely distributed inhibitory neurotransmitter, also found in the spinal cord. It is well-known that hypo function of GABA ergic tone leads to development of neuropathic pain in animal models [47]. Treatment with GABA agonists reduces central neuropathic pain behavior and neuronal hyper excitability after SCI. Injection of GABA after SCI attenuated mechanical allodynia and hyper excitability of the spinal dorsal horn neurons. This reduction is regulated by both GABAA and GABAB receptors. Moreover, bicuculline, a GABAA receptor antagonist, induces hyper excitability and pain behavior in normal rats. The number of GABA ergic in neurons is also decreased in a neuropathic pain model [48].

Bradykinin Receptors:

Bradykinin (BK), an inflammatory mediator, is a vasodilator and is known to induce neuropathic pain by binding to the BK1 and BK2 receptor. Several studies have shown the participation of kinins and their receptors in neuropathic pain development [49]. Nerve injury induces an increase in BK1 receptor mRNA in the spinal cord and sciatic nerve and also produces mechanical allodynia and hyperalgesia. The BK1-knockout mice show reduction in both allodynia and hyperalgesia in a neuropathic pain animal model. Inhibition of BK1 and BK2 reverses the effect of dynorphin A, an endogenous opioid peptide, inducing persistent neuropathic pain [50].

Opioid Receptors:

Most opioids are used as second-or third-line analgesics that may provide reasonable analgesia to some neuropathic pain [51]. Because opioid treatment may require relatively higher doses, opioid-related adverse reactions are common. Morphine is an opioid analgesic and reduces neuropathic pain, but the mechanisms underlying this reduction are unclear [52]. There are four types of known opioids receptors: delta (DORs), kappa (KORs), and mu-opioid receptors (MORs) and opioid receptor like-1 (ORL1).DOR-knockout mice showed increased neuropathic pain, implying that endogenous delta opioid activity reduces chronic pain [53]. TCAs alleviate allodynic effects in a neuropathic pain model; however, in DOR-knockout mice, the efficacy of these drugs was reduced [54]. Antidepressant drugs are still effective in MOR-knockout animals, suggesting that these drugs are regulated by DOR rather than MOR [55]. KORs are also not necessary for the effect of TCAs against neuropathic allodynia. These data indicate that DOR is the only opioid receptor that is necessary for the anti allodynic action of antidepressants [56]. In addition, ORL1 receptor agonist relieves thermal hyperalgesia after nerve injury [57].

Histamine Receptors:

Histamine is an organic nitrogenous compound in volvedinloc alimmune responses as well as in regulating physiological function. As mentioned above, Nav1.8 up regulation in primary afferents plays a critical role in the development and persistence of neuropathic pain, although the mechanisms underlying this up regulation are not fully understood. Histamine increases Nav1.8 expression in primary afferent neurons [58]. While histamine receptor antagonists suppress mechanical allodynia in neuropathic rats [59].

Prostaglandin E2 Receptors:

Prostaglandin E2 (PGE2) is a well-known mediator of inflammation and pain and plays a pivotal role in nociceptive processing and sensitization in the spinal cord. After nerve injury, the pain mediator, cyclo oxygenase 2 (COX2), and its end product, PGE2, are persistently up regulated in invading macrophages. Nervous tissue damage induced PGE2 contributes to up regulation of BDNF in DRG neurons, leading to neuropathic pain [60].

CCR2:

Among GPCRs, chemokines associated with the immune system are remarkable neuropathic pain modulators. Chemokines constitute ealarge family of relatively low molecular weight proteins, thatis, chemo attract antcytokines controlling immune cell trafficking. MCP1(CCL2). Is amember of the CC chemokine family that specifically attracts and activates monocytes to sites of inflammation. This chemokine is absent from the normal CNS and is found after inflammation and pain, including neuropathic pain, development. CCR2, the receptor

for MCP1, is expressed selectively on cells of the monocyte/macrophage lineage in the periphery and in neurons and astrocytes in the brain. Peripheral nerve injury can result in a disruption of the blood spinal cord barrier (BSCB), allowing influx of peripheral immune cells, which ismediatedbyMCP1.Additionally, activated micro glial cells express CCR2 and modulate the CCR2-CCL2 interaction between injured primary afferent fiber terminals and dorsal horn microglia [61].

Interestingly, spinal microglia activation occurs during the early phase of neuropathic pain, suggesting that microglia may be important for initiation of neuropathic pain, while astrocytes are important for its maintenance. In addition, one study has demonstrated that CCL2/CCR2 signaling in the DRG and spinal cord is involved in neuropathic pain via distinct mechanisms [62]. Nucleus pulposus-induced mechanical allodynia is attenuated by treatment with the CCR2 antagonist RS504393 in radicular neuropathic pain. RS504393 decreased lipopoly saccharide evoked up regulation of the CCL2 and CCR2 expression and protein level in primary microglial cell cultures [62]. Mice lacking CCR2 showed substantially less hypersensitivity to mechanical stimulation after nerve injury but showed a normal response in acute pain.Currently, CCR2 antagonists are in clinical trials and may be promising medicines for neuropathic pain patients in the future [63].

