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Chapter

Pharmaceutical and Botanical Management of Pain Associated with Psychopathology: A Narrative Review

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Abstract

Generally, pain can be described as an unpleasant sensory or emotional experience associated with tissue damage. Chronic pain has become a public health problem because among 35 and 75% of the world population has shown the symptom. In particular, neuropathic pain has shown high comorbidity disorders such as anxiety and depression. Conventional therapies for treating pain include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, tricyclic antidepressants, anticonvulsants, and opioids, which usually cause some side effects such as gastritis, headache, liver and kidney toxicity, and drug dependence. Conventional pharmaceuticals also tend to be expensive, and they cannot be easily afforded in developing countries, which have led to the use of natural products as an alternative treatment. In this chapter, we reviewed the current research of natural products for pain treatment. We also describe preclinical studies that assess the effect of some natural products on pain therapy, phytochemistry research, toxicity, adverse effects, and biosecurity. We also describe how conventional pain is managed and the possible use of compounds obtained from vegetable species for pain treatment.

Keywords: pain, analgesic, anti-inflammatory, herbal medicine, phytopharmaceuticals

1. Introduction

Over the course of history, the pain has been manifested in a wide range of forms, and it has not been treated properly. It is estimated that approximately 116 million

Kind of drug	Type of pain	Examples	Doses	Side effect
NSAIDs	Nociceptive	Acetaminophen	325–1000 mg PO every 4–6 h; max dose 4 g per day	GI irritation, renal, and hepatic dysfunction
		Diclofenac	50 mg PO every 8 h; max dose 150 mg per day	GI irritation, bleeding, hepatic, and renal dysfunction
		Ibuprofen	200–400 mg PO every 6 h; 1.2 g per day	GI irritation, bronchospasm, bleeding, and renal dysfunction
		Naproxen	250 mg PO every 6–8 h; max dose 1 g per day	GI irritation, bleeding, renal dysfunction, and bronchospasm
		Indomethacin	25 mg PO every 8–12 h; max dose 100 mg per day	GI irritation, renal, and hepatic dysfunction
Opiates	Nociplastic/ neuropathic	Tramadol	25–50 mg PO every 6–8 h; max dose 400 mg per day	Dizziness, drowsiness, nausea, dry mouth, vomiting, and constipation
		Morphine	10–15 mg PO 3–6 h; 0.1 mg/kg IV	Nausea, vomiting, drowsiness, constipation, and sedation
		Oxycodone	5–10 mg PO every 3–6 h	Constipation, nausea, vomiting, drowsiness, dry mouth, hallucinations, and delirium
		Hydromorphone	2–4 mg PO; 0.25–0.5 mg/kg every 6 h	Pruritus, nausea, and rapid sedation
		Fentanyl	0.5 mcg/kg	Blurred vision, nausea, confusion, dizziness, and irregular heartbeats
Anticonvulsants	Nociplastic/ neuropathic	Gabapentin	Stepwise increase every 3–5 days from 300 mg to 1200 PO every 8 h; max dose 3.6 g per day	Fatigue, ataxia, nystagmus, weight gain, and dizziness
		Pregabalin	50–75 mg PO every 12 h	Dizziness, fatigue, weight gain, and thrombocytopenia
		Phenytoin	100 mg PO every 12 h; max dose 200 mg per day	Nausea, vomiting, constipation, dizziness, drowsiness, trouble sleeping, or nervousness
Antidepressants	Neuropathic	Amitriptyline	Stepwise increase every 7–10 days from 25 mg to 50 PO every 6 h; max dose 200 mg per day	Vomiting, nausea, diarrhea, mouth pain, unusual taste, weight gain, urinary retention, and rash
		Venlafaxine	Stepwise increase every day from 75–150 mg PO every 8 h; max dose 150 mg per day	Libido reduction, loss of appetite, nausea or vomiting, constipation, dry mouth, trouble sleeping, and lack of energy
		Mirtazapine	Stepwise increase every 2 weeks from 15 to 45 mg PO a day; max dose 45 mg per day	Dry mouth, drowsiness, constipation weight gain, weakness, lack of energy, and dizziness

Kind of drug	Type of pain	Examples	Doses	Side effect
Others	Neuropathic	Ketamine	0.115–0.3 mg/kg IV	Nausea or vomiting, agitation, dizziness, and a sensation of unreality
		Propofol	30–40 mg IV repeating 10 mg every 3–5 min; max dose 120 mg per day	Hypotension, sedation, respiratory depression, and hypertriglyceridemia
		Capsaicin	Cream: 3–4 times per day; patches: one time a day and repeated as often as every 3 months	Burning, dryness, itching, redness, swelling, or soreness at the application site

PO, per os rout; IV, intravenous rout; GI, gastrointestinal.

Table 1.
Drugs used in acute and chronic pain.

Americans have experienced chronic pain, which is higher than those affected by chronic diseases, such as heart disease, cancer, and diabetes, among others. The simplest way to classify pain is based on its intensity as mild, moderate, and severe or using a scale from 0 to 10, where 0 is the lowest and 10 the highest. Other scales that are typically used are the unimodal scale such as the Analog Verbal Scale (AVS), the Visual Analog Scale (VAS), and the Numerical Scale (NS), among others. These scales are somewhat informal because pain is not easy to measure. Therefore, variations might affect critical evaluation when pain is manifested in all forms. Some authors refer to the use of the one-dimensional test to reach a standardized measure of pain; however, the researcher must adjust the test depending on the type of pain and type of research.

Aspirin and morphine, which are derived from plants, have been widely used for analgesic purposes. These compounds belong to nonsteroidal anti-inflammatory (NSAIDs) and opiate drug groups, respectively, and they are the most used nowadays [1]. Once the pain evolves and becomes chronic, several types of oral neuromodulators are often included in the patient treatment, for example, certain anticonvulsants and antidepressants [2], see **Table 1**.

In 2012, the use of NSAIDs in North America represented 98 million of the total prescriptions, and more than 29 million adults were regular users of these medications. Furthermore, a study in Sweden showed that these types of medications were the most commonly prescribed oral analgesics for the musculoskeletal system, with 79% of prescriptions for a period of 5 years [3]. Opioid consumption causes side effects such as physical dependence, tolerance, and addiction, while NSAIDs cause intestinal disorders and ulceration [4]. Because the long-term pain treatment with conventional medicine is expensive and people commonly know the side effects that these may cause, patients tend to look at alternative drugs, most of the times based on herbal treatments. However, patients do not inform the use of natural products to their physicians, which may lead to potential health problems caused by pharmacological interactions with other drugs prescribed. This represents a relevant issue in countries where the use of plants is common but not necessarily regulated [5]. In the search for new effective and safe alternatives to treat several processes of pain, natural resources have been a relevant option for current medicine. Considering that pain is one of the most persistent and disabling manifestations present in several diseases, it has been increasingly becoming a major health problem, and it is also a challenge for modern medicine. Therefore, it is necessary to fully understand the pathophysiology of pain as well as alternatives that might be effective for treating it.

