Project On

A Review on Flavonoids in Neuropathic Pain

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APPROVAL

This project, A review on Flavonoids in Neuropathic Pain, submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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DECLARATION

I, at this moment, announce that I am carrying out this project study under the supervision of "Ms. Aklima Akter." Assistant Professor, Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, Impartial Compliance with the Bachelor of Pharmacy Degree Requirement (B. Pharm). This project, I declare, is my original work. I also state that neither this project nor any part thereof has been submitted for the Bachelor's award or any degree elsewhere.

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Author

Shahzadi feroza sultana

DEDICATION

I dedicate this work to my parents and my teachers and my friends.

ABSTRACT

The US healthcare system continues to bear a heavy burden from chronic pain. Despite intensive research efforts, neuropathic pain, a common type of chronic pain, is still very difficult to treat. The efficacy of current pharmacologic regimens is limited, and a variety of potentially harmful side effects are present. A thorough preclinical analysis of the literature on the use of flavonoids in the management of neuropathic pain is provided in this review. Flavonoids are naturally occurring substances that can be found in a variety of dietary sources, including plants, and they may be useful in treating neuropathic pain. This advantage has been shown in numerous studies using animal models, including the reversal of allodynia and hyperalgesia. As shown by the decline in numerous pro-inflammatory mediators like TNF-, NF-B, IL-1, and IL-6, flavonoids have also demonstrated an anti-inflammatory effect relevant to neuropathic pain. For neuropathic pain, flavonoids show promise in preclinical models but have not yet been tested in humans.

Keywords: Neuropathic, Pharmacological, Anti-Inflammatory, Drug, Flavonoids

Table of content

Chapter One: Introduction

Chapter Two: Literature Review

Chapter Three: Goal of my study

Chapter Four: Methodology

Chapter Five: Outcome & Discussion

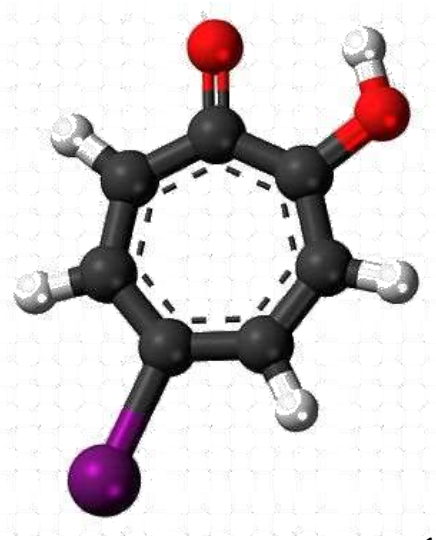
Chapter Six: Conclusion

Chapter Seven: Reference

List Of Figures-

List of Table-

Introduction



The International Association for the Study of Pain (IASP) previously defined neuropathic pain as "pain initiated or caused by a primary lesion or dysfunction of the nervous system," but the NeuPSIG recently revised this definition to "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system." Therefore, under the revised description, this pain has been primarily connected to being the result of a disease impairing the "somatosensory system" rather than the "nervous system," further elucidating its origin. Under normal conditions, hazardous information is sent to the central nervous system via the somatosensory system. As a result, in addition to preventing nerve cell innervation, a somatosensory system injury may also result in pain at the site of the discomfort, with or without a sensory hypersensitivity episode. When the somatosensory system is damaged, both positive and negative sensory problems may appear. Negative sensory symptoms are brought on by a partial or total loss of input to the neurological system, while positive sensory symptoms result from nerve cell regeneration and disinhibition as a result of reduced sensory input. In reaction to a stimulus or spontaneously, positive symptoms might appear. While hyperalgesia and allodynic pain are stimulus-evoked positive symptoms of neuropathy, paraesthesias (tingling or ant-crawling sensations across the skin), spontaneous continuous or shooting pain (stimulus-independent), and electric shock-like sensations are not. Negative signs and symptoms of neuropathic pain include hypoalgesia (abridged impression to noxious stimuli), pallyhypoesthesia (reduced sensations to vibration), and thermohypoesthesia (abridged impression to cold/warm). Opioids, tricyclic antidepressants, gabapentin, pregabalin, phenytoin, lamotrigine, dextromethorphan, tramadol, and mexiletine may be effective treatments for painful sensory neuropathy, according to multiple controlled studies. These therapies, with sedation being the most frequent, do not completely eliminate pain; rather, they only lessen it by 30 to 50 percent and are often only temporary.

Pain

4.1. Pain

An unpleasant emotion is often brought on by powerful or potentially harmful stimuli. According to the International Association for the Study of Pain, pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage."[1] Pain is considered to be a symptom of an underlying condition when performing a medical diagnosis. Pain causes an individual to remove themselves from potentially harmful situations, to protect a damaged body part while it heals, and to steer clear of similar experiences in the future. [2] The majority of pain disappears once the noxious stimulus is removed and the body has healed, but it is possible for the pain to persist despite the removal of the stimulus and apparent healing of the body. [Case in Sometimes a person may experience pain even when there is no obvious cause, injury, or illness present.[3] Pain is the most common reason people seek medical attention in most developed countries [4-5]. It is a major symptom of many medical conditions, and it can interfere with a person's quality of life and general functioning.[6] Simple pain medications are effective in 20% to 70% of cases.[7] Psychological factors such as social support, cognitive behavioral therapy, excitement, or distraction can affect the intensity or unpleasantness of pain.[8-9]It has been argued that allowing those who are suffering from terminal illnesses to end their lives via euthanasia or physician-assisted suicide is the compassionate thing to do since they are in agony.[10]

Fig 01 : Pain

Etymology

The word "penalty" first appeared in the English language in the year 1297. It is derived from the Old French word "ensure," which originated from the Latin word "poena," which meant "punishment" (and also "torment, hardship, and suffering" in Late Latin), which in turn originated from the Greek word "v" (point), which generally meant "price paid, penalty, and punishment." [12-13]

4.2.Classification

Specific characteristics should be included when describing a patient's pain, as recommended by the International Association for the Study of Pain:

- ✓ region of the body involved (e.g., abdomen, lower limbs),
- ✓ a system whose dysfunction may be causing the pain (e.g., nervous, gastrointestinal),
- ✓ duration and pattern of occurrence,
- ✓ intensity, and
- ✓ cause[14]

Chronic versus acute

Rheumatoid arthritis, peripheral neuropathy, cancer, and idiopathic pain may endure for years. Chronic pain lasts longer than acute pain. Acute and chronic pain has traditionally been distinguished by an arbitrary period of time between onset and remission, with 3 months and six months being the most popular markers [15]. Some theories and researchers have put the shift from acute to chronic pain at 12 months. [16]: 93 Others call "acute" pain less than 30 days, "chronic" pain more than six months, and "subacute" pain one to six months. "Pain that lingers beyond the usual time of recovery" is a common definition of chronic pain. Cancer-related or benign chronic discomfort. [17]

Allodynia

A typically painless stimulation causes allodynia. Stimuli classify it as dynamic mechanical, punctate, or static. [18-19]

Phantom

Phantom pain is perceived in an amputated or non-signaled bodily component. Neuropathic pain. [20] Phantom pain affects 82% of upper-limb amputees and 54% of lower-limb amputees. One research indicated that 72% of patients experienced phantom limb discomfort eight days after amputation and 67% six months afterward. [21-22] Some amputees have daily agony, while others have it less frequently. Shooting, crushing, scorching, or cramping are common descriptions. Long-term pain may cause sensitive areas of the intact body, causing the phantom limb to hurt when touched. Phantom limb pain may precede urination or feces.