Nociceptor:

A nociceptor is a sensory neuron that responds to damaging or potentially damaging stimuli by sending "possible threat" signals to the spinal cord and the brain. If the brain perceives the threat as credible, it creates the sensation of pain to direct attention to the body part, so the threat can hopefully be mitigated; this process is called Nociceptor [64].

Types of Function:

The peripheral terminal of the mature nociceptor is where the noxious stimuli are detected and transduced into electrical energy [65]. When the electrical energy reaches a threshold value, an action potential is induced and driven towards the central nervous system (CNS). This leads to the train of events that allows for the conscious awareness of pain. The sensory specificity of nociceptors is established by the high threshold only to particular features of stimuli. Only when the high threshold has been reached by either chemical, thermal, or mechanical environments are the nociceptors triggered. The majority of nociceptors are classified by which of the environmental modalities they respond to. Some nociceptors respond to more than one of these modalities and are consequently designated polymodal. Other nociceptors respond to none of these modalities (although they may respond to stimulation under conditions of inflammation) and are referred to as sleeping or silent [66].

Thermal:

Thermal nociceptors are activated by noxious heat or cold at various temperatures. There are specific nociceptor transducers that are responsible for how and if the specific nerve ending responds to the thermal stimulus. The first to be discovered was trpv1, and it has a threshold that coincides with the heat pain temperature of 42 °c [67]. Other temperature in the warm–hot range is mediated by more than one trp channel. Each of these channels express a particular c-terminal domain that corresponds to the warm–hot sensitivity. The interactions between all these channels and how the temperature level is determined to be above the pain threshold are unknown at this time. The cool stimuli are sensed by trpm8channels. Its c-terminal domain differs from the heat sensitive trps. Although this channel corresponds to cool stimuli, it is still unknown whether it also contributes in the detection of intense cold. An interesting finding related to cold stimuli is that tactile sensibility and motor function deteriorate while pain perception persists [68].

Mechanical:

Mechanical nociceptors respond to excess pressure or mechanical deformation. they also respond to incisions that break the skin surface. The reaction to the stimulus is processed as pain by the cortex, just like chemical and thermal responses [58]. These mechanical nociceptors frequently have polymodal characteristics. It is possible that some of the transducers for thermal stimuli are the same for mechanical stimuli. The same is true for chemical stimuli, since trpa1 appears to detect both mechanical and chemical changes [69].

Chemical:

Chemical nociceptors have channels that respond to a wide variety of spices. The one that sees the most response and is very widely tested is capsaicin. Other chemical stimulants are environmental irritants like acrolein, a chemical weapon and a component of cigarette smoke. Apart from these external stimulants, chemical nociceptors have the capacity to detect endogenous ligands, and certain fatty acid amines that arise from changes in internal tissues. like in thermal

nociceptors, trpv1 can detect chemicals like capsaicin and spider toxins [70].

Sleeping/Silent:
Although each nociceptor can have a variety of possible threshold levels, some do not respond at all to chemical, thermal or mechanical stimuli unless injury actually has occurred. These are typically referred to as silent or sleeping nociceptors since their response comes only on the onset of inflammation to the surrounding tissue [71].

Sensitivity:
Nociceptor neuron sensitivity is modulated by the large variety of mediators in the extracellular space. peripheral sensitization represents are of functional plasticity of the nociceptor. The nociceptor can be change from being. The simply a noxious stimulus detector to a detector of n on-noxious stimuli. The result is that low intensity stimuli from regular activity, initiates a painful sensation [72]. This is commonly known as hyperalgesia. Inflammation is one of the common cause that results in the sensitization of nociceptors. Normally hyperalgesia ceases a when inflammation goes down, a however, sometimes genetic defects and/or repeated injury can result in the allodynia: a completely non-noxious stimulus like light touch causes extreme pain. Allodynia can also be caused when a nociceptor are damaged in the peripheral nerves. This can result in differentiation, which means the development of different central processes from the surviving afferent nerve. with this situation, surviving dorsal root axons of the nociceptors can make contact with the spinal cord, thus changing the normal input [73].

Research Methodology:
The information's of this review were obtained from databases such as, PubMed, Web of Science, Google Scholar, Scopus, using the following keywords: neuropathic pain, medicinal plants, natural products. . All studies such as, in vitro studies, animal studies, review articles and clinical studies with the outcome of changes in the neurotransmitter releasing, behavioural changes, oxidant/anti-oxidant parameters and pro-inflammatory cytokines were included. Letter to the Editor and Unpublished data were the exclusion criteria[74].