2. Pain classification, semiology, and diagnosis

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [6]. Each person reacts differently to a pain stimulus, even before similar situations and injuries. Since pain is learned and sensed from the early stages of life, how people describe is often related to a particular personal experience including a patient's culture, traumatic experiences, mood, biological aspects, and genetics. The words "pain" and "suffering" have often been used as synonyms, but the experience of suffering has been differentiated from pain. Suffering has been defined not only as a complement to the pain experience but also as vulnerability, dehumanization, a lost sense of self, lack of control over time and space, and the inability to find a meaning or purpose of the painful experience. The term "suffering" conveys the experience of pain beyond sensory attributes [7].

There are several ways to classify pain. The most common classification considers aspects such as origin, duration, neurophysiological characteristics, and intensity.

Based on its origin, pain could be oncological and nononcological. Oncological pain is caused by a cancerous process (invasion, understanding, infiltration, obstruction, etc.), associated with therapy (chemotherapy, radiotherapy, etc.), acute pain caused by diagnostic procedures (lumbar puncture, pleurodesis, embolization, opioid-induced hyperalgesia, etc.), and that is associated with neoplastic or related pathology (vertebral collapse, intratumoral hemorrhage, myalgia associated with sepsis, etc.) [8]. Noncancer pain is classified based on its duration as acute and chronic. The first one is limited to the time duration of fewer than 3 months. Noncancer pain has a little psychological component and usually affects somatic or visceral structures. By contrast, chronic pain has an unlimited duration, lasting more than 3 months. Chronic pain differs from acute pain in the pathophysiological mechanisms and in its temporality in which the adaptive physiological process that characterizes is shown [9–11]. In 2019, a new classification of chronic pain was proposed by the World Health Organization (ICD-11) [12], according to its neurophysiological characteristics, as nociceptive, neuropathic, and nociplastic [6, 12], see **Table 2**.

Recently, an international multidisciplinary research group proposed to the scientific community a fifth definition of pain called mixed pain, which is produced by a complex overlap of the different types of pain known (nociceptive, neuropathic, and nociplastic) in any combination, acting simultaneously and/or concurrently to cause pain in the same area of the body, either acutely or chronic [13]. This difficulty of evaluating pain makes possible to resort to instruments that, with the minimum effort of the patient, are easily understandable, reliable, and valid.

Type of pain	**Nociceptive**		**Neuropathic**	**Nociplastic**
Origin	**Somatic**	**Visceral**	**Central nervous system**	**Neurophysiologic**
Receptors	Cutaneous or deep tissues such as skin, muscles, tendons, fascia, bones, or periosteum nociceptors	Walls of abdominal viscera nociceptors	Produced by dysfunction or injury to peripheral nerve pathways in the absence of demonstrable tissue damage	Peripheral receptors or injury of the somatosensory system
Characteristics	Specific localization stabbing, acute, or chronic and shows periods of exacerbation with variable intensity depending on the inducing stimulus	Deep, spastic, and oppressive, poorly located or may be referred to as cutaneous surface distant from the origin of pain	Stabbing, burning, paroxysmal accompanied by paresthesia, dysesthesia, hyperalgesia, and allodynia, with a sensory deficit	Altered nociception even though there is no clear evidence of actual or potential tissue damage
Examples	Burns, bumps, bruises, sprains, and bone fractures	Shoulder pain in myocardial infarction	Postherpetic neuralgia, carpal tunnel syndrome, peripheral neuropathy, and phantom limb pain	Fibromyalgia, chronic fatigue, vulvodynia, and interstitial cystitis

Table 2.
Classification of the chronic pain according to the World Health Organization.

These include the McGill Pain Questionnaire (MPQ), Lattinen Test, Spanish Pain Questionnaire (CDE), Chronic Pain Coping Questionnaire (CAD), West Haven-Yale Multidimensional Pain Inventory (WHYMPI), Brief Pain Inventory, and the scales of assessment of neuropathic pain: the LANSS Pain Scale, the Neuropathic Pain Questionnaire (NPQ), Questionnaire DN4 (DN4), and Pain DETECT, among others [14]. It is important to note that the purpose of these tests is to assist the clinicians in assessing the severity of the pain or its causes. Tests correctly classify the patients as suffering from nociceptive and neuropathic pain.

3. Pain epidemiology

Epidemiological studies have shown that in the last month approximately half of people will have experienced an episode of pain that lasted at least 1 day, and the most common sites reported, in a study in the UK population, were the part lower back (30%), hip (25%), neck and shoulder (25%), and knee (24%) [15]. According to the US Institute of Medicine, 80% of patients who undergo surgery report postoperative pain, and 88% of these patients indicate moderate, severe, or extreme pain levels, if improperly managed between 10 and 60% of them will develop persistent pain postoperative [16].

Concerning to oncologic pain, a systemic review that covered the period from 1966 to 2005 documented that the prevalence of pain after curative procedures of cancer pathology was 33% (95% CI 21–46%). While in those who were managed with anticancer therapy, pain occurred in 59% (CI 44–73%); in those with an advanced, terminal disease and with metastasis in 64% (CI 58–69%) and patients with any disease status in 53% (CI 43–63%). Of the patients with pain, more than a third presented moderate to severe intensity, with a high prevalence in patients with head and neck cancer (70%; 95% CI 51–88%) [8]. To chronic pain, the higher prevalence was unemployed, people without one university degree who live in poverty or rural areas. About the prevalence by sex and age, women and the elderly showed an elevation of this kind of pain [17].

Regarding the bad management of acute pain, there is a risk that a chronic painful syndrome will develop, with all its consequences for the patient, for his family and his environment. The chronicity of pain commonly involves anxiety, depression, fatigue, cognitive difficulty, and insomnia. Functional limitations and the consequent absence from work have been considered as part of the impact on the quality of life of high-impact diseases. It is currently known that people with chronic pain are more likely to have disabilities than those without pain. In addition, this disability is more likely in this condition than in any chronic health condition, including stroke, kidney failure, cancer, diabetes, and heart disease. The impact in terms of work absenteeism is evident both for the individual (loss of self-esteem, income, and low quality of life) and for the society (loss of productivity and higher health care expense) [18].

Pain is a major global public health problem because it has an important social and economic impact. It is necessary to have a clear understanding of the types of sensory signs and symptoms that should be assessed as pain since it is an individual and subjective experience.