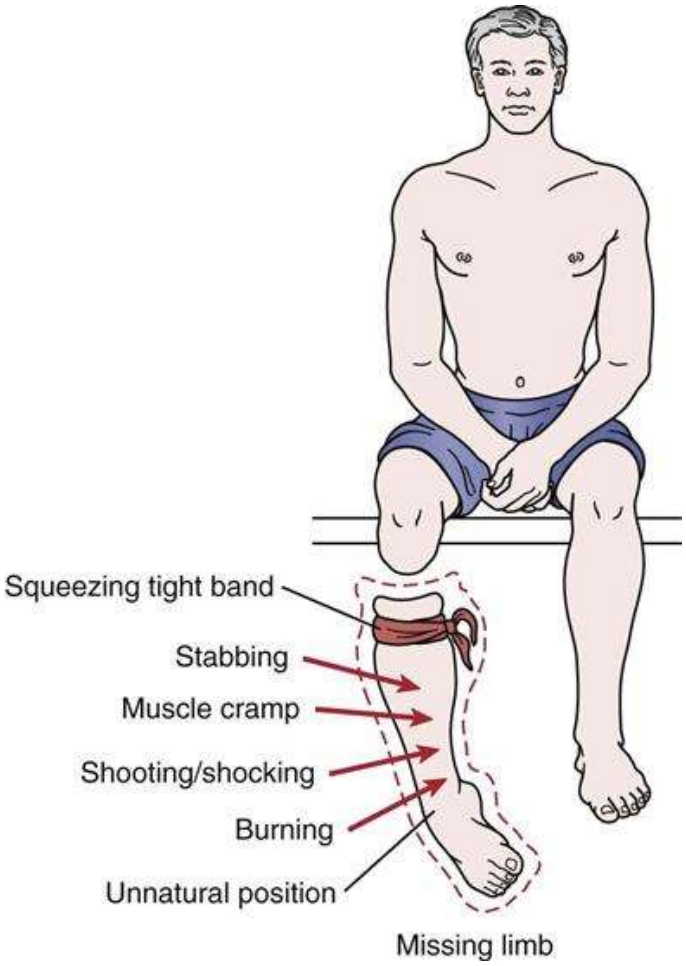


Fig 02: Phantom limb pain

Local anesthetic injections into the nerves or sensitive areas of the stump may relieve pain for days, weeks, or even permanently, despite the drug wearing off in hours. Small injections of hypertonic saline into the soft tissue between vertebrae produce local pain that radiates into the phantom limb for ten minutes and may relieve phantom pain for hours, weeks, or even longer.[23] Some individuals get relief with vigorous stump vibration, electrical stimulation, or spinal cord electrodes. Mirror box treatment may reduce phantom limb discomfort by creating the appearance of movement and touch.[24] Paraplegia, the loss of feeling and voluntary motor control following substantial spinal cord injury, may be accompanied by girdle pain at the spinal cord damage, visceral discomfort from a filled bladder or bowel, or phantom body pain in regions of total sensory loss in five to ten percent of paraplegics. Phantom bodily pain starts as scorching or tingling and progresses to crushing, pinching, fire flowing down the legs, or a knife twisting in the skin. Onset may be instantaneous or years after the crippling injury. Surgery seldom lasts.

Breakthrough

Breakthrough pain is abrupt, untreated pain. Cancer patients frequently have background pain that is well-controlled by drugs but sometimes has extreme pain that "breaks through" the medication. Breakthrough cancer pain varies by individual and cause. Breakthrough pain may need fentanyl and other medications. [25-26]

Insensitivity and asymbolia

Pain helps prevent and detect harm. A soldier on the battlefield may not experience pain after a catastrophic amputation or other serious injuries for hours because of episodic analgesia. [27-28] Morphine injection or psychosurgery may elicit extreme pain without unpleasantness in certain people, despite the IASP definition of pain requiring unpleasantness. [29] Patients report feeling pain but not being troubled by it. [30] Rarely do those born indifferent to pain have normal nerves, find pain unpleasant, and repeat the pain stimulation. Nervous system problems may potentially cause pain insensitivity. Spinal cord injury, diabetes mellitus (diabetic neuropathy), and leprosy in places where it is common to cause this. Undiscovered injuries may cause tissue damage and infection in these people. Due to diminished sensitivity, diabetics' foot sores heal poorly. Congenital insensitivity to pain is rare and caused by a neural system defect. This disorder repeatedly damages tongues, eyes, joints, skin, and muscles. Some die young; others have shorter

lives. (ref) Five genetic sensory and autonomic neuropathies cause most congenital insensitivity to pain (which includes familial dysautonomia and congenital insensitivity to pain with anhidrosis). These diseases include autonomic nervous system anomalies and diminished pain sensitivity. [31] Mutations in the SCN9A gene, which encodes a sodium channel (Nav1.7) that conducts pain nerve inputs, have been related to a rare disease of isolated congenital insensitivity to pain.

4.3.Neuropathic

Neuropathy may refer to either a disruption in nerve function or a change in the nerves themselves. Diabetes is responsible for around thirty percent of instances of neuropathy. Sometimes it might be difficult to determine what exactly is causing the neuropathic pain. This particular form of suffering may be attributed to any one of several hundred different illnesses.

4.4.Neuropathic pain

Pain that is caused by injury or illness that affects the somatosensory system is referred to as neuropathic pain. [32-33] Pain caused by neuropathy may be coupled with aberrant sensations known as dysesthesia or with pain triggered by stimuli that are not typically uncomfortable (allodynia).

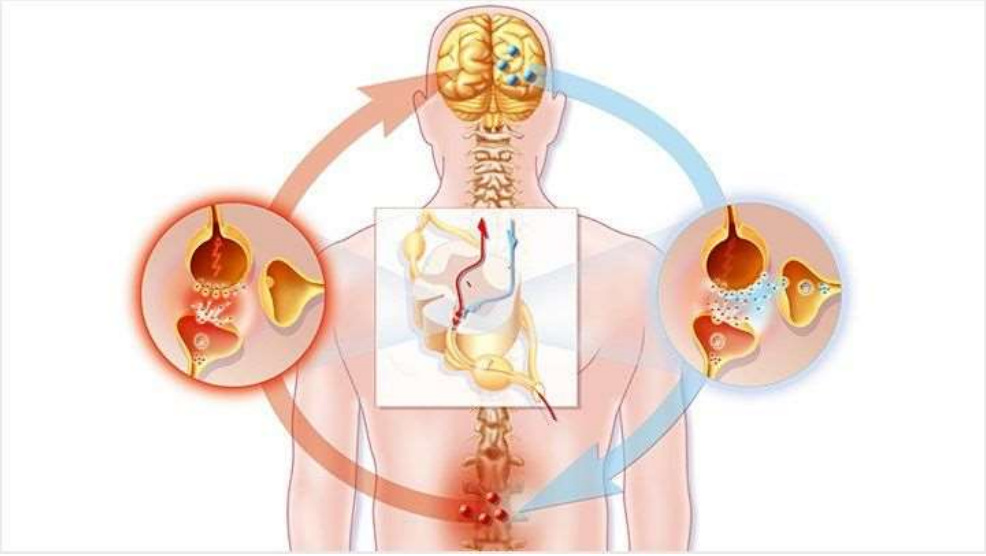


Fig 03: Neuropathic pain

It is possible that it will have both continuous and episodic (paroxysmal) features. The latter feels like being stabbed or getting an electric shock. The feeling of "pins and needles," itching, burning, numbness, and general itchiness are all often experienced symptoms. As much as 7%-8% of the population in Europe is affected,[34] and the severity of the condition may vary from person to person. [35-36] Pain that is classified as neuropathic may be caused by dysfunctions in either the central nervous system or the peripheral nervous system (brain and spinal cord). Accordingly, neuropathic pain may be classified as either peripheral neuropathic pain, central neuropathic pain, or mixed neuropathic pain (which includes both peripheral and central components). Pain due to neuropathy may occur by itself or in conjunction with other types of pain. The primary goals of medical therapies are to ascertain the root cause of the problem and to alleviate suffering. In certain forms of neuropathy, the sensation of pain might eventually be replaced by numbness.

4.5.History

It is possible to trace the origins of pain treatment all the way back to ancient times. Galen also theorized that nerve tissue served as a conduit for the transmission of pain signals from the body to the brain through an unseen psychic pneuma. [37] Medieval medical experts, including Rhazes, Haly Abbas, and Avicenna, put forward the concept that pain originates from the nerve itself and that there should not be any stimulating disease in other organs in order for there to be a pain. They referred to this unique kind of pain as "Vaja al as" (which translates to "pain originating in the nerves"), characterized its numbness, tingling, and needling nature, and spoke about its genesis as well as the distinguishing qualities. [38] John Fothergill is the one who first characterized the condition known as neuralgia (1712-1780). Gordon used the term "neuropathy" for the very first time in 1924 in a medical publication that was titled "Clinical Lecture on Lead Neuropathy," which was sent to medical professionals at that time. [39]

4.6.Cause

Multiple sclerosis, spinal cord damage, and spinal neuropathic pain are all examples of central neuropathic pain. [40] Diabetes, metabolic diseases, herpes zoster infection, HIV-related neuropathies, nutritional deficiencies, toxins, distant manifestations of malignancies, immunologically mediated illnesses, and physical damage to a nerve trunk are among the major causes of peripheral neuropathies. [41-42] As a direct outcome of cancer on peripheral nerves

(such as compression by a tumor) or as a side effect of chemotherapy (chemotherapy-induced peripheral neuropathy), neuropathic pain is frequent in cancer patients. [43] surgery or radiation harm.

4.7.What signs are present?