Neuroprotective Effects of Medicinal Plants:
Butea Monosperma:
B. monosperma is distributed in deciduous forest and in open areas. It has been used in traditional medicine for various therapeutic effects such as diuretic, anti-diabetic, anthelmintic, antimicrobial, arthritis, wound healing in addition to treating burning sensation of the body [75]. Pretreatment with B. monosperma significantly increased the behavioral (i.e. hyperalgesia and allodynic pain sensation) changes and decreased thiobarbituric acid reactive substances (TBARS), total calcium levels besides increased the glutathione (GSH) levels in the sciatic nerve tissue when compared with the normal control group on vincristine-induced neuropathic pain model in rats, that may be due to its potential of neuroprotective, antioxidant and calcium channel inactivation [76].

Another study are investigated the ameliorative effect of ethanolic extract from a leaves of B. monosperma in CCI model. Pretreatment of B. monosperma attenuated CCI induced development of histopathological, biochemical and behavioral the alterations dose dependently, which is a comparable to that of pregabalin pretreated group. This may be due to it's potential anti-oxidant neuroprotective and calcium channel modulatory effect of B. monosperma [77].

Ginkgo Biloba
G. biloba is the popular herb that has shown some neuroprotective effects such as protective activity against transient and permanent focal cerebral ischemia and dementia [78]. The most unique constituents of the G. biloba extracts are the terpene trilactones, ginkgolides and bilobalide. In a study, conducted by Kim, et al., administration of G. biloba extract, EGb 761, lead to reduction time a of the paw with drawal thresholds to mechanical stimuli and withdrawal frequencies to cold stimuli in the rat model of neuropathic pain induced by spinal nerve ligation (SNL). The beneficial effect of G. biloba extract on neuropathic pain was likely due to a combination of an anti-inflammatory, antioxidant effect, a platelet activating factor antagonist and a protective effect against NMDA induced neurotoxicity [79]. Administration of EGb 761, a standardized extract of G. biloba, after the third week of STZ administration for 14 days reversed diabetes induced thermal hyperalgesia and mechanical allodyania on STZ-induced neuropathic pain in rats by inhibiting oxidative and nitrosative stress [80].

Coriandrum Sativum:
Coriander (Coriandrum sativum L.), is an annual herb of the parsley family (Apiaceae). This plant is generally called Geshniz in Persian. Coriandrum sativum is native to the Mediterranean region and is extensively grown in all over the world [81]. The aliphatic aldehydes (mainly C10-C16 aldehydes) with fetidlike aroma are predominant in the fresh herb oil.

Where as major components in the oil isolated from coriander fruit include linalool and some other oxygenated monoterpenes and monoterpene hydrocarbons. Coriander is also a potential source of lipids such as petroselinic acid and a high amount of essential oils (EO) that are very important for growth and brain functions. The main coriander EO is linalool, linoleic and linolenic acids. Coriander seed oil was contains linalool (60e70%) and 20% hydrocarbons but the composition of the herb oil was completely differs from the seed oil [82].

Nigella Sativa:
Nigella sativa L. (N. sativa) is an annual herbaceous and belonging to Ranunculaceae family, which widely grown in the Mediterranean countries, Western Asia, Middle East and Eastern Europe. The N. sativa seeds have been added as a spice to range of Persian foods such as, bread, pickle, sauces and salads [83]. Chemical components of N. sativa seeds include oil, protein, carbohydrate, and fiber. The fixed oil chemical compositions of N. sativa are linoleic acid, oleic acid, Palmitic acid, Arachidic acid, Eicosadienoic acid, Stearic acid, Linoleic acid and Myristic acid. The major phenolic compounds of N. sativa seeds are p-cymene (37.3%), Thymoquinone (TQ) (13.7%), carvacrol (11.77%), and thymol (0.33%) [84].

Ginseng:
Ginsenosides are major bioactive constituents of ginseng agent that are thought to be the main components responsible for its antidiabetic effect. Some ginsenosides, such as Rb1, Rb2, Rc, Re, Rg3, Rh2, and compound K have been shown to possess anti-diabetic activities [85]. Panax no ginseng saponins (PNS) produced anti-hyperglycemic and anti-obesity effects by improving a sensitivity to insulin and the leptin in KK-Ay mice. Rb1 may be the primary hypoglycemic component of PNS extract. Due to their hypoglycemic nature, ginseng constituents interact with conventional anti-diabetics [86].