4. Pain comorbidity

The pain usually accompanies various diseases, such as organ failure or mental disorder. A high number of patients with a mental disorder show some type of pain, but not all have any significant physical injury to justify such pain [19]. The relationship

between chronic pain and psychiatric disorders in addition to comorbidity is that these disorders may arise the risk of chronic pain, as well as the pain can contribute to developing psychiatric disorders. Among the most common diseases with which it is related are anxiety, depression, dementia, and schizophrenia [20].

Pathological anxiety is one of the most common mental disorders. It is an emotion that is characterized by an exaggerated concern for future events or situations of uncertainty [21]. Anxiety disorder can affect the response of pain in various forms or states. A clinical study assayed on healthy female volunteers explored the effects of a particular type of anxiety (pain anxiety). The volunteer received electrocutaneous pain stimuli and the pain anxiety where measured by the Fear of Pain Questionnaire and Pain Anxiety Symptoms Scale. Three or six months later, the evaluated group was asked to rate the pain anxiety that they felt when the test was developed. It was demonstrated that pain anxiety can influence the memory of unpleasant experiences like experimental pain [22].

Anxiety is also common in diseases involving chronic pain stages such as multiple sclerosis and arthritis, in which anxiety disorder is more prevalent than in the general population. This psychiatric disorder also can contribute to the development and severity of symptoms of inflammatory arthritis [23]. A study conducted in patients (58% female, mean age 43) who were receiving opioid agonist therapy for chronic pain showed that the weekly practice of hatha yoga for 3 months can reduce the level of pain and perhaps mediated by the decrease of emotional symptoms such as anxiety [24].

Neuroanatomical correlates to the response to anxiety are very complex, involving various structures such as the medial prefrontal cortex, hypothalamic and amygdaloidal nuclei, the hippocampal formation, and the gray matter of the central portion of the midbrain. Patients with some anxiety disorder show a common pattern of activity of the hypothalamic-pituitary-adrenal (HPA) axis [21]. These areas are also related to the activation of the pain signaling pathway. On the other hand, when there is chronic pain, there is also hyperadrenalism and a decrease in the catecholaminergic pathway, as well as the activation of the HPA axis with continuous release of corticosteroid hormones. These alterations are also present in the population with some anxiety disorder and are prior to the onset of pain, so when activated, it works as a modulator for the response and activation of pain [25].

Depression is another mental illness that has grown in incidence and prevalence in recent years. This disorder is responsible for more lost each year than any other disorder, and this is mainly because many people suffer from this (about 350 million people worldwide) [26]. Patients with this disorder experience different types of pain, such as chronic pain, fibromyalgia, rheumatoid arthritis, headache, neck, abdominal, pelvic, and neuropathic pain [20], among others. Depression and pain share neurobiological pathways and neurotransmitters: depression is the result of an imbalance or functional deficiency of monoamines such as dopamine, serotonin, and norepinephrine. When these neurotransmitters decrease, the modulating effect of the GPA (periaqueductal gray) system is lost, which is the anatomical key to modulating pain or nociceptive pathway. When this happens, the lower body signals are amplified, and more emotions and attention are focused on it, that is why depressed patients report feeling pain in various body parts [27].

Dementia is a syndrome of damage or cognitive impairment that affects the lifestyle of people. The incidence of this disorder is high; it is estimated that in the world a new case of dementia occurs every 4 s. The most common form is associated with Alzheimer's disease in the elderly [28]. There are proposals on the mechanism that takes place to develop dementia, such as alterations in the immune system, cholesterol metabolism, endocytosis of neurotransmitters in the central nervous system, alterations in the vascular system, and frontotemporal lobar degeneration

(FTLD) [29]. Almost half of older people with dementia suffer any type of pain. Some of the most important changes related to dementia may arise cognitive domain of pain, such as alterations in semantic and episodic memory, executive function, and anticipation of it. Some studies have shown that dementia reduces the experience of pain, although what is suggested is that patients cannot recognize or remember this symptom [30]. Recognition of pain in people with this condition should be considered because it changes the quality of life of patients. If they cannot recognize the pain, or cannot to verbalize it, they will not be evaluated or treated properly [31].

Schizophrenia is another heterogeneous psychiatric disorder with a broad spectrum of clinical and biological manifestations. Patients with this disorder show structural changes in the brain, as well as the decreased volume of the hippocampus and cortex, and the lengthening of ventricular spaces. There are also changes in the organization and size of neurons and other brain cells. It has been shown that there are alterations in the dopaminergic and glutamatergic neurotransmission in the limbic system. On the other hand, peripheral molecular markers have been associated with developing this disease, such as IL-1β, IL-6, and TNF-α, which are known as pro-inflammatory cytokines [32]. With the release of these cytokines, an activation state of low-grade inflammation is reached, which worsens the prognosis of patients in relation to positive and negative psychotic symptoms, cognitive impairment, and loss of brain volume. In addition, an over activation of the HPA axis is observed, with a sustained release of cortisol [33]. One of the classic symptoms of schizophrenia, but which is not given much attention, is a pain without experimental provocation, including the percentage of people with this disease indicating which pain is not high. This may be due to reduced pain sensitivity in these patients produced by neuroanatomical alterations in the medial prefrontal and temporal areas of the brain since it is known that motivational-affective pain processing requires this intact neural circuit [34].

In summary, pain can modify the course of psychopathologies, as well as these conditions may alter the perception or memory pain (how it is recalled). Knowing how the neurobiological substrates in both (psychiatric disorders and pain) converge, help a better way to treat pathologies, and provide an opening to new forms and strategies to face or prevent them.

5. Conventional pain management

The pharmacological treatment of pain includes a wide range of medications, which mainly include nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, antidepressants, and anticonvulsants. Classic NSAIDs were developed in the early 1900s, being the prototype the acetylsalicylic acid (aspirin), which possess antipyretic, anti-inflammatory, and analgesic actions. Subsequently, other molecules with similar activity were incorporated as paracetamol (acetaminophen), phenylbutazone, indomethacin, fenamates, naproxen, and ibuprofen [35, 36]. These drugs are prescribed for the management of inflammatory pain, and their analgesic effects of the latter are partly explained by reducing the biosynthesis of prostaglandins mediated by the inhibition of cyclooxygenase (COX), which leads to a reduction or reversal of peripheral sensitization. However, NSAIDs also modulate pain intensity by suppressing prostanoid biosynthesis in the central nervous system, thus affecting central sensitization [37].