Although each person's neuropathic pain symptoms may vary significantly, the following ones are often experienced:

- ✓ Pain that is stabbing, scorching, or shooting
- ✓ Tingling and numbness, or a sensation of "pins and needles."
- ✓ Spontaneous pain, or discomfort that develops without cause
- ✓ Induced pain, also known as pain brought on by circumstances that ordinarily aren't uncomfortable, such as combing your hair, rubbing up against anything, or being in a chilly environment.
- ✓ A persistent sense of being uneasy or strange
- ✓ Having trouble sleeping or relaxing
- ✓ Emotional issues brought on by persistent discomfort, slumber loss, and difficulties sleeping
- ✓ Communicating your feelings

4.8.Diagnosis

Sharp, stabbing pain, as well as the presence of specific traits like mechanical allodynia and cold allodynia, are used in the diagnosis of many pain syndromes. Neuropathic pain also has a tendency to impact certain dermatomes, and its distribution may be restricted. Clinicians treating patients with neuropathic pain seek damage to the nervous system or an initiating reason that is consistent with the onset of neuropathic pain. In circumstances when the identification of the underlying lesion leaves the patient in pain for an extended length of time, the patient's reaction to therapy may be utilized as a proxy to determine the existence of an underlying characteristic or cause. The main manifestation of a tumor or multiple sclerosis is two examples of dangerous underlying illnesses that may be diagnosed with MRI's aid.[44] Numerous studies have employed quantitative sensory testing (QST), a method of an in-depth examination of the somatosensory system, to detect neuropathic pain and dissect its components. Some experts have hypothesized that QST might one

day be used to help diagnose neuropathic pain and, more specifically, help distinguish between the many subtypes of neuropathic pain. It is possible for neuropathic pain to coexist with other forms of pain. Different types of analgesics are needed; therefore, learning how to categorize neuropathic pain is crucial. Skin biopsies are the gold standard for determining whether or not small fiber neuropathy is the underlying cause of neuropathic pain. A screening approach to reduce the number of patients who need a skin biopsy is electrochemical skin conductance evaluation, which is an accurate, objective procedure. [45-46]

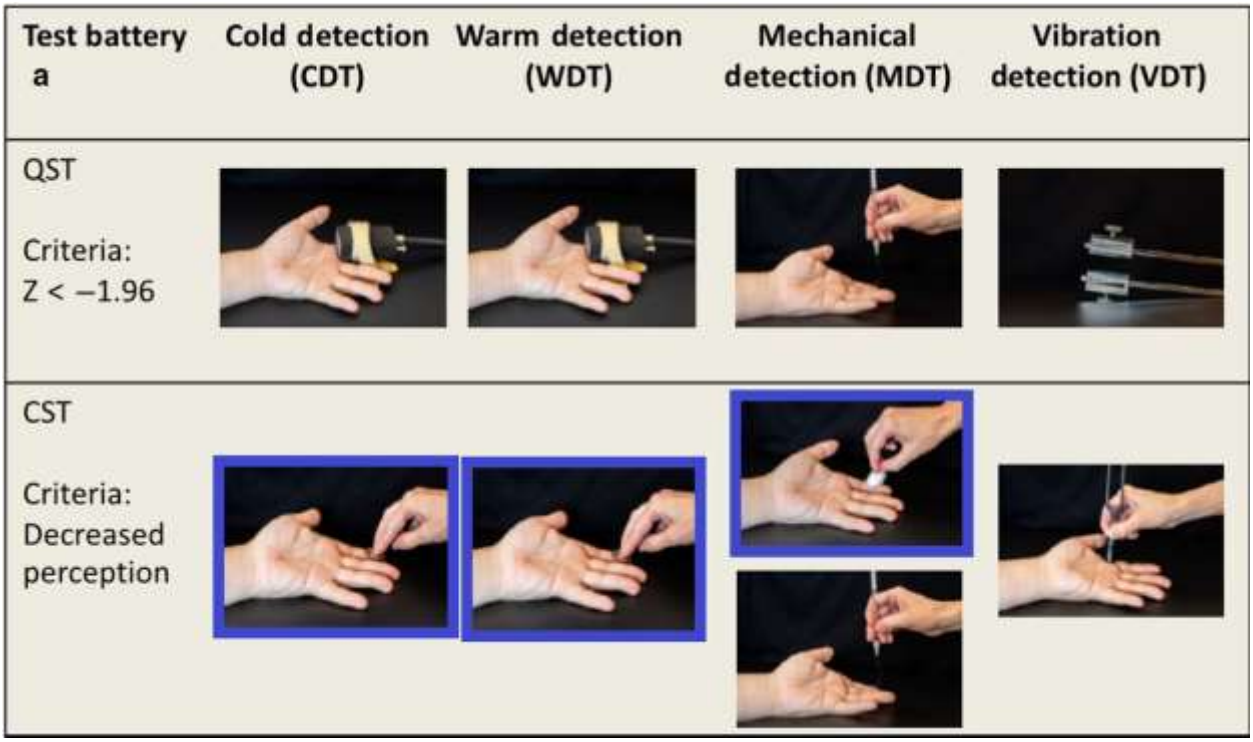


Fig 04: Quantitative sensory testing (QST)

4.9. Treatment

Over time, some of the symptoms of neuropathy will begin to improve. The symptoms of neuropathic pain may sometimes be alleviated by treating or controlling the underlying source of the pain. People who suffer from chronic neuropathic pain may need therapy in order to get relief from the uncomfortable or disabling symptoms they experience. In most cases, using nonsteroidal anti-inflammatory medications will not be helpful for treating neuropathic pain.

Additional drugs that might help alleviate nerve discomfort include the following:

- ✓ antiepileptic medications
- ✓ antidepressants
- ✓ Injections of capsaicin cream, lidocaine patches, or nerve blocks, which may be a mix of steroids, opioids, and anesthetics, are some of the treatment options.
- ➢ The use of transcutaneous electrical nerve stimulation (TENS) equipment is another therapy option that a doctor could recommend. A transcutaneous electrical nerve stimulation (TENS) machine works by sending a mild electrical impulse to the site of the pain through an electrode that is adhered to the skin.
- ➢ It's possible that the impulse will activate some neurons while also blocking pain signals. This may aid in the relaxation of the muscles and reduce the intensity of unpleasant sensations.
- ➢ A person may choose to attempt percutaneous electrical nerve stimulation (PENS) in the event that a TENS machine is not successful in relieving pain (PENS). PENS operates in a manner that is similar to that of TENS; however, as opposed to placing the electrode on the surface of the skin, a medical expert will insert the electrode under the surface of the skin using a needle.
- ➢ Acupuncture may provide some relief from the neuropathic pain experienced by certain patients. It's possible that this may assist activate the neural system and bring about a healing response, which will make the pain easier to bear.
- ➢ Surgery is another option for patients suffering from severe instances of some forms of nerve injury, such as compression mononeuropathy, who are seeking relief from their symptoms.[64-65]

Neuropathic pain types

5.1. Neuropathic pain types

- Peripheral neuropathy
- Autonomic neuropathy
- Focal neuropathy
- Proximal neuropathy
- Diabetic neuropathy
- Compression mononeuropathy
- Phantom limb syndrome
- Trigeminal neuralgia

Peripheral neuropathy

Weakness, numbness, and pain often manifest in the hands and feet as symptoms of peripheral neuropathy, which results from damage to the nerves outside of the brain and spinal cord. Digestion, urine, and circulation are just a few of the numerous bodily processes that may be impacted.[47]