Goshajinkigan:
In Japan, TJ-107 (Goshajinkigan) is a complex drug containing 10 medicinal herbs that has been commonly prescribed to improve symptoms of diabetic peripheral neuropathy for example numbness, cold sensation, and paresthesias/dysesthesia [87]. In a phase 2 randomized, double-blind, placebo-controlled study, oral administration of TJ-107 had acceptable margins of safety and tolerability and a promising influence in delaying the onset of grade 2 or greater oxaliplatin induced peripheral neurotoxicity in colorectal cancer patients treated with oxaliplatin [89]. In a randomized open-labeled clinical trial study, long term administration of Goshajinkigan showed beneficial effects on macrovascular diseases, retinopathy or nephropathy in type2 diabetic mellitus patients [90].

Koumine:
Gelsemium is a genus of the family Loganiaceae, G. elegans Benth. Has long been used in Chinese traditional medicine to relieve pain, inflammation, and cancer [91]. Koumine is an alkaloid monomer found abundantly in Gelsemium plants [92]. Koumine attenuated tactile allodynia, improve sensory nerve conduction, and mitigate the pathology of sciatic nerves in STZ-induced diabetic rats [93]. In another study koumine suppressed thermal hyperalgesia and mechanical allodynia more potently than gabapentin in CCI rats [94].

Upregulation of allopregnanolone induced significant analgesia, indicating that allopregnanolone in the spinal cord (SC) may be an essential key modulator of neuropathic pain [95]. 3α-Hydroxysteroid oxidoreductase (3α-HSOR) is responsible for allopregnanolone upregulation in the SC [96]. The activity of 3α-HSOR in the SC of koumine-treated CCI rats increased by 15.8% as compared to untreated CCI rats. Also, the intrathecal injection of medroxyprogesterone acetate, a selective 3α-HSOR inhibitor, dose-dependently reversed the analgesic effect of koumine on CCI-induced mechanical pain perception [97,98]. The authors suggested that koumine altered 3α-HSOR-regulated allopregnanolone levels in the SC of rat [99]. Elevated allopregnanolone levels may exert analgesic effects through allosteric modulation of GABAA and by suppressing the release of microglia activation-induced inflammatory cytokines [100].

CONCLUSION:

In this review we propose to focus on neurotoxicity in various studies in vivo and in vitro and investigated the effect of medicinal plants on neural system. As neuropathic pain has multiple etiology, different animal models of neuropathic pain have been created. Model based on ligation mediated peripheral nerve injury have been more commonly employed. The mentioned medicinal plants play their protective roles via increased SOD and catalase level, restoration of GSH, decreased MDA levels and also protects neurons against ROS as antioxidant activities. This issue has raised the concern of several research studies in the scientific filed. one of these measures is the management of NP through phytotherapies, although

not yet well studied, offering relatively low-risk option in neuropathic pain patients and having an increasing evidence to be the future of NP management.

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REFERENCE:

1. Jensen TS, Baron R, Haanp M ¨ a¨a et al., "A new definition of neuropathic pain," Pain, vol.152, no.10,pp.2204–2205,2011.
2. Finnerup TB, Haroutounian S, Kamermanetal P, "Neuropathic-pain:an updated grading system for research and clinical practice,"Pain,vol.157,no.8,pp.1599–1606,2016.