The production of prostaglandins depends on the release of arachidonic acid, which in turn is released as a result of the action of phospholipase A2 on cell membrane phospholipids. The cyclooxygenase and lipoxygenase pathways represent the main routes for the oxidative metabolism of arachidonic acid. The catabolism of eicosanoic acid by cyclooxygenase produces cyclic prostaglandins. The peroxidation

catalyzed by lipoxygenase gives rise to straight-chain hydroperoxyeicosatetraenoic acids (HPETEs), which may then be converted into hydroxyeicosatetraenoic acids (HETEs) and leukotrienes (LTs). Prostanoids (prostaglandins and thromboxane) do not activate nociceptors directly but sensitize them to both mechanical stimuli and other chemical mediators of nociception, such as bradykinin and histamine. However, stable E-series prostaglandins are clearly involved in the hyperalgesia observed in acute inflammation. Prostaglandin E2 (PGE2) is the predominant eicosanoid in many inflammatory conditions, acting synergistically with other mediators to sensitize receptors in afferent nerve endings to produce inflammatory pain. All NSAIDs inhibit the synthesis of prostaglandins at one or more points in the endoperoxide biosynthesis pathway. This unique property is a general characteristic and is believed to be the basis of their analgesic action [38].

Combinations of analgesics (Ketoprofen and Nefopam) with different mechanisms of action have been evaluated in distinct animal models of pain (acetic acid-induced writhing, formalin-induced licking in mice, induction of carrageenan unilateral hind-paw inflammation, and, induction of unilateral hind-paw incision in rat). Ketoprofen is an NSAID, which exhibits efficient antinociception in humans and animal models, particularly in inflammatory pain; its main mechanisms of action involve the inhibition of COX and lipoxygenase decreasing the production of prostaglandins and leukotrienes, respectively. On the other hand, Nefopam is an antinociceptive compound with both supraspinal and spinal sites of action, and its mechanism of action involves the inhibition of monoamine reuptake in the central nervous system; it increases the inhibiting tone of serotonergic and norepinephrine descending pathways by inhibiting the synaptosomal uptake of dopamine, norepinephrine, and serotonin. This study concluded that the co-administration is synergistic and should allow either to increase their analgesic efficacy or to reduce their side effects [39].

In a recent study of preclinical research, it was observed that pretreatment of male CF-1 mice with either clomipramine [1.0 mg/kg i.p. or 0.8 mg/kg intrathecal (i.t.)] or risperidone (0.01 mg/kg either i.p., as intrathecal) increased the antinociceptive potency of several NSAIDs, expressed by a decrease in the values of antinociceptive ED_{50} in a chemical model of inflammatory acute visceral pain, the abdominal acetic acid induced a writhing test in mouse. For the study, dose-response curves, i.p. or i.t., were performed to determine the ED_{50} of each of the NSAIDs: Ketoprofen (3, 10, 30, and 100 mg/kg, i.p. or 0.1, 0.3, 1, and 3 mg/kg, i.t.), Piroxicam (1, 3, 10, 30, and 100 mg/kg, i.p. or 0.1, 0.3, 1, and 3 mg/kg, i.t.), Nimesulide (1, 3, 10, and 30 mg/kg, i.p. or 0.03, 0.1, 0.3, and 1 mg/kg, i.t.), Parecoxib (0.3, 1, 3, and 10 mg/kg. i.p. or 0.1, 0.3, 1, and 3 mg/kg. i.t.), or Paracetamol (10, 30, 100, and 200 mg/kg, i.p. or 1, 3, 10, and 30 mg/kg, i.t.) [40].

Opioids are the main group of pharmacological therapies for pain. Useful guidelines for their administration have been developed for several clinical situations, including treatment of acute pain, trauma, cancer, nonmalignant chronic pain, and pain in children. In the case of cancer pain, adherence to standardized protocols can improve pain management significantly [41, 42]. Opioids should be prescribed concomitantly with other analgesics such as NSAIDs or paracetamol since they show a synergistic effect, and by reducing the dose of both, the possible adverse effects are reduced. This "opioid-sparing" strategy is the backbone of the "analgesic ladder" for pain management proposed by the WHO. If the intensity of pain is increased, weak-to-strong opioid medication can be adjusted, in which case they should be prescribed for continued dose or infusion, so that plasma levels remain stable and unnecessary suffering is avoided [4].

Gabapentinoids are recommended as first-line agents for neuropathic pain [43, 44]. Two examples of these substances are Pregabalin and Gabapentin

not only used as an anticonvulsant but also prescribed to the management of postherpetic neuralgia without effects in painful sciatica [45]. Carbamazepine, Lamotrigine, and Oxcarbazepine are the first choice for the medical treatment of trigeminal neuralgia [46, 47]. They act as a dependent sodium channel blocker. Because of the unexpected drug interactions caused by a reduction in the activity of various hepatic cytochrome P450 enzymes that affect drug metabolism, carbamazepine is not recommended to treat any other types of neuropathic pain [44].

The first-line drugs to neuropathic pain include tricyclic antidepressants (TCAs) and selective serotonin-norepinephrine reuptake inhibitors (SSNRI). TCAs are recommended based on efficacy, safety, toxic effects, and cost [44]; they are efficacious for several types of neuropathic pain including diabetic peripheral neuropathy (DPN), nerve injury pain, PHN, and central post-stroke pain. The analgesic effects of TCAs are related to inhibiting the reuptake of noradrenaline and serotonin from presynaptic terminals [48]. Amitriptyline is the TCAs most prescribed in many circumstances where neuropathic pain is presented as central pain, DPN, and PHN [44]. SSNRIs, such as Venlafaxine and Duloxetine, are an effective drug in the treatment of neuropathic pain [49, 50]. They are mainly studied on painful polyneuropathy.

In recent years, connexins (Cxs) have been studied as targets for the development of new analgesic drugs. Connexins are a family of proteins with 20 subtypes and function as channels, junctions between cells, and hemichannels that sample the extracellular space and release substances such as neurotransmitters. One of the Cxs, Cx43, is expressed in astrocytes at the level of the central and peripheral nervous system. This has been studied in animal models and related to the genesis and maintenance of chronic pain, so it could be a promising therapeutic target for future treatments that act as Cx43-gap junction blockers, at the level of the trigeminal ganglion and the sciatic nerve [51].

6. Side effects and toxicity in pain pharmacotherapy

NSAIDs can promote various degrees of toxicity related to their pharmacokinetic and pharmacodynamic properties [11]. Its long-term use is a leading cause of morbidity especially in patients with risk factors, such as peptic ulcer and myocardial infarction, among others. The administration of these drugs or paracetamol frequently produces adverse effects such as gastrointestinal bleeding, hypertension, risk of infarction, hepatotoxicity, and renal failure [52–55]. Up to 25% of patients treated with NSAIDs have sodium retention, resulting in weight gain and developing peripheral edema. Likewise, hypersensitivity phenomena may occur, such as fever, rash, and eosinophilia [56]. About 15% of patients treated with NSAID presented significant elevations of liver-damaging enzymes, primarily alanine transaminase (ALT) and aspartate transaminase (AST), especially when administering Diclofenac and Sulindac [11]. Also, prostaglandins have an important role in female reproduction processes; it has been demonstrated by testing in mice the inhibition of COX-2 activity given by NSAID results in ovulation failure, fertilization, and implantation. Studies in animal models have also shown that these treatments modify the correct healing and union of fractures. Studies have not been conclusive since recovery depends on the type of wound, duration, and dose of the drug [57]. An increased risk of myocardial infarction has also been found in COX-2 inhibitors, presenting effects on blood pressure and nitric oxide production. Such is the case that ibuprofen interferes with the platelet effect and increases up to 35% risk of having myocardial infarction [58, 59].