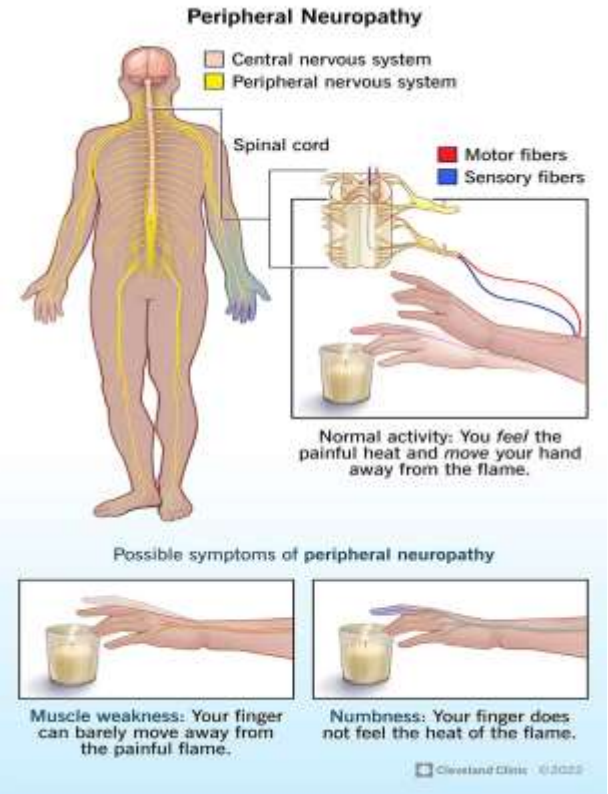


Fig 05: Peripheral neuropathy

Autonomic neuropathy

Autonomic neuropathy (AN or AAN) is a kind of polyneuropathy that mostly affects the internal organs, including the bladder muscles, cardiovascular system, digestive system, and genital organs since it affects the non-voluntary, non-sensory nerve system (i.e., the autonomic nervous system). These nerves do their job automatically, outside of a person's awareness. Large groups of autonomic nerve fibers congregate in locations beyond the spinal cord, including the thorax, belly, and pelvis. However, they are linked to the spinal cord and, from there, the brain. Individuals with type 1 and 2 diabetes mellitus who have had the disease for a very long time can get autonomic neuropathy. Autonomic neuropathy is often seen in conjunction with other types of neuropathy, such as sensory neuropathy. However, this is not always the case. Symptoms similar to autonomic neuropathy can be caused by a number of different conditions, not just autonomic neuropathy, which is just one cause of autonomic nervous system dysfunction (dysautonomia). Conditions affecting the brain or spinal cord, such as multiple system atrophy, can also cause autonomic dysfunction.[48]

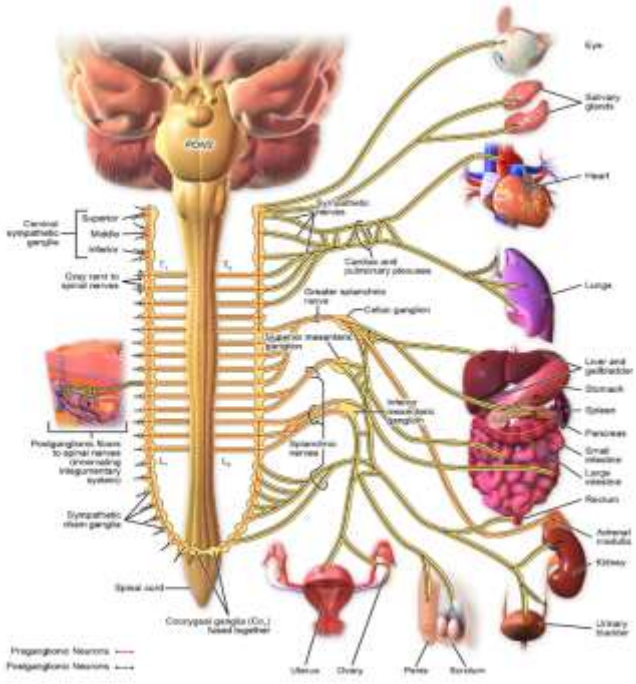


Fig 06: Autonomic neuropathy

Diabetic neuropathy

Diabetes-related neuropathy encompasses a spectrum of symptoms caused by nerve injury. Motor changes like weakness; sensory changes like numbness, tingling, or pain; and autonomic changes like urine symptoms may occur when nerve injury occurs anywhere in the body. It is hypothesized that damage to the tiny blood capillaries that nourish nerves causes these alterations (vasa nervorum). Distal symmetric polyneuropathy; third, fourth, or sixth cranial nerve palsy;[49] mononeuropathy; mononeuropathy multiplex; diabetic amyotrophy; autonomic neuropathy; these are all rather frequent disorders that may be linked with diabetic neuropathy.

Trigeminal neuralgia

Trigeminal neuralgia (TN or TGN), also known as Fothergill disease, tic douloureux, or trifacial neuralgia, is a chronic pain ailment that affects the trigeminal nerve. Other names for this condition are trifacial neuralgia, Fothergill disease, and tic douloureux. The nerve that is responsible for feeling in the face and motor processes such as biting and chewing; is also known as the trigeminal nerve. It is a kind of nerve pain known as neuropathic pain. Trigeminal neuralgia may be divided into two primary categories: normal and atypical. The normal type is characterized by attacks of acute, abrupt, electric-like pain on one side of the face that may last anywhere from a few seconds to a few minutes at a time. Clusters of these episodes may take place over the course of a few hours. The atypical variant causes a continuous searing pain that is not as intense as the normal form. An episode may be brought on by even the slightest contact to the face. Both manifestations are possible in the same individual. It is considered to be one of the most painful conditions that can be treated by medication, and the accompanying depression is a common side effect. Although the precise origin is uncertain, it is thought to entail a degeneration of the myelin sheath around the trigeminal nerve.[50]This might be the result of multiple sclerosis, a stroke, trauma, or any other condition in which the neuron, as it leaves the brain stem, is compressed by a blood vessel. A tumor or an arteriovenous malformation are two examples of less frequent causes of this condition. It's a kind of nerve pain that may be rather severe. [51] The symptoms are often used to make a diagnosis after other probable reasons, such as postherpetic neuralgia, have been eliminated from consideration. A patient may be treated with either medicine or surgery. The anticonvulsant medications carbamazepine or oxcarbazepine are often used as the first line of therapy, and they are successful in around 90% of patients. Patients regularly report experiencing side effects, and

in as many as 23% of cases, these symptoms require them to stop taking the medication. [52] Lamotrigine, baclofen, gabapentin, amitriptyline, and pimozide are among the other alternatives available. The conventional preparation of opioids does not often result in the desired therapeutic impact. A variety of surgical procedures may be attempted on patients who do not show signs of improvement or who develop resistance to conventional treatments. It is anticipated that one in every 8,000 persons may get trigeminal neuralgia in their lifetime. It often first appears in persons over the age of 50. However, it may strike anyone of any age. The condition affects women more often than it does males. In 1773, John Fothergill was the first person to provide a detailed description of the disease. [53]

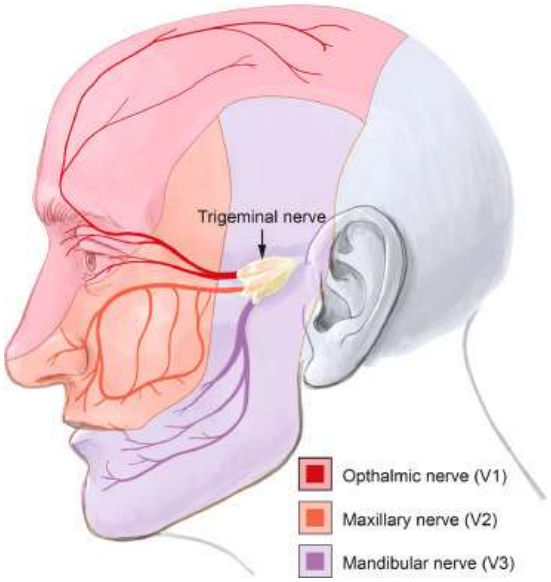


Fig 07 : Trigeminal neuralgia

A theoretical framework for neuropathic pain

6.1.Theoretical framework for neuropathic pain

The debate over what causes neuropathic pain continues. It is the source of the pain that determines its etiology and its mechanism. Some types of neuropathic pain, such as thalamic pain caused by lesions (like strokes) to the thalamus [54], originate in the central nervous system, whereas other types, like traumatic neuropathies, involve a peripheral initiating injury. Different tissues and cells are involved in neuropathy. Hence the triggering reason has significant implications for its mechanistic foundation. Both the proportional contributions of each route and the underlying molecular basis of neuropathic pain are still up for debate. Notably, while investigating these tissues in live humans is challenging, rat models have been crucial in driving our knowledge of these processes.

Peripheral

Lesions in the peripheral nervous system may lead to a variety of symptoms and conditions. It is possible for intact neurons to become too sensitive, exhibit aberrant activity on their own, and exhibit abnormal excitability. During neuropathic pain, alterations in the expression of ion channels at the peripheral level seem to contribute to the development of ectopic activity in peripheral nociceptors. Action potential generation might be bolstered by an uptick in the expression or activity of voltage-gated sodium and calcium channels. Likewise, potassium channels, which would typically function as a brake on action potential formation, may be less abundant. All of these alterations lend credence to the idea that excitability has been raised, perhaps making endogenous stimuli capable of eliciting pain on their own. [55]

Central

Neuropathy pain has a few different primary mechanisms. Normally, the spinal cord, the spinothalamic tract, the thalamus, and finally, the cortex are all involved in the polysynaptic transmission of nociception. Hypersensitization of neurons, activation of glia, and a reduction in inhibitory tone are all features of neuropathic pain.