3. Wang LX, Wang ZJ. Animal and cellular models of chronic pain. Adv Drug Deliv Rev 2003;55:949-965.
4. Razavi BM, Hosseinzadeh H. A review of the role of orex in system in pain modulation. Biomed Pharmacother 2017;90:187-193.
5. Treede RD. et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 2008;70(18):1630-5.
6. Szczudlik A, et al. Diagnosis and management of neuropathic pain: review of literature and recommendations of the Polish Association for the Study of Pain and the Polish Neurological Society-Part Two. Neurol Neurochir Pol. 2014;48(6): 423-35.
7. Basbaum AI, et al. Cellular and molecular mechanisms of pain. Cell. 2009;139(2):267-84.
8. Dworkin RH, Portenoy RK. Pain and its persistence in herpes zoster. Pain. 1996;67(2-3):241-51.
9. Thyregod HG, et al. Natural history of pain following herpes zoster. Pain. 2007;128(1-2):148-56.
10. Jung BF, et al. Risk factors for postherpetic neuralgia in patients with herpes zoster. Neurology. 2004;62(9):1545-51.
11. Partanen J, et al. Natural history of peripheral neuropathy in patients with noninsulin-dependent diabetes mellitus. N Engl J Med. 1995;333(2):89-94.
12. Zychowska M, et al. Mechanisms and pharmacology of diabetic neuropathy - experimental and clinical studies. Pharmacol Rep. 2013;65(6):1601-10.
13. Boulton AJM, et al. Diabetic Neuropathies: A statement by the American Diabetes Association. Diabetes Care. 2005;28(4):956-62.
14. Raafat K, Lakany EL, A. Acute and sub chronic in-vivo effects of Ferula hermonis L. and Sambucus nigra L. and their potential active isolates in a diabetic mouse model of neuropathic pain. BMC Complement Altern Med. 2015;15:257.
15. Fallon MT. . Anaesth Br.Neuropathic pain in cancer 2013;111(1):105-11.
16. Fitzgerald M, McKelvey R, Nerve injury and neuropathic pain - A question of age. Exp Neurol. 2016;275 Pt 2:296-302.
17. Hathway GJ, et al. Brief, low frequency stimulation of rat peripheral C-fibres evokes prolonged microglial-induced central sensitization in adults but not in neonates. Pain. 2009;144(1-2):110-8.
18. Kobayashi K. et al. Minocycline selectively inhibits M1 polarization of microglia. Cell Death Dis. 2013:4:e525.
19. Koopman JS, et al. Incidence of facial pain in the general population. Pain. 2009;147(1-3):122-7.
20. Zakrzewska JM. Diagnosis and differential diagnosis of trigeminal neuralgia. Clin J Pain. 2002;18(1):14-21.
21. Childs EA, et al. Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. Neurology. 1999;52(3):607-13.
22. Koopman JSHA, et al. A nationwide study of three invasive treatments for trigeminal neuralgia. Pain. 2011;152(3):507-13
23. Rauck RL, et al. Treatment of post-amputation pain with peripheral nerve stimulation. Neuromodulation. 2014. 17(2): p. 188-97.
24. Rosenstock J, et al. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. Pain. 2004;110(3):628-38.
25. Knotkova H, et al. Current and future options for the management of phantomlimb pain. J Pain Res. 2012;5:39-49
26. Sharma L, Kapoor D, Issa S, Epidemiology of osteoarthritis: an update. Curr Opin Rheumatol. 2006;18(2):147-56.
27. Zhang J, et al. Risk factors for and prevalence of knee osteoarthritis in the rural areas of Shanxi Province, North China: a COPCORD study. Rheumatol Int. 2013;33(11):2783-8.
28. Nho SJ, et al. The burden of hip osteoarthritis in the United States: epidemiologic and economic considerations. J Am Acad Orthop Surg. 2013;21 Suppl 1:S1-6.
29. Sommer C. Painful neuropathies. Curr Opin Neurol. 2003;16(5):623-8.
30. Moore KA, et al. Partial peripheral nerve injury promotes a selective loss of GABAergic