On the other hand, the side effects of opioids include dry mouth [41], constipation, respiratory depression, nausea and urinary retention, motor impairment [60],

as well as addiction, tolerance, and paradoxically hyperalgesia [42, 53]. Depression and respiratory disorders are a common and known treatment effect, caused by the activation of opioid receptors (*mu*, *kappa*, and *delta*) expressed in the brainstem respiratory centers [61]. In addition, opioids affect dopaminergic and adrenergic systems that can mediate reward and addiction pathways [62, 63]. Preclinical and clinical research has concluded that chronic opioid use alters endocrine functioning and food intake and increases body weight, which in turn is related to constipation and nausea [53, 64]. Excessive exposure to opioids may develop tolerance, through activation mediated by the NMDA receptor (N-methyl-D-aspartate) and an increase in pain sensitivity that manifests as hyperalgesia and/or allodynia in patients. NMDA receptor antagonists relieve tolerance and dependence on morphine [62, 63].

Due to their anticholinergic effect, TCAs can increase the risk of cardiovascular events and reduce secretions, so they are contraindicated in patients with kidney disease, urinary retention, glaucoma, or serious cardiovascular diseases. On the other hand, SSNIRs can cause hives, itching or rash, headache, restlessness, nausea, and dry mouth; they have also been associated with an increased risk of suicide in people suffering from major depression [44].

In synthesis, conventional therapies to treat different types of pain are not exempt from serious side effects and toxicity, particularly opioids, whose effects on the central and peripheral nervous system promote life-threatening respiratory depression, addiction, pruritus, nausea, and constipation [2]. This situation represents a serious health problem that has been increasing due to the practice of prescribing opioids for pain management [65].

7. Medicinal plants as potential treatment of pain: preclinical research

7.1 Animal models of pain

Animal experimentation has been a very important tool in elucidating the mechanism that underlies certain diseases [66] and contributes to the improvement of diagnostic and prophylactic procedures as well as the understanding of the etiology and pathogenicity of different diseases [67]. These animal models offer the advantage of their standardization, genetic, and environmental background [68].

Animal pain perception shows similarities to human pain; thus, animal models mimic the persistent pain found in the clinic, and thus, animal studies give an idea of certain aspects of human pain conditions and lead to better pain management in patients [69]. Most nociceptive assays involve a noxious stimulus that can be thermal, chemical, mechanical, or electrical to specific parts of the body, resulting in simple noxious behaviors that can be easily qualified [70]. On the other hand, neuropathic pain models involve an injury or disease that affects the somatosensory system and include spontaneous pain, painful hyperalgesia, or allodynia [71].

Although we define pain as a homogeneous sensory entity, it is important to emphasize the etiological distinction of pain, as it is one of the most important and studied to define the neurobiological mechanisms responsible and provide an idea of how different types of pain are generated [72].

Research into new treatments for pain relief and their mechanisms has justified the use of different animal models developed to better understand the progress of specific disease issues. However, one of the most important needs when implementing an experimental model is that it reflects the necessary clinical conditions, from inflammatory pain to chronic low back pain. Therefore, over time several animal

models have been standardized that can evaluate different characteristics of pain. The **Table 3** shows the most important experimental pain models [1, 73–77].

7.2 Effects of medicinal plants on animal models of pain

Most often, pain is treated with allopathic or conventional pharmacological medicine, a vast pain conditions are complex to treat because of financial strains or adverse side effects. However, complementary and alternative medicine might be a novel solution because their great repertoire of techniques includes nonpharmacological remedies (massage, acupuncture, yoga, etc.) and the use of herbal medicine [5] to reduce opioid misuse, diminish avoidable costs, and improve health outcomes [78]. Therefore, herbal medicine is an important element of health systems in many developing and industrialized countries [79].

For the World Health Organization (WHO), "herbal medicines include herbs, herbal material, herbal preparations, and finished herbal products, which contain as active ingredients parts of plants, or other plant materials, or combinations of those elements" [80]. The popular use of medicinal plants in health care in many tropical and subtropical countries is widely described because of their enormous plant diversity. The consumption of medicinal plants has been important not only for the treatment of pain but also for treating diseases and metabolic disorders [81]. Therefore, the urge to gather more ethnobotanical and preclinical evidence to support the traditional uses of plants.

Nociceptive pain models		
Model	**Type of stimulus or injury**	**Natural metabolites evaluated**
Hot plate test Hargreaves test	Thermal	Organic compounds with possible antiharmful activity Substances with antiharmful properties, Flavonoids, Triterpenes, Carbohydrates, Phenols, Terpenoids, Coumarins, and Saponins, among others
Tail flick test	Thermal	
Tail immersion test	Thermal	
Paw/tail pressure test and Von Frey Randall-Selitto	Mechanical	
Electric stimulation of the tail	Electric	
Abdominal constriction test	Chemical	
Formalin test	Chemical	
Inflammatory pain models		
Model name	**Kind of stimulus or injury**	**Natural metabolites evaluated**
Capsaicin	Injection into skin, muscles, or joints	Phytochemical compounds with possible anti-inflammatory activity Polyphenols, Flavonoids, Quercetin, Phenolic compounds, Carotenoids, Quercetin, Catechin, Kaempferol, Epicatechins, Lupeol, Triterpenes, Phytosterols, Sterols, Lignans, Anthocyanins, and Alkaloids, among others.
Carrageenan	Injection into the leg, muscle, and joint	
Complete Freund Adjuvant (CFA)	Injection into the tail, leg, muscle, and joints	
Kaolin/carrageenan	Injection into knee or ankle joint	
Zymosan	Injection into knee or ankle joint	