Gates of pain

The gate control theory of pain, introduced by Wall and Melzack in 1965, is a major concept in the study of pain perception. Non-pain-detecting neurons, according to the hypothesis, may limit

the transmission of benign stimuli to pain centers by activating central pain-inhibitory neurons. Some systems, such as those of rats and mice, show a loss of inhibitory neurons, as measured by GAD65/67 expression (the enzymes that synthesize GABA, the major inhibitory transmitter in the adult brain). [56] Although these findings have been widely shared, they are still debated since not all researchers have seen a shift. In the absence of inhibitory inputs, sensory fibers may instead send pain signals through the spinothalamic tract. Loss of GABA has been identified in the thalamus of chronic pain sufferers, suggesting that this loss of inhibition is not confined to the spinal cord. [57]

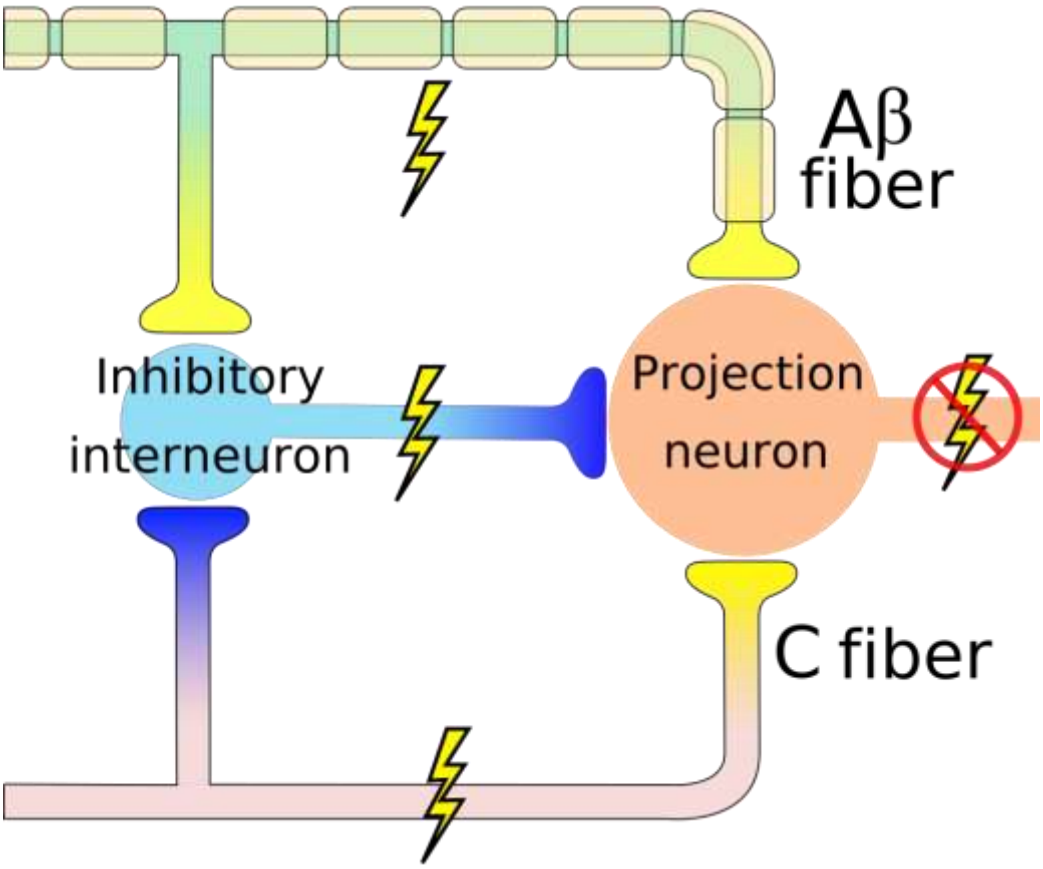


Fig 08: Gate control theory of pain

Glia

Cultures of microglia (labeled with alpha-coronin1a) and neurons. It has been hypothesized that microglia emit chemicals that modify neuronal excitability. Neuron support cells called glia become "active" and secrete substances that regulate neuronal activity while experiencing neuropathic pain. Researchers are still very interested in glial activation. Microglia, immunological cells found in the central nervous system, react to stimuli from the outside world. These signals may originate from neurons that release chemokines like CCL21 or from surface-immobilized chemokines like CX3CL1. These extrinsic signals for microglia may be released by other glia, such as astrocytes and oligodendrocytes, or they may be amplified by proteins produced by microglia themselves. [58] Microglia's sensitizing impact on neurons is hotly debated. Microglia may generate brain-derived neurotrophic factors, prostaglandins, tumor necrosis factor, and interleukin-1, all of which may alter neurons and result in hyperexcitability. [59-60]

Sensitization of the central nervous system

As a possible contributor to neuropathic pain, central sensitization is discussed. The uncoupling of noxious inputs is a result of a shift in synaptic plasticity, effectiveness, and inherent disinhibition. A sensitized neuron's outputs are neither time nor intensity-dependent, and many inputs may be mixed. [61]

Elevation of Potential in a Circuit

An effect analogous to long-term potentiation may occur during high-frequency stimulation, making synapses that carry nociceptive information more efficient. Substance P and other molecules may play a role in potentiation by activating neurokinin receptors. Activation of NMDA receptors also causes modifications in the postsynaptic region, where receptor kinases are activated, leading to an increase in receptor trafficking and subsequent post-translational modifications that alter the receptors' excitability. [62]

Cellular

A shift at the molecular or cellular level is necessary for the aforementioned events to occur. Changes in gene expression in response to brain input, alterations in the expression of ion channels,

and alterations in neurotransmitters and their receptors all play a role. Pain caused by neuropathy has been linked to alterations in the function of sodium and calcium channels caused by altered expression of their subunits. Sodium and calcium channel subunits are redistributed and altered in chronic nerve damage, leading to ectopic firing at points throughout the sensory route.[63]

Flavonoid

7.1.Flavonoid

Flavonoids, sometimes called bioflavonoids, are a kind of polyphenolic secondary metabolite present in plants and, therefore, in the diets of people. Their name comes from the Latin word flavus, meaning yellow, which describes their natural hue. Flavonoids are compounds with a 15-carbon skeleton consisting of two phenyl rings (A and B) plus a heterocyclic ring (C, the ring containing the embedded oxygen).[66]

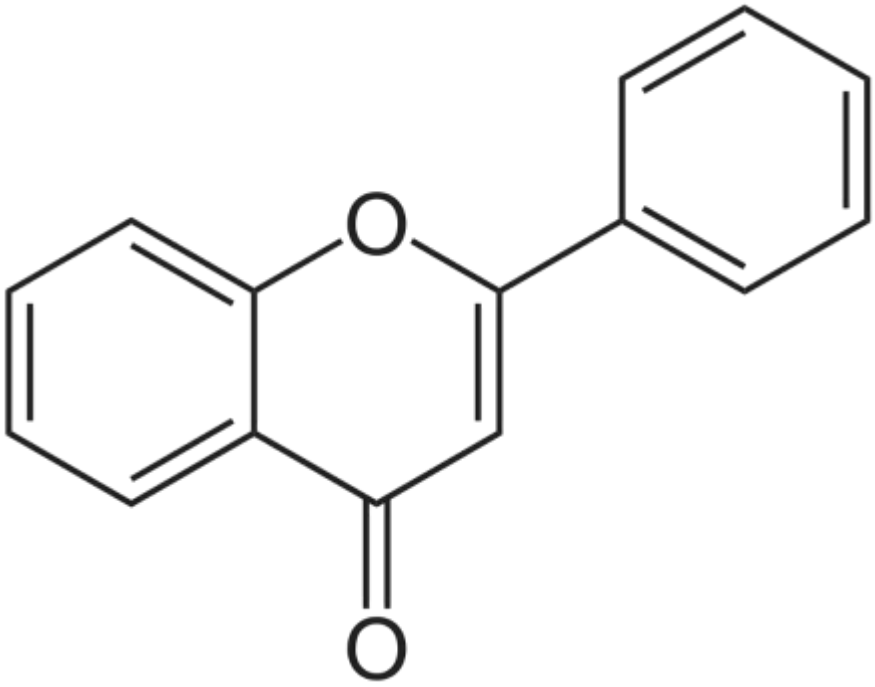


Fig 09: Molecular structure of the flavone backbone

The abbreviation for this carbon structure is "C6-C3-C6." Groups into which they fall, according to the nomenclature established by the International Union of Pure and Applied Chemistry (IUPAC), are as follows:

- ✓ antioxidant flavonoids; bioflavonoids
- ✓ 3-phenylchromen-4-one (3-phenyl-1,4-benzopyrone) structural isoflavonoids
- ✓ four-phenylcoumarine-derived (four-phenyl-1,2-benzopyrone-structured) neoflavonoids