inhibition in the superficial dorsal horn of the spinal cord. J Neurosci. 2002;22(15):6724-31.
31. Dimitroulas T, et al. Neuropathic pain in osteoarthritis: a review of pathophysiological mechanisms and implications for treatment. Semin Arthritis Rheum. 2014;44(2):145-54
32. Mooradian AD. Pathophysiology of central nervous system complications in diabetes mellitus. Clin Neurosci 1997; 4(6):322-6
33. David P, Perlmutter Health Center. The Role of Inflammation in Neurodegenerative Disorders: Integrative Approaches to Challenging Neurological Disorders. chapter 30, 151-156.
34. Korf ES, White LR, Scheltens P, Launer LJ. Brain aging in very old men with type 2 diabetes: the Honolulu-Asia aging study. Diabetes Care 2006; 29:2268-74.
35. Ott A, Stolk RP, van Harskamp F. Diabetes mellitus and the risk of dementia: The Rotterdam Study. Neurology 1999; 53:1937-42.
36. Hassing LB, Johansson B, Nilsson SE. Diabetes mellitus is a risk factor for vascular dementia, but not for Alzheimer's disease: a populationbased study of the oldest old. Int Psychogeriatr 2002; 14:23948.
37. Xu WL, Qiu CX, Wahlin A. Diabetes mellitus and risk of dementia in the Kungsholmen project: a 6-year follow-up study. Neurology, 2004; 63:1181-1186.
38. Vinik A, Mehrabyan A. Diabetic neuropathies. A complete review of the diagnosis and treatment of diabetic neuropathy, with useful tables and figures that aid in the differential diagnosis and correct selection of treatment. Med Clin North Am 2004; 88:947-999.
39. James LE, Andrea MV, Hsinlin TC, Eva LF. Diabetic neuropathy: Mechanisms to management. Pharmacology & Therapeutics 2008, 120:1-34.
40. Watkins LR and Maier SF, "Beyond neurons: evidence that immune and glial cells contribute to pathological pain states," Physiological Reviews,vol.82,no.4,pp.981–1011,2002.
41. Liou JT, Liu FC, Mao CC, Lai YS, and Day YJ, "Inflammation confersdual effects on nociceptive processing in chronic neuropathic pain model," Anesthesiology,vol.114,no.3, pp.660–672,2011.
42. Ji RR, Xu JJ, and Gao YJ, "Emerging targets in neuro inflammation-driven chronic pain," Nature Reviews Drug Discovery, vol. 13,no.7,pp.533–548,2014.
43. Ellis A and Bennett DLH, "Neuro inflammation and the generation of neuropathic pain," British Journal of Anaesthesia, vol.111,no.1,pp.26–37,2013.
44. Marchand F, Perretti M, and McMahon SB, "Role of the immune system in chronic pain," Nature Reviews Neuroscience, vol.6,no.7,pp.521–532,2005.
45. Svenss CI on, Sch¨afers M, Jones TL, Powell H, and Sorkin LS, "Spinal blockade of TNF blocks spinal nerve ligation induced increases in spinal P-p38," Neuroscience Letters, vol. 379,no.3,pp.209–213,2005.
46. Taves S, Berta T, Chen G, and Ji RR, "Microglia and spinal cord synaptic plasticity in persistent pain," Neural Plasticity, vol. 2013, Article ID753656,10pages,2013.
47. Kelvey RMC, Berta T, Old E, .Ji RR, and Fitzgerald M, "Neuropathic pain is constitutively suppressed in early life by anti-inflammatory neuro immune regulation," The Journal of Neuroscience,vol.35,no.2,pp.457–466,2015.
48. Renand K, Dubner R, "Interactions between the immune and nervous systems in pain," Nature Medicine, vol. 16, no. 11, pp. 1267–1276,2010.
49. Zuo Y, Perkins NM, Tracey DJ, and Geczy CL, "Inflammation and hyperalgesia induced by nerve injury in the rat :a key role of mast cells," Pain,vol.105,no.3,pp.467–479,2003.
50. Paladini A, Fusco M, Coaccioli S, Skaper SD, and Varrassi G, "Chronic pain in the elderly: the case for new therapeutic strategies,"PainPhysician,vol.18,no.5,pp.E863–E876,2015.
51. Borregaard N, Sørensen OE, and Theilgaard-M¨onch K, "Neutrophil granules: a library of innate immunity proteins," TrendsinImmunology,vol.28,no.8,pp.340–345,2007. [30] N. M. Perkins and D. J. Tracey, "Hyperalgesia due to nerve injury:roleofneutrophils,"Neuroscience,vol.101,no.3,pp.745– 757,2000.
52. Peters CM, Jimenez-Andrade JM, Jonas MB et al., "Intravenous paclitaxel administration in the rat induces a peripheral sensory neuropathy characterized by macrophage infiltration and injury to sensory neuron sand their supporting cells," Experimental Neurology, vol.203,no.1,pp.42–54,2007.
53. Liu T, van Rooijen N, and Tracey DJ, "Depletion of macrophages reduces axonal degeneration and hyperalgesia followingnerveinjury,"Pain,vol.86,no.1-2,pp.25–32,2000.
54. Campana WM, "Schwann cells: activated peripheral gliaand their role in neuropathic pain," Brain, Behavior, and Immunity, vol.21,no.5,pp.522–527,2007.