Neuropathic pain models		
Model name	**Type of stimulus or injury**	**Natural metabolites evaluated**
Axotomy	Complete sciatic nerve transection	Opioids and tricyclic antidepressants, calcium antagonist (Verapamil, Nifedipine), sodium channel blockers (Lidocaine, Mexiletine, Tocainide), NMDA receptor antagonist (Dextromethorphan, Ketamine, Memantine), calcium N-channel blockers (Ziconotide), Antiepileptics (Gabapentin, Topiramate, Lamotrigine, Felbamate)
Chronic constriction injury	Four loose ligatures around sciatic nerve	
Partial sciatic nerve ligation (Seltzer Model)	Tight ligation of one-third to half of the sciatic nerve	
Spared nerve injury	Axotomy of tibial and common peroneal nerves	
Tibial and sural nerve transection	Axotomy of tibial and sural nerves	
Sciatic cryoneurolysis	Freezing of the sciatic nerve	
Sciatic inflammatory neuritis	Injection of zymosan, HMG, TNF-α around the sciatic nerve	
Laser-induced sciatic nerve injury	Radiation mediated reduction in blood supply to the sciatic nerve	
Excitotoxic spinal cord injury	Intraspinal injections of excitatory amino acids	
Spinal hemisection	Laminectomy of T11–T12 segments	
Diabetes-induced neuropathy	Persistent hyperglycemia-induced changes in the nerves	
Trigeminal neuralgia	Compression of trigeminal ganglion chronic constriction injury to the infraorbital nerve	
Orofacial pain	Injection of formalin, carrageenan into temporomandibular joints and maxilla	

Table 3.
Principal animal models of pain.

Several biological effects of extracts and purified compounds from herbal species have been tested *in vivo* and *in vitro* models. Extracts have shown antimicrobial, antiviral, and antimutagenic activity; cytotoxic activity for cancer cell lines and antinociceptive, anti-inflammatory activity; and antiatherogenic, antioxidant, and biocide for various food pests [82]. Based on the biological models of neuropathic pain, we can mention neuropathic pain induced by paclitaxel, chronic constriction injury, alcoholic neuropathy, streptozotocin-induced diabetic, partial sciatic nerve ligation, and model of sodium monoiodoacetate. Among the main secondary metabolites that have diminished pain are alkaloids, carotenes, flavonoids, phenols, and terpenes, among others [83]. Some species with analgesic profile and their metabolites are shown in **Table 4**.

The *Pterodon pubescens* (Benth) has been described as an analgesic. Phytochemistry studies have reported the presence of a high concentration of terpenes. The analgesic properties of *Pterodon pubescens* are attributed to these compounds [103]. An experimental study conducted in mice using the model of

Group of metabolite	Isolated metabolite	Plant containing the metabolite	Pharmacological effects	References
Alkaloid	Morphine Codeine Thebaine Papaverine	*Papaver somniferum* *Woodfordia fruticosa* *Peganum harmala*	Antinociceptive, anti-inflammatory, and antineuropathic	[84–86]
Flavonoid	Quercetin Rutin Kaempferol Luteolin Myricetin Apigenin	*Azadirachta indica* *Aloe vera* *Allium cepa* *Calamus scipionum* *Camellia sinensis* *Carica papaya* *Psidium guajava*	Peripheral neuropathy, anti-inflammatory, and antinociceptive	[87–90]
Carotene	β-carotene Lycopene	*Capsicum annuum* *Ginkgo biloba* *Solanum lycopersicum* *Daucus carota*	Acute or chronic pain: i.e. inhibiting the release of TNF-α and stimulating IL-10 production	[91, 92]
Phenol	Catechol Resorcinol Hydroquinone Phloroglucinol Vanillic acid Gallic acid	*Siegesbeckia orientalis* *Ageratum conyzoides* *Mikania cordifolia* *Moringa oleifera* *Plantago altissima* *Plantago lanceolata*	Antinociceptive and anti-inflammatory	[93–96]
Terpene	Thymoquinone Linalool Menthol Eugenol Fenchone Citronella	*Hyptis pectinata* *Hyptis fruticosa* *Erythrina velutina* *Aniba rosaeodora* *Mentha piperita* *Daphne aurantiaca*	Antinociceptive and anti-inflammatory	[97, 98]
Saponin	Digitonin Sarsasapogenin Dioscin	*Asparagus racemosus* *Tribulus terrestris*	Acute or chronic pain; antinociceptive, anti-inflammatory, and neuropathic	[99, 100]
Statins	Atorvastatin Lovastatin	*Trianthema portulacastrum*	Anti-nociceptive and anti-inflammatory	[101, 102]

Table 4.
Secondary metabolites with analgesic potential.

neuropathic pain induced by partial sciatic nerve ligation showed that the administration of ethanolic extract of *Pterodon pubescens*, at an oral dose of 300 mg/kg, was effective in exerting antinociceptive effects, revealing a possible mechanism of action associated with the significant bite suppression induced by kainate, glutamate, NMDA, and trans-ACPD. Also, the plant extract decreased the concentration of proinflammatory cytokines like TNF-α and IL-1β and the inhibition of channels of capsaicin (TRPV1) and cinnamaldehyde (TRPA1), respectively, without pharmacological tolerance. The most abundant metabolites extracted from these plants were sesquiterpenes and diterpenes, which suggest that these compounds are responsible for the therapeutic effect [104]. There is interest in the study of other plant species, including *Woodfordia fruticosa, Adhatoda vasica, Chenopodium ambrosioides, Viburnum cotinifolium, Vitex negundo, Peganum harmala,* and *Broussonetia papyrifera* because of the presence of effective alkaloids for pain treatment. The crude alkaloid extracts of all selected medicinal herbs were active at an oral dose of 1250 mg/kg of body weight in mice, where they reduced abdominal contractions

caused by acetic acid and increased the latency time between the licks of the legs in both phases of pain (neuropathic and inflammatory) produced with formalin. In addition, the alkaloid-specific antinociceptive response was significantly in the naloxone model [86].

Another group of plants of pharmacological interest is the genus *Polygala* and the *Lamiaceae* family that have been widely used in pain therapy [105]. *Polygala molluginifolia* has shown important antinociceptive effects in mice. An experimental study showed that the hydroalcoholic extract of this plant, administered at a dose of 1000 mg/kg, exerted analgesic effects in a model of mechanical and thermal hyperalgesia to postoperative pain in mice. The mechanism of action of the experiment revealed that the effect of the natural product might be associated with a modulation of the TRPV1 and TRPA1 channels involved in nociceptive behavior and was demonstrated that *Polygala molluginifolia* has an antinociceptive potential without collateral effects like locomotor dysfunctions or sedation [106].

The phytochemistry of the species of the genus *Agastache* (Family *Lamiaceae*) is generally similar among them and consists of two classes of major metabolites: phenylpropanoids and terpenoids. The essential oils obtained from the family that has been identified more than 50% of estragole and volatile compounds such as methyl eugenol, pulegone, menthone, isomenthone, and spathulenol. The main nonvolatile metabolites are phenolic compounds, such as those derived from caffeic acid, especially rosmarinic acid, as well as several flavones and flavone glycosides such as acacetin, tilianin, agastachoside, and agastachin. Lignans, agastenol and agastinol, were also isolated, as well as terpenoids include oleanane type (maslinic acid, oleanolic acid, and β-amirin), ursane type (ursolic acid, corosolic acid, and α-amirin), typical plant sterols, and diterpenes (agastaquinone, agastol, and others) [82]. The plants of the *Lamiaceae* family are widely used as condiments, and some popular are oregano, thyme, and rosemary, but aromatic ones such as mint, basil, and sage are also part of this family [107].