For example, anthoxanthins, like the aforementioned three types of flavonoids, are ketone-containing molecules (flavones and flavonols). This group was the first to be dubbed "bioflavonoids," so named because of its unique chemical composition. Non-ketone polyhydroxy polyphenol chemicals are more precisely called flavonoids. However, the labels flavonoid and bioflavonoid have been used more generally to characterize them. Ring A, ring B, and ring C are common names for the three cycles or heterocycles that make up the flavonoid backbone. Typically, phloroglucinol substitution is seen in ring A.[67]

7.2. Flavonoids in the Treatment of Neuropathic Pain

As a primary source of disability and disease load [68], chronic pain management remains a formidable obstacle for healthcare systems everywhere. One of the most common and debilitating medical diseases is chronic pain, which affects over 100 million individuals in the United States. Moreover, taking into consideration the yearly cost of chronic pain is between $560 and $635 billion [69-70], which is more than the cost of cancer, heart disease, and diabetes put together in healthcare expenses and lost productivity. Despite the widespread effects of chronic pain, its incidence continues to rise in the United States. As a kind of persistent pain, neuropathy is quite prevalent." pain induced by a lesion or illness of the somatosensory nervous system" [71] has been used to define neuropathic pain. Multiple factors contribute to the development of neuropathic pain, and its underlying pathophysiology remains poorly understood. The value of an interdisciplinary team in relieving neuropathic pain has been demonstrated to reduce pain, boost mood, and enhance functioning [72]. Normal analgesics, such as NSAIDs and opioids, are less effective in neuropathic pain than they are in nociceptive pain. Tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, gabapentinoids, and topical medications are the pharmacological therapy of choice for neuropathic pain. Although these drugs may be effective, they come with a variety of risks that must be weighed carefully, particularly for those who have renal impairment, liver disease, heart irregularities, mood disorders, etc. [73]

7.3. Flavonoids as $GABA_A$ Receptor Modulators

Studies employing rat and bovine brain membrane binding tests have demonstrated flavonoids' preferential affinity for GABAA receptors, despite the fact that previous attention has mostly been paid to their peripheral actions. In addition to binding investigations, various behavioral research

has been conducted, all of which point to the absence of the excess side effects of BDZs (benzodiazepines) in the anxiolytic effects of flavonoids in rat anxiety models. Interestingly, the positive, negative, and neutralizing \sallosteric modulatory activities of flavonoids across a wide \srange of ionotropic GABA receptors have been focused \sand substantially supported by a significant mass of data. The extraction of isoflavones from bovine urine that \sdisplaced 3[H]-diazepam binding in rat brain lay the \sfoundation of the interaction of flavonoids with BDZ \sreceptors . This novel class of BDZ receptor ligands, flavonoids, was identified in the 1990s. They were previously thought to be acting on BDZ receptors, leading to the development of a number of synthetic flavonoids with a high affinity for the BDZ binding site. However, it was later discovered that they were resistant to the BDZ receptor antagonist flumazenil, indicating that this class of compounds acts on a different target. The replacement at 6- or 3'-positions of flavones with an \selectronegative functional group improved the affinity \stowards the BDZ receptors. Furthermore, the influence of ligand binding on the GABA \sbinding was employed to establish the GABA ratios. Flavones' strong biological activity at BDZ receptors was shown by these ratios. Full agonist partial agonist and antagonist at these receptors were reported for 6-bromoflavone, 6-Bromo-3'-nitroflavone, and 6- chloro-3'-nitroflavone, respectively, with a GABA ratio of 1.6-2.0, 1.38, and 2.0, respectively. [74-78]

Positive ionotropic modulators of GABAA receptors \senhance the chloride ion flow and produce a strong \sinhibitory effect. Therefore, these modulators have great prospects for treating a wide range of conditions related to the central nervous system, such as anxiety disorders, seizures, muscular spasm, neuropathic pain, and sleep problems. Moreover, with the revelation of the fact that \sflavonoids may operate upon unique binding sites other than \sthe conventional benzodiazepine binding site, chances to \ssearch for new therapeutic agents with fewer adverse effects have been presented. According to the literature, 6-Methoxyflavonone is a positive allosteric modulator of the 122L and 222L GABAA receptor subunits. Changes in recombinant GABAA receptor activity are associated with flavone 6-position substitution. Flumazenil-sensitive BDZ site was significantly affected by 6-hydroxy flavone. Six-methoxyflavanone and six-methoxy flavone have been shown to have potent anti-allodynic effects in models of neuropathic pain caused by streptozotocin and cisplatin, respectively. The positive allosteric modulatory actions of these compounds on opioid and GABAA receptors have been linked to their protective benefits against neuropathic pain. Moreover, myricetin and baicalin generated significant \ Santi-

allodynic effects in sciatic nerve ligation models. Inhibiting oxaliplatin-induced chronic painful peripheral neuropathy with rutin and quercetin has been described. Naringin is also described as displaying anti \sallodynic potential in the streptozotocin-induced painful \sdiabetic neuropathy. [79-82].

7.4. Other Neuropathic Pain Modulating Mechanisms of Flavonoids

Flavonoids are known to operate on GABAA receptors, but they also have antioxidant and anti-inflammatory properties. Oxidative stress is the root cause of almost all metabolic disorders. In addition to being vulnerable to damage from the outside world, cells and tissues are also constantly threatened by free radicals and reactive oxygen species, which are produced as a byproduct of the body's normal oxygen metabolism. Flavonoids are well known for their antioxidant capacity and have been shown to have beneficial benefits in a wide variety of disorders.[83]

The contribution of lipid peroxidation leading to cellular membrane destruction and activation of inflammatory mediators by the free radicals culminating in ultimate tissue damage can provide a lot of help in conceiving a pharmacological target, even if the underlying set of events behind the damage caused by the free radicals to the cellular functions is not fully understood. The body's innate defenses against reactive oxygen species (ROS) include enzymes like superoxide dismutase and glutathione peroxidase, catalase, and nonenzymatic substances like ascorbic acid and beta-tocopherol. However, increasing oxidative stress induced by numerous pathological states, particularly diseases that result in neuropathic pain, such as diabetes mellitus, may deplete these endogenous scavenging chemicals.[84]

There is evidence that epicatechin and rutin may be oxidized by free radicals, resulting in a stable, less reactive species. Also, quercetin prevents cell death caused by nitric oxide (NO). When NO reacts with free radicals, it creates the highly toxic byproduct peroxynitrite, which oxidizes LDL directly and destroys the cell membrane. While silibinin reacts directly with NO, quercetin scavenges free radicals, preventing them from contributing to NO reactions.[85]

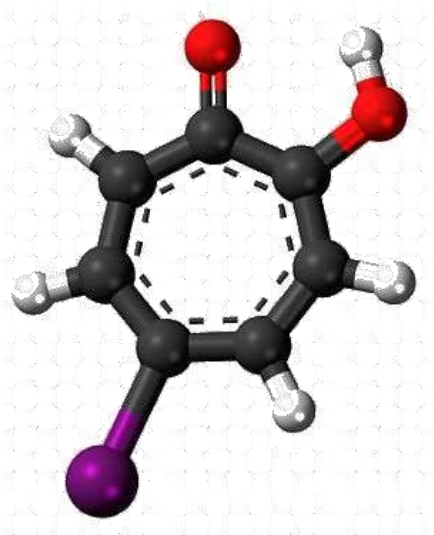
Normally, xanthine dehydrogenase is responsible for converting xanthine into uric acid; however, after an ischemic-reperfusion event, this enzyme transforms into xanthine oxidase, a precursor of free radicals. The flavonoids quercetin, luteolin, and silybin are well-researched for their antioxidant effects through the inhibition of xanthine oxidase. As with ischemia, reperfusion

triggers the complement system by mobilizing leucocytes, which then release inflammatory mediators and cytotoxic oxidants. Numerous flavonoids are said to have a role in immobilizing leucocytes, which in turn decreases the serum complement system and inflammation. Inflammation and peripheral neuropathic pain have common pathophysiological pathways, according to a large body of research. Both disorders present themselves clinically as abnormally elevated pain perception (allodynia) or abnormally low pain perception (hyperallergic).[86]