55. X. Li, Gonias SL, and Campana WM, "Schwann cells express erythropoietin receptor and represent a major target for Epoin peripheral nerve injury," Glia,vol.51,no.4,pp.254–265,2005.
56. Keswani SC, U. Buldanlioglu, A. Fischer et al., "A novel endogenous erythro poietin mediated pathway prevent saxonal degeneration,"Annal so Neurology,vol.56,no.6,pp.815–826, 2004.
57. Moalem G, Xu K, and Yu L, "T lymphocytes play a role in neuropathic pain following peripheral nerve injury in rats," Neuroscience,vol.129,no.3,pp.767–777,2004.
58. Tracey DJ and Walker JS, "Pain due to nerve damage: are inflammatory mediator sin volved," Inflammation Research,vol. 44,no.10,pp.407–411,1995.
59. Machelska H, Cabot PJ, Mousa SA, Zhang Q, and Stein C, "Pain control in inflammation governed by selectins," Nature Medicine,vol.4,no.12,pp.1425–1428,1998.
60. Gui W, Wei W, Mai C et al., "Interleukin-1 overproduction is a common cause for neuropathic pain, memory deficit, and depression following peripheral nerve injury in rodents," MolecularPain,vol.12,2016.
61. Kawasaki Y, Xu ZZ, Wangetal X, "Distinct roles of matrix metal oproteases in the early- and late-phase development of neuropathic pain," Nature Medicine, vol. 14, no. 3, pp. 331–336, 2008.
62. Feng T, Yin Q, Weng ZL et al., "Rapamycin ameliorates neuropathic pain by activating autophagy and inhibiting interleukin-1β in the rat spinal cord," Journal of Huazhong University of Science and Technology—Medical Science, vol. 34, no.6,pp.830–837,2014.
63. Kawasaki Y, Zhang L, Cheng JK, and Ji RR, "Cytokine mechanisms of central sensitization: distinct and over lapping role of inter leukin-1β, interleukin-6, and tum or necrosis factor α in regulating synaptic and neuronal activity in the superficial spinal cord," Journal of Neuroscience, vol. 28, no. 20, pp. 5189– 5194,2008.
64. George A, Schmidt C, Weishaupt A, Toyka KV, and Sommer C, "Serial determination of tumor necrosis factor-alpha content in rat sciatic nerve after chronic constriction injury," ExperimentalNeurology,vol.160,no.1,pp.124–132,1999.
65. Andrade P, Hoogland G, DelRosario JS, Steinbusch HW, Visser-Vandewalle V, and Daemen, "Tumornecrosis factor α inhibitors alleviation of experimentally induced neuropathic pain is associated with modulation of TNF receptor expression," Journal of Neuroscience Research,vol.92,no.11,pp.1490–1498, 2014.
66. Xu J, X. E, H. Liu et al., "Tumor necrosis factor-alpha is a potential diagnostic biomarker for chronic neuropathic pain after spinal cord injury," Neuroscience Letters, vol. 595, pp. 30– 34,2015.
67. Cui JC, Holmin S, Mathiesen T, Meyerson BA, and Linderoth B, "Possible role of inflammatory mediators in tactile hypersensitivity in rat models of mono neuropathy," Pain, vol. 88,no.3,pp.239–248,2000.
68. Ramer MS, Kawaja MD, Henderson JT, Roder JC, and Bisby MA, "Glial over expression of NGF enhances neuropathic pain and adrenergic sprouting into DRG following chronic sciatic constriction in mice," Neuroscience Letters, vol. 251, no. 1,pp.53–56,1998.
69. Tanaka T, Minami M, Nakagawa T, and Satoh M, "Enhanced production of monocyte chemo attract an protein-1inthedorsal root ganglia in a rat model of neuropathic pain: possible involvement in the development of neuropathic pain," Neuroscience Research, vol.48,no.4,pp.463–469,2004.
70. Nassar MA, Levato A, Stirling LC, and Wood JN, "Neuropathic pain develops normally in mice lacking both Nav1.7andNav1.8,"MolecularPain,vol.1,article24,2005.
71. Minett MS, Falk S, Santana-VS., "Pain without nociceptors? Nav1.7- in dependent pain mechanisms," Cell Reports, vol.6,no.2,pp.301–312,2014.
72. Dong XW, Goregoaker S, Engleretal H, "Small interfering RNA-mediated selective knockdown of NaV1.8 tetrodo toxinresistant sodium channel reverses mechanical allodynia in neuropathicrats,"Neuroscience,vol.146,no.2,pp.812–821,2007.
73. Yan J, Zou K, Liuetal X., "Hyper excitability and sensitization of sodium channels of dorsal root ganglion neurons in a rat model of lumber discherniation," European Spine Journal,vol. 25,no.1,pp.177–185,2016.
74. Hains BC, Klein JP, Saab CY, Craner MJ, Black JA, and Waxman SG, "Upregulation of sodium channel Nav1.3 and functional involvement in neuronal hyper excitability associated with central neuropathic pain after spinal cord injury," The JournalofNeuroscience,vol.23,no.26,pp.8881–8892,2003.
75. Samad OA, Tan AM, Cheng X, Foster E, Dib-Hajj SD, and Waxman SG, "Virus-mediated sh RNA knockdown of Nav1.3 in rat dorsal root ganglion attenuates nerve injury-induced neuropathic