About 250 species belong to the genus *Lippia* (Family *Verbenaceae*) and are distributed throughout Central and South America, as well as in the African continent. They are usually sold for the treatment of different types of pain, including stomach pain, abdominal pain, and headache, and are used as sedatives, anxiolytics, and anticonvulsants [108]. *Lippia alba, L. multiflora, L. gracilis, L. grata, L. origanoides, L. graveolens, L. geminata, L. origanoides,* and *L. adoensis* are the species that have reports worldwide on their effect on system disorders such as central nervous, pain, and inflammation [109].

Lippia origanoides commonly known in Mexico as "*oregano*" and *Lippia multiflora* also known in Africa are popularly used to control fever treat gastrointestinal disorders, enteritis, and cough. Composite leaves and flowers such as p-cymene, thymol, and carvacrol [110] were isolated from which the analgesic and antipyretic properties have been attributed, evaluated in mice and rats using carrageenan-induced hind paw as model of acute inflammation, and the analgesic effects were assayed by thermal, mechanical, and chemical models of antinociception, and this was correlated with an increase in glutathione and a decrease in nitric oxide and malondialdehyde, demonstrating a decrease in the levels of nitric acid and malonyl aldehyde process mediators such as inflammatory and pain [110]. A monoterpene called carvacrol has been isolated from oregano, which has shown antinociceptive effects. This metabolite was studied in an orofacial pain model and demonstrated that when administered at a dose of 20 mg/kg, it exerts antinociceptive effects in mice; however, this effect is punctuated more effectively if the metabolite is administered concomitantly with β-cyclodextrin [111]. Carvacrol/β-cyclodextrin has also been studied in cancer-induced pain models. Administered at a dose of 50 mg/kg, they exert antinociceptive effects in rodents that have tumors implanted in their hind

paw [112]. An interesting fact about carvacrol is that its analgesic effects decrease when administered alone and increase when administered with cyclodextrin. On the other hand, carvacrol and p-cymene have an analgesic effect related to the decrease of pain mediators such as proinflammatory cytokines (IL-1, TNF, IL-4, TGF and IL-17) and anti-inflammatory (IL-10) [113, 114].

Hexane, ethyl acetate, and ethanol extracts from *Agastache mexicana subsp. xolocotziana* showed an antinociceptive effect in rats and mice. The ethyl acetate extract (containing significant amounts of ursolic acid) was the most active in the formalin-induced pain model, mainly in the inflammatory (second) phase; hexanic extract (present pulegonic and oleanolic acid) decreased thermal pain. The methanolic extract (rich in flavonoids such as acacetin and tilianin) was more active in the formalin model and in the acetic acid contortion model [82].

Rosemary plant has been assessed in Diabetes Mellitus cases of pain models. A study in rats showed that rosemary extract administration at 100, 150, and 200 mg/kg doses decreased hyperalgesia through the suppression of caspase-3. In this study, the neuroprotective effect of rosemary was also demonstrated, so that the authors suggested that the mechanisms of action might be involved in the inhibition of neuronal apoptosis [115].

The *Mentha spicata* plant, popularly known as garden mint, showed significant analgesic effects at the preclinical level. Phytochemical studies have revealed the presence of metabolites such as carvone, limonene, and menthol. Basil plant (*Ocimum basilicum*) has also shown analgesic effects combined with β-cyclodextrin. Studies have been conducted from basil essential oils, which are rich in monoterpenes. A study conducted in animal models of fibromyalgia showed that essential oils administered orally, at doses of 25, 50, and 100 mg/kg, significantly reduced mechanical hyperalgesia in mice [116, 117].

In addition to the plants described above, many others have presented significant effects in pain therapy in preclinical models associated with certain metabolites (see **Table 5**). Nevertheless, further molecular studies on secondary metabolites are needed, which allow to accurately indicate the mechanisms of action, and the effects can be compared with those analgesics already in the market. Further research is required to achieve analgesic effects at the lowest possible doses to significantly reduce the number of adverse reactions in organisms, particularly because the use of natural resources has become increasingly active in recent years because of the belief that natural products lack side effects [118]. Nevertheless, herbal therapy is risky because there are effects caused by plant metabolites that may vary depending on several external factors such as pollution, conservation processes, and the presence of pesticides, among others yet to be evaluated. As a result, the use of botanical medicine requires rigorous standardization processes that guarantee safety in its use [119]. The variety of soils and climates in such countries facilitates the growth of a wide range of plants. Nevertheless, the native people use plants empirically, which had led to the lack of standards in their use in terms of effectiveness, safety, and quality [120]. This idea has triggered the worldwide development of drugs used in plants, which lead to the phytomedicine trade worldwide [118].

Phytomedicine differs from synthetized chemical-pharmaceutical drugs in their components. A chemical-pharmaceutical drug is synthesized and designed in such a way we can have a pure compound or at least a small mixture of chemical molecules. Conversely, phytomedicine is plant extracts that contain numerous and not well-known compounds. As a result, the source of the plant material requires quality production and standardization of the extracts to guarantee the identification and purification of the compounds that target pain [121]. The increased popularity of herbal medicine worldwide had led to numerous reports that support its regulation. In some countries, regulations have been legally established in order