Chronic pain is caused by peripheral nerve damage, which leads to the infiltration of inflammatory cells and their waste products, including arachidonic acid and cytokines (issued for nerve regeneration). Mechanical and thermal hyperalgesia was induced in rats after injections of cytokines such as tumor necrosis factor- (TNF-), interleukin-1 (IL-1), and interleukin-6 (IL-6). Hyperalgesia has been reduced in mouse models of painful neuropathy when TNF- was blocked. Once released, cytokines trigger the creation of more cytokines and the release of prostanoids in a COX-2-dependent manner. Inflammation and increased pain sensitivity are two effects of PGs that have been well-documented to be caused by these molecules. Allodynia was elicited in awake mice after intrathecal infusion of PGs such as PGE2 and PGF2, whereas hyperalgesia was induced after intrathecal injection of PGD2 and PGE2. In addition, peripheral nerve damage causes hypersensitivity by increasing microglial production of prostaglandin (PG) and nitric oxide (NO) through cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS). Flavonoids have been shown to reduce inflammation both in animal studies and in laboratory dishes. Inhibition of eicosanoid-generating enzymes such as cyclooxygenase (COX), lipoxygenase (LOX), and phospholipase A2 is responsible for the anti-inflammatory effects seen in vivo.[87]

Flavonoids are known to affect a variety of enzyme systems, preventing, for example, arachidonic acid from inhibiting the inflammatory response. This adds anti-inflammatory and anti-thrombotic properties to the group. They also prevent neutrophils from releasing peroxidase and producing ROS. The activation of alpha-1 antitrypsin is inhibited as a result of this. By preventing iron chelation, which leads to lipid peroxidation, some flavonoids eliminate a potentially chaotic element in the formation of free radicals.[88]

Literature Review



2.1. Rao, P. N., Mainkar, O., Bansal, N., Rakesh, N., Haffey, P., Urits, I., ... & Jones, M. (2021). Flavonoids in the Treatment of Neuropathic Pain. Current Pain and Headache Reports, 25(7), 1-10.

Flavonoids are natural substances that may be found in plants and other food sources. They have been studied for their ability to alleviate neuropathic pain. This advantage, which includes the reversal of hyperalgesia and allodynia, has been proven in a variety of animal models. Multiple pro-inflammatory mediators, including tumor necrosis factor alpha (TNF-), nuclear factor kappa beta (NF-), interleukin (IL)-1, and interleukin (IL)-6, have been shown to be reduced by flavonoids, demonstrating their anti-inflammatory impact relevant to neuropathic pain.

2.2. Basu, P., & Basu, A. (2020). In vitro and in vivo effects of flavonoids on peripheral neuropathic pain. Molecules, 25(5), 1171.

Having neuropathic pain is quite prevalent and is linked to a worse quality of life. Somatosensory damage or sickness is to blame. There are two types of neuropathic pain syndromes: central neuropathic pain and peripheral neuropathic pain. Spared nerve damage, spinal nerve ligation, partial sciatic nerve injury, diabetes-induced neuropathy, chemotherapy-induced neuropathy, chronic constriction injury, and associated disorders are highlighted in this overview of peripheral neuropathic models. Antidepressants, anticonvulsants, baclofen, and clonidine, some of the medications now used to mitigate peripheral neuropathy, are linked to undesirable side effects. As a result of these drawbacks, we need to look at other therapeutic options for relieving neuropathic pain. In mouse models, flavonoids have been shown to reduce neuropathic pain. Several flavonoids are shown in this review to alleviate peripheral neuropathic pain in a variety of mouse models at the behavioral, electrophysiological, biochemical, and molecular biology levels. Accordingly, the flavonoids have great potential and may be employed to cure or alleviate peripheral neuropathic disorders. Therefore, in order to further improve their antineuropathic benefits, future research should examine the structure-activity connections among various classes of flavonoids.

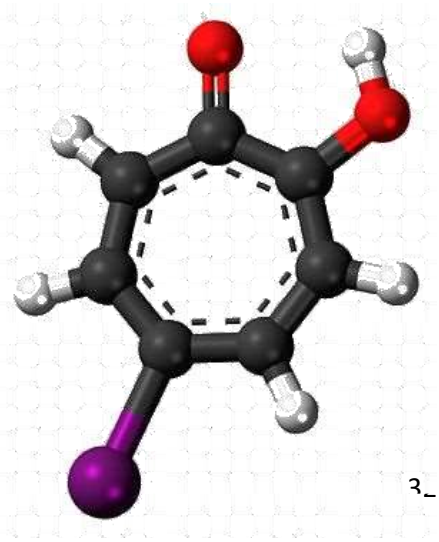
2.3. Sood, A., Kumar, B., Singh, S. K., Prashar, P., Gautam, A., Gulati, M., ... & Porwal, O. (2020). Flavonoids as potential therapeutic agents for the management of diabetic neuropathy. Current Pharmaceutical Design, 26(42), 5468-5487.

Flavonoids are a kind of secondary metabolite that may be found in almost any plant. Flavones, flavonols, isoflavones, flavanones, and anthocyanins are only few of the subgroups that fall under the umbrella of phenolic chemicals. Antioxidant, antiinflammatory, anticancer, antibacterial, antidiabetic, antiallergic, etc. are only few of the pharmacological functions attributed to them. Neuropathy, retinopathy, nephropathy, and cardiomyopathy are all secondary consequences caused by diabetes, a chronic, progressive metabolic illness that affects several biochemical pathways. One of the greatest difficulties doctors and drug companies have is dealing with diabetic neuropathy. The antioxidant capabilities of naturally occurring flavonoids have made them widely employed in the treatment of diabetes and its associated problems. Additionally, flavonoids suppress the -glucosidase enzyme, oxidative stress, glycogenolysis, glucose consumption, advanced glycation end product generation, and glucose homeostasis, all of which have a role in the development of diabetic neuropathy. Current information on the therapeutic potential of flavonoids in the management of neuropathic pain is included in this review. In this publication, we discuss the pathological causes of neuropathic pain, the chemical makeup of flavonoids, and their use in reducing neuropathic pain in animal models and in human trials in conjunction with other treatments.

2.4. Uddin, M. S., Mamun, A. A., Rahman, M. A., Kabir, M. T., Alkahtani, S., Alanazi, I. S., ... & Abdel-Daim, M. M. (2020). Exploring the promise of flavonoids to combat neuropathic pain: from molecular mechanisms to therapeutic implications. Frontiers in Neuroscience, 14, 478.

Neuronal damage is the most common cause of neuropathic pain (NP), which is the consequence of abnormal processing in the central or peripheral nervous system. NP is difficult to control because of the wide variety of the condition and the serious drawbacks of the most used psychoactive medications, such as benzodiazepines (BDZ). Antidepressants, anticonvulsants, topical lidocaine, and opioids are now utilized to treat NP, but they all come with their own set of side effects. Alternative treatments for the therapy of NP should be explored to lessen the load of unwanted effects. It has been suggested that flavonoids, the most frequent secondary metabolite of plants used in traditional medicine as sedatives, have a specific affinity for the BDZ binding site. In a number of research using animal models, flavonoids were shown to be effective in lowering NP. In this work, we highlight flavonoids' potential for use in NP control.

The goal of my studies

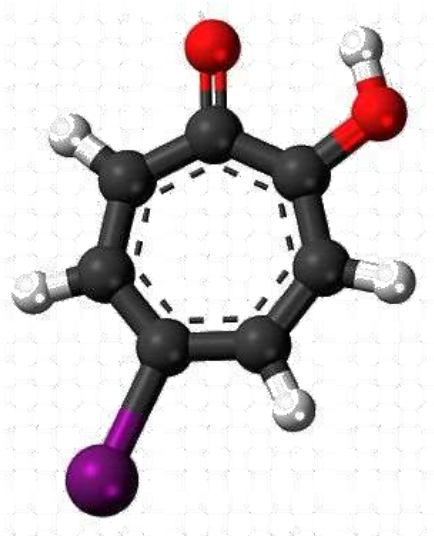


The feeling of nerve pain is often described as shooting, stabbing, or scorching. It may sometimes be as abrupt and harsh as an electric shock. People who suffer from neuropathic pain are often very sensitive to touch and cold, and they may also be painfully sensitive to stimuli like stroking their skin.

My aim of this study is,

- To see the pathophysiological mechanisms of neuropathic pain.
- To see flavonoids in the treatment of neuropathic pain.
- To overview current neuropathic pain classification and its treatment.
- To open a new area of higher studies.

Methodology



3.1. Introduction:

A literature review leads the examination. Around 78 papers are reviewed for this study.

3.2. Research Design:

This exploration was planned through google scholar, PubMed, and many other websites to find literature.