pain,"MolecularTherapy,vol.21,no.1,pp.49–56, 2013.
76. Aurilio C, Pota V, Pace MC, Passavanti MB, and Barbarisi M, "Ionic channels and neuropathic pain: phisiopatology and applications," Journal of Cellular Physiology, vol.215,no.1, pp.8–14,2008.
77. Jagodic MM, Pathirathna S, Joksovicetal PM., "Upregulation of the T-type calcium currentin small rat sensory neurons after chronic constrictive injury of the sciatic nerve," Journal of Neurophysiology,vol.99,no.6,pp.3151–3156,2008.
78. Dogrul A, Gardell LR, Ossipov MH, Tulunay FC, Lai J, and Porreca F, "Reversal of experimental neuropathic pain by T-type calcium channel blockers," Pain,vol.105,no.1-2,pp.159–168,2003.
79. Saegusa H, Kurihara T, Zongetal S, "Suppression of inflammatory and neuropathic pain symptom sin micelacking the N type Ca2+ channel," EMBO Journal, vol. 20, no. 10, pp. 2349–2356,2001.
80. Richardson JD, Kilo S, and Hargreaves KM, "Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors," Pain, vol.75,no.1,pp.111–119,1998.
81. Bley KR, "Recent development sin transient receptor potential vanilloid receptor 1agonist-based therapies," Expert Opinion on Investigational Drugs, vol.13,no.11,pp.1445–1456,2004.
82. Vilceanu D, Honore P, Hogan QH, and Stucky CL, "Spinal nerve ligation in mouse up regulates TRPV1 heat function in injuredIB4-positive nociceptors," Journal of Pain,vol.11,no.6, pp.588–599,2010.
83. Qu YJ, Zhang X, Fanetal ZZ, "Effect of TRPV4-p38 MAPK pathway on neuropathic pain in rats with chronic compression of the dorsal root ganglion," Bio Med Research International, vol. 2016,ArticleID6978923,12pages,2016.
84. Olney JW and Farber NB, "NMDA antagonists as neurotherapeutic drugs, psychotogens, neurotoxins, and research tools for studying schizophrenia," Neuropsychopharmacology,vol.13, no.4,pp.335–345,1995.
85. Klabunde T and Hessler G, "Drug design strategies for targeting G-protein-coupled receptors,"ChemBioChem,vol.3,no.10, pp.928–944,2002.
86. Leeand GHS, Kim S, "Therapeutic strategies for neuropathic pain: potential application of pharmaco synthetics and optogenetics, "Mediators of Inflammation, vol.2016,ArticleID5808215, 11pages,2016.
87. Gwak YS and Hulsebosch CE, "GABA and central neuropathic pain following spinal cord injury," Neuropharmacology, vol.60,no.5,pp.799–808,2011.
88. Drew GM, Siddall PG, and Duggan AW, "Mechanical allodynia following contusion injury of the rat spinal cord is associated with loss of GABA ergic inhibition in the dorsal horn,"Pain,vol.109,no.3,pp.379–388,2004.
89. Gwak YS, Crown ED, Unabia GC, and Hulsebosch CE, "Propent of ylline attenuates allodynia, glial activation and modulates GABA ergic tone after spinal cord injury in the rat," Pain, vol.138,no.2,pp.410–422,2008.
90. Meisner JG, Marsh AD, and Marsh DR, "Loss of GABA ergic interneurons in laminae I-III of the spinal cord dorsal horn contributes to reduced GABA ergic tone and neuropathic pain after spinal cordinjury," Journal of Neuro trauma,vol.27,no.4, pp.729–737,2010.
91. Kim HJ, "Berberineamelio rates allodynia induced by chronic constriction injury of the sciatic nerve in rats," Journal of MedicinalFood,vol.18,no.8,pp.909–915,2015.
92. Zhang K, Ramamurthy S, Prihoda TJ, and Eckmann MS, "Effect of delayed intrathecal administration of capsaicin on neuropathic pain induced by chronic constriction injury of the sciatic nerve in rats," Journal of Pain Research, vol. 7, pp. 547– 554,2014.
93. Klauke AL, Racz I, Pradier B et al., "The cannabinoid CB2 receptor-selective phyto cannabinoid beta-caryophyllene exerts analgesic effects in mouse models of inflammatory and neuropathic pain," European Neuropsychopharmacology, vol.24, no.4,pp.608–620,2014.
94. Lim DW, Kim JG, Han T et al., "Analgesic effect of Ilex paraguariensis extract on postoperative and neuropathic pain in rats," Biological and Pharmaceutical Bulletin, vol. 38, no. 10, pp.1573–1579,2015.
95. Hara K, Haranishi Y, Kataoka K et al., "Chlorogenic acid administered intrathecally alleviates mechanical and cold hyperalgesia in a rat neuropathic pain model," EuropeanJournal ofPharmacology,vol.723,no.1,pp.459–464,2014.
96. Kumar TP, Antony S, Gireesh G, George N, and Paulose CS, "Curcumin modulates dopaminergic receptor, CREB and phospholipase Cgene expression in the cerebral cortex and cerebellum of streptozotocin induced diabetic rats," Journal of BiomedicalScience,vol.17,article43,2010.

97. Zhang Y, Wang C, Wang L et al., "A novel analgesic isolated from at raditional Chine semedicine,"CurrentBiology,vol.24, no.2,pp.117–123,2014.
98. Kono T, Hata T, Morita S, Munemoto Y, Matsui T, Kojima H, et al. Goshajinkigan oxaliplatin neurotoxicity evaluation (GONE): a phase 2, multicenter, randomized, doubleblind, placebo-controlled trial of goshajinkigan to prevent oxaliplatin-induced neuropathy. Cancer Chemother Pharmacol 2013;72:1283-1290.
99. Watanabe K, Shimada A, Miyaki K, Hirakata A, Matsuoka K, Omae K, et al. Long-term effects of Goshajinkigan in prevention of diabetic complications: a randomized open-labeled clinical trial. Evid Based Complement Alternat Med 2014;2014.
100. Qiu H-Q, Xu Y, Jin G-L, Yang J, Liu M, Li S-P, et al. Koumine enhances spinal cord 3α-hydroxysteroid oxidoreductase expression and activity in a rat model of neuropathic pain. Mol Pain 2015;11:1-13.