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Review Article

Potential Activity of Medicinal Plants as Pain Modulators: A Review

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ABSTRACT

This review aims to demonstrate the relevance that medicinal plants and their promising results have in prevention and treatment of pain. The neurophysiological bases of pain have been analyzed and the potential mechanisms of action have been proposed, it has also been determined that the main experimental models used for the evaluation of the analgesic potential are: acetic acid-induced writhing test, formalin test, hot-plate test, capsaicin-induced nociception, cinnamaldehyde-induced nociception, glutamate-induced nociception, tail–flick test and tail immersion test. There are countless medicinal plants with potential analgesic activity, in some of them main responsible compounds for the activity are flavonoids (vitexin, quercetin, naringenin, astragalin, eupatilin), alkaloids (scotanamine B, bullatine A, S-(+)-dicentrine, stephalagine, lappaconitine), terpenoids (p-cymene, thymol, menthol, citronellol, myrcene, carvacrol, linalool) and saponins (siolmatroside I, cayaponoside D, cayaponoside B4, cayaponoside A1); however, all studies have only been carried out up to pre-clinical stages. Therefore, it is recommended to carry out kinetic studies of the most remarkable natural compounds, evaluate mixtures of active compounds for diminishing doses to avoide possible side effects, and continue with clinical studies of medicinal plants whose safety has already been reported.

Key Words: Pain, Analgesic, Antinociceptive, Natural product, Extract.

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INTRODUCTION

Although pain is a defense mechanism, that acts as an alarm signal to protect the organism and extend the human survival, it is considered one of the most important public health problems in the world, especially chronic pain that is still an important challenge of modern medicine.[1,2] The International Association for the Study of Pain (IASP), defines it as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.[3]

Pain is a dynamic phenomenon that is characterized by going from the periphery to the brain and the nociceptive signal is modulated at every level of Central Nervous System (CNS).[4] A disease or injury at the Central Nervous System (CNS) or at the Peripheral Nervous System (PNS) causes a potential risk to the body, whose will activate free nerval terminals in response to nociceptive stimulation.[3] Most of these nervous fibers are polymodal and will respond to mechanical, thermal and chemical stimulation.[2,4]

Non-opioid drugs have been used in treatment of mild to moderate pain, while opioid drugs are used in the treatment of moderate pain.[5] Conventional therapy for neuropathic pain includes: non-steroidal anti-inflammatory drugs (ketorolac), opioids (morphine), tricyclic antidepressants (amitriptyline, duloxetine), and some anticonvulsants (gabapentin);[6] however, all these drugs have shown moderate efficacy, often being associated with adverse effects and use of opioid drugs, in most of the patients have generated addiction and its excessive use even produced death by overdose.[5]

Classic analgesic drugs such as morphine, codeine and aspirin have been isolated from natural products, which has attracted the attention of many researchers as a source that could provide the discovery of new analgesic drugs.[5,7] In addition, medicinal plants and their metabolites have a reduced number of side effects and they are used as an unexpensive therapeutic resources for management of chronic pain.[2,8]

Evaluation of medicinal plants on pain has been studied using different experimental models including writhing test, light tail movement test, tail immersion test, hot plate test and formalin test.[9] Results obtained in these tests show that most important secondary metabolites with analgesic effect include flavonoids, volatile oils, phenolic compounds and alkaloids.[10]

Despite actual pain treatments, they reduces the quality of life, increases health costs and generates economic losses to society, either due to mechanical, inflammatory or neuropathic pain from a disease or injury to nervous system.[11] That is the reason of the importance of continuing with the search for new analgesic compounds that supplement or enrich preexisting alternatives. Throughout history, multiple natural extracts have been studied as

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sources of active ingredients with analgesic activity, many of them with great potential to continue in the search for new chemical entities that become candidates for new drugs aimed at controlling pain syndromes.

This review aims to enhance the rol of medicinal plants and their promising results for the prevention and treatment of pain. Indeed, the neurophysiological bases of pain will be analyzed first, for allowing us to predict possible mechanisms of the natural compounds reported as potential pain modulators.