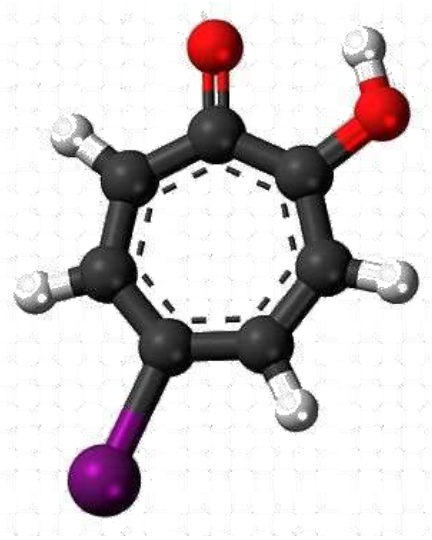
3.3. Method of Data Analysis:

After compiling a large amount of information, it was examined for accuracy and coherence within itself to rule out the possibility of missing or conflicting data, both of which were afterward thrown out. The Microsoft Dominant Refreshed Version was used in the information inquiry that was carried out. All of the information gathered is from 1969 all the way until 2022.

3.4. Ethical Considerations

Before beginning the process of information collection, informed verbal consent was obtained from those participating in the inquiry. A veil of secrecy was maintained over the identities of those who participated in the research, and participants in the studies were informed that they were free to withdraw from the program at any point throughout the process of data collection. The inquiry garnered the backing of the Department of Pharmacy.

Outcome & Discussion



8.1. Cell line pre-clinical studies of different flavonoids.

Hesperidin is a flavonoid compound that has activity on mediated dilation and reduced concentrations of circulating inflammatory biomarkers, and Silymarin has activity to reduce joint swelling, tenderness, and pain, according to a review paper. Flavonoid-based compounds have multifunctional activity in cell lines, including flavanones, anthocyanins, and flavan-3-ols, which have activity to reduce Parkinson disease risk, particularly in men [89].

Flavonoid/Flavonoid-Based Compound	Treatment	Duration	Outcome
Flavanones, anthocyanins, flavan-3-ols	Food frequency questionnaire	20–22 years of follow-up	Intake of some flavonoids may reduce Parkinson disease risk, particularly in men
Hesperidin	500 mg, daily	3 weeks	Mediated dilation and reduced concentrations of circulating inflammatory biomarkers
	379 mg of green tea extract	3 months	Improvements in blood pressure, insulin resistance, inflammation and oxidative stress, and lipid profile in patients with obesity-related hypertension
Silymarin	420 mg, daily	90 days	Joint swelling, tenderness, and pain were reduced

Table 1: Cell line pre-clinical studies of different flavonoids.

8.2. Neuropathic pain treatment using flavonoids.

In this study, flavonoid-based compounds have been used in a variety of species, such as genistein, which ameliorates diabetic peripheral neuropathy by reducing pro-inflammatory cytokines and the excessive formation of reactive oxygen species and restores NGF levels in diabetic sciatic nerve. Wistar adult male rats were given epigallocatechin gallate to treat neuropathic pain, Wistar rats were given proanthocyanidins, which reduce nociceptive pain by altering the oxido-inflammatory pathway, while male Sprague-Dawley rats were given 6 Methoxyflavone, which reduces neuropathic pain by interacting with the GABAergic and opioidergic systems [90].

Flavonoids	Species/studied material	Effects
Genistein	C57BL/6J male mice	Ameliorates diabetic peripheral neuropathy by inhibiting proinflammatory cytokine and the overproduction of reactive oxygen species, as well as restored the NGF content in diabetic sciatic nerve
Epigallocatechin gallate	Adult male wistar rat	Reduces neuropathic pain through the modulation of oxido-inflammatory pathway
Proanthocyanidins	Wistar Rats	Anti-nociceptive and anti-inflammatory effect by inhibiting the inflammatory pathways
6 Methoxyflavone	Male Sprague-Dawley rats	Attenuates neuropathic pain through interactions with the GABAergic and opioidergic systems

Table 2: Neuropathic pain treatment using flavonoids.

8.3. Anthocyanin for Pain Relief compare to turmeric and heat/ice

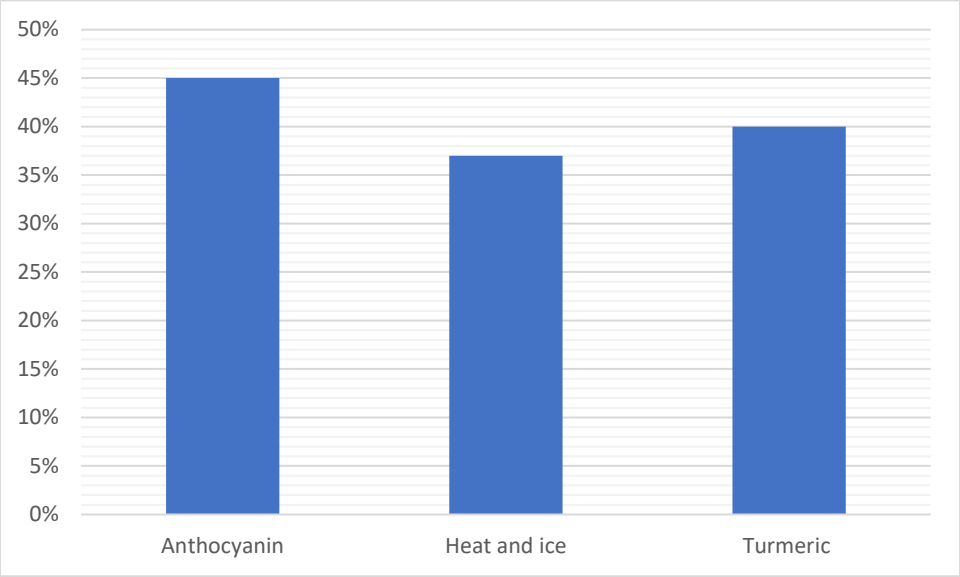
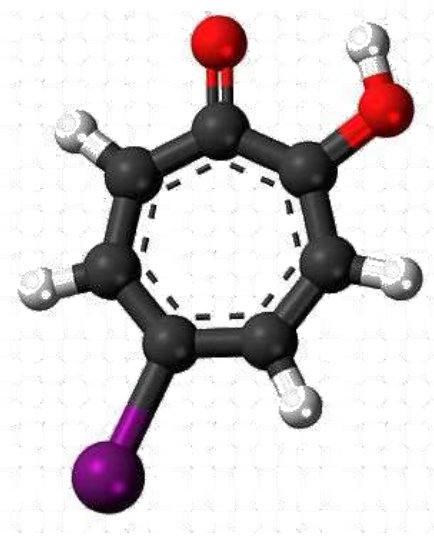


Fig 10: Anthocyanin for Pain Relief compare to turmeric and heat/ice

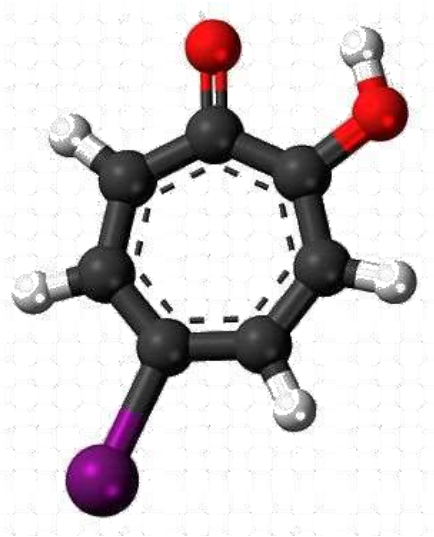
Anthocyanin has analgesic effects on chronic inflammatory pain brought on by CFA, according to review research, and its mechanism may be connected to an increase in antioxidant capacity and a decrease in TRPV1 phosphorylation. Anthocyanin has a 45% pain-relieving mechanism, compared to 40% in turmeric and 37% from heat and ice [91].

Conclusion



In preclinical models, flavonoids have been shown to be a possible new way to treat neuropathic pain. However, human clinical data is still being looked into. Allosteric modulators of GABAA receptors change either how well or how strongly agonists like GABA work, which controls how they work. In the last ten years, a lot of attention has been paid to these modulators because we know more about how GABAA receptor subtypes work. Flavonoids are strong allosteric modulators, which means they may be useful for treating painful conditions like neuropathic pain. More research is needed to figure out where these bioactive compounds work over the GABAA receptors, though. In this review, the effects of flavonoids like Genistein on male C57BL/6J mice are discussed. It proves Helps diabetic peripheral neuropathy by stopping the production of pro-inflammatory cytokines and reactive oxygen species and restoring the NGF content in the diabetic sciatic nerve. Hesperidin 500 mg has been used for 3 weeks to achieve this effect. It caused dilation and decreased the amount of inflammatory biomarkers in the blood. Silymarin 420 mg has been used every day for 90 days to reduce swelling, tenderness, and pain in the joints.

Reference



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