Plant	Potential active metabolite involved	Animal model used	Effects on pain	References
Cannabis sativa	Δ9-Tetrahydro-cannabinol Cannabidiol	Male and female mice in a chronic neuropathic sciatic nerve injury model	Reduce allodynia, hyperalgesia, and ultrasonic clicks	[123]
Papaver somniferum	Morphine	Male and female mice in a chronic neuropathic sciatic nerve injury model.	Reduce allodynia, hyperalgesia, and ultrasonic clicks but develop tolerance after 1 week	[123]
Urtica dioica, Urtica urens, and Urtica circularis	Phenolic compounds and hydroxy fatty acids	Anti-inflammatory *in vitro* COX-1 enzyme; Swiss mouse females in the formalin test and acetic acid-induced abdominal writhing test	Reduce the nociceptive response	[124, 125]
Verbesina persicifolia	Sesquiterpene-lactones (eudesman, cadinane, germacrane, and elemane)	TPA (12-O-tetradecanoylphorbol-13-acetate)-induced ear edema test	Anti-inflammatory activity	[126, 127]
Costus pictus, Costus spicatus	Flavonoids, flavonol glycosides, and polysaccharides	Male OF-1 mouse in formalin, acetic acid-induced abdominal writhing models; hot plate	Antinociceptive but not anti-inflammatory effect	[128, 129]
Valeriana officinalis	Sesquiterpene and iridoids	Orofacial formalin test	Reduce the nociceptive response	[130, 131]
Calotropis gigantea (L) R. Br.	Flavonoids, alkaloids, triterpenoids, steroids, saponins, phenols, and glycosides	Hot plate and acetic acid-induced abdominal writhing model	Decrease the number of paws licking and writhing	[132]
Curcuma longa L.	Alkaloids, flavonoids, saponins, and tannins Curcumin Demethoxy-curcumin Bisdemethoxy-curcumin	Acetic acid-induced induced abdominal writhing model. Tail flick test; tail immersion test	Reduce the number of writhing. Increase latency; reduce the tail withdrawal time	[133–135]
Gastrodia elata	4-Hidroxy-benzaldehyde 4-Hidroxybenzyl alcohol Benzyl alcohol Vanillin Vanillic acid	Carrageenan, acetic acid, arachidonic acid (AA)-induced paw edema and writhing models. Cyclooxygenase activity.	Analgesic and anti-inflammatory activity Inhibit the activity of COX-I/II	[136]
Spilanthes acmella, Acmella oleracea	Alkaloids, flavonoids, tannins, and carotenoids N-alkylamides Spilanthol	Formalin, capsaicin and cinnamaldehyde, carrageenan-induced paw edema models; hot plate and tail flick; traumatic sciatic nerve injury	Antinociceptive and anti-inflammatory effect; increase paw withdrawal latency and reduce mechanical allodynia	[137, 138]

Plant	Potential active metabolite involved	Animal model used	Effects on pain	References
Zingiber officinale	Alkaloid, flavonoids, and tannins	Hot plate, tail flick test; acetic acid-induced pain model	Antinociceptive effects against thermally and chemically stimulus	[139–141]
Salix alba	Alkaloids, tannins, polyphenolic salicin and glycosides 2-(hydroxymethyl)-phenyl-B-D-glucopyranoside Salicyl-alcohol	Formalin-induced paw edema model Enzymatic action of hyaluronidase	Inhibit the paw edema Inhibitory actions on biochemical pathways of arachidonic acid	[85, 142, 143]
Ammi majus	Furocoumarins and coumarins	Hot plate; formalin, carrageenan-hind paw edema models	Anti-inflammatory and antinociceptive; inhibition of the writhing number	[144, 145]
Arnica montana	Phenolic acids (caffeic, chlorogenic), flavonoids (quercetin, palutelin), sesquiterpene lactones (helenalin, dihydrohelenalin)	Hot plate; carrageenan, formalin-hind paw edema models; cytokines determination by ELISA	Inhibition of the licking, writhing, and biting response; decrease secretion of IL-6 and IL-8 proinflammatory cytokines	[146, 147]

Table 5.
Active metabolites in pain relief.

to safeguard public health, ensuring quality, efficiency, and safety. For instance, the European Union has one of the most complete regulatory systems for the use of herbal medicine [122]. Since the combination of both conventional and traditional herbal therapy has been poorly explored, it must be careful to avoid serious adverse reactions [81].

8. Final comments and conclusion

Pain is unpleasant sensory and emotional experience associated with actual or potential tissue damage, being one of the most persistent and disabling manifestations present in several conditions and diseases mentioned in this chapter, such as tissue injuries and bumps, postoperative surgery, cancer, diabetes, mood disorders, dementia, and schizophrenia, among others.

In this chapter, it was highlighted that the pain is continually reclassified due to its severity and complexity, coupled with the difficulty of describing it, despite the fact that there are currently more reliable and valid instruments. This activity is of great importance to improve the diagnosis and sure adequate therapeutic management.

Because pain is a global public health problem, there is a large class of drugs used for its treatment, such as opiates, tricyclic antidepressants, and antiepileptic drugs. As shown in this review, the prescription of this conventional painkiller depends on the type of pain, its duration, origin, and intensity. However, the side effects shown by these compounds hinder in many instances, their safe and effective use,

particularly opioids, which could promote life-threatening respiratory depression, addiction, pruritus, nausea, and constipation. Therefore, new molecules are being sought with specific mechanisms of action that act from the genesis and maintenance of pain at different levels of the nervous system, for example, on the connexins, which would represent an outstanding advance.

On the other hand, in many countries, herbal medicine is used as a complementary or an alternative strategy to treat pain because it usually lowers costs, is more within reach of patients, and has an important cultural root. In this sense, species such as *Papaver somniferum, Pterodon pubescens, Capsicum annuum, Chenopodium ambrosioides, Polygala molluginifolia, Lippia alba, Agastache mexicana, Allium cepa, Moringa oleífera,* and *Hyptis pectinata,* among others described in this chapter are used due to their analgesics and anti-inflammatory properties. Secondary metabolites such as alkaloids, flavonoids, carotenes, terpenes, and other polyphenolic compounds seem to be responsible for the pharmacological effect reported, which has been demonstrated from the use of animal models, which show similar perception to chemical, thermal, electrical, and mechanical stimuli that can induce pain than in humans and that constitute one way to approach the study of new molecules or herbal extracts with analgesic activity.

Since the combination of both conventional and traditional phytotherapy has been poorly explored, this can often lead to harmful effects rather than improving pain treatment. Meanwhile, most analgesics and herbal products for pain treatment are accessible because they do not require a prescription for sale, their consumption has been exceeded, and self-medication has led to a major concern in several countries. Not regulated herbal therapies can trigger several conditions that may further compromise the patient's well-being. Currently, research on natural products includes the use of organic synthesis for improving natural product characteristics. Some research groups synthesize analogs of natural compounds and modify its activity to improve the effectiveness of the drug lead. Since the use of natural compounds might be risky because of the multiple active molecules present in plants, mimicking the targets that produce the desired effect, such as diminish pain, it is a useful alternative and avoids the burden of isolating molecules from natural resources. In this regard, it is possible to obtain a purified compound that can be tested. Molecular biology is a powerful tool to identify receptors and proteins, so a perspective in the pharmacological treatment of pain could be the development of further research in molecular biology for studying the targets of pain and therefore for designing specific molecules that can bind directly to pain receptors.

In conclusion, it is crucial that pharmaceutical, neuroscientists, and other healthcare professionals must be involved in well-designed preclinical trials to fully understand the effects of herbal medicines and phytopharmaceuticals and to study the molecular mechanisms and biological targets in which they operate. In terms of regulation, it would be important for organisms other than the Food and Drug Administration (FDA) in developing countries to establish the mechanisms such as to conduct all the preclinical trials before releasing a new drug.

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Conflict of interest

The authors declare no conflict of interest.

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