NEUROPHYSIOLOGICAL BASES OF PAIN

From the neurophysiological point of view, perception of pain requires participation of the CNS and the PNS, triggering a series of reactions in both systems that allow the perception of it, in order to reduce the cause and limit the consequences.[1] Pain is classified as acute or chronic, nociceptive or neuropathic and, depending on the driving speed, fast or slow. Stimuli that cause pain are detected by nociceptor receptors and free nerve terminals that respond to painful stimuli and communicate nociceptive information through C fibers and Aδ fibers.[12-13]

In neural process of pain transmission, transduction is considered, which is the conversion of nociceptive stimulus into an electrical signal in the nociceptors; transmission, when pain stimuli are referred to the dorsal horn of the spinal cord and pain neurotransmitters are released (Glutamate, substance P, peptide related to the calcitonin gene) and; modulation, which is the pain signal in the dorsal horn of the spinal cord that can be inhibited and modified for supra pain centers.[12,14] In conclusion, the stimuli are transmitted to the spinal cord, by nerve fibers, and then travel later to the central areas of the brain, where the perception of pain occurs.[12,15]

From the spinal cord, pain is transmitted to the brain through several different pathways. Most of the afferents travel in the spinothalamic tract to the thalamus. They have been described from the projections of the thalamus to the insula, the hypothalamus and the amygdala, as well as to supra cortical levels such as the cingulate and prefrontal cortices.[16-17] The anterior cingulate cortices and the prefrontal cortices are part of the medial pain system, that mediates the affective, emotional, and cognitive components of the pain experience.[17-18] The pain system has several inherent mechanisms by which incoming pain signals can be modulated. The multiple complex pathways involved in this modulation comprise both spinal and supraspinal regions. In particular, the connections between these sites, commonly known as the descending modulator pain pathways, develop a central role.[19-20]

In response to a noxious stimulus or tissue damage, a series of neurotransmitters are released which are collectively known as "inflammatory soup".[21] Inflammation can be acute or chronic and it has been found that the transcription factors NF-κB and STAT3 are the ones that regulate the expression of inflammatory gene products[22] and; inflammatory enzymes such as cyclooxygenase-2 (COX-2) and matrix metalloproteinase-9, inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukins (IL) such as IL-1, IL-6 and IL-8 and chemokines are the main molecular mediators of the inflammatory response. Among these mediators, the ubiquitous transcription factor NF-κB is the key mediator of inflammation, since it regulates large sets of genes that encode cytokines, cytokine receptors and cell adhesion molecules that participate in the triggering of inflammation.[23- 24]

Nuclear translocation of transcription factors is initiated by cytokine signaling, it has been shown that cytokines can also induce nociceptive plasticity through local protein synthesis in peripheral processes of sensory afferents.[25] Although cytokines can induce nociceptive plasticity by the synthesis of local proteins in the peripheral processes of sensory input, it is not clear how these pathways intersect directly with the activities of ion channels or G[26] protein-coupled receptors The inflammatory soup will sensitize the nociceptor and increase the expression of sodium channels thus facilitating the generation and transmission of stimuli; This is called peripheral sensitization, which lowers the nociceptive threshold and facilitates noxious responses to promote adequate tissue recovery; this is the pathophysiological basis of acute pain.[21]

Pain modulation can lead to increased transmission of pain impulses (facilitation) or decreased transmission (inhibition). Balance between these states ultimately determines the quality and strength of the pain signals that lead to the perception of pain in the brain. Alterations in the state of the descending modulatory pathways toward facilitation have been associated with the transition from acute to chronic pain.[27]

Sensitization of peripheral nociceptors underlies hyperalgesia that develops immediately around the injury site; afferent fibers can be sensitized by endogenous chemicals. This results in an increase in their responsiveness to a given stimulus and/or an increase in spontaneous activity.[28] In addition, during inflammation an upregulated expression of nociceptors such as sodium channels is observed, receptors of transient potential (TRPV1), pH detection ion channels (ASIC) and purinergic receptors (P2X). As a consequence of all these changes, sensitivity to pain at the site of inflammation increases.[29]

Central sensitization with enhanced spinal information of inflammation can activate intracellular signaling cascades within neurons of the spinal dorsal horn, this results in increased synaptic efficiency and is known as central sensitization Deep pain and visceral pain input to spinal cord are more potent than cutaneous pain in inducing central sensitization.[30] Entry leads to activation of the N-methyl-D-aspartic acid receptor and results in changes in the resting potential of the neuron of the spinal cord. Second order. Therefore, it is more pobably to trigger when stimulated by transmitters.[16]

Besides, of such a multiplicity of mechanisms that are known to modulate pain transmission, the appearance in the literature of so many compounds that can directly or indirectly modulate pain transmission is not surprising. However, few of them achieve sufficient selectivity of action or potency and consequently are of little clinical interest. Therefore, most of the analgesics reported produce their effects by modulating the release of endogenous analgesic mediators or by inhibiting algogenic neurotransmitters, through presynaptic or postsynaptic mechanisms at the central and peripheral levels.[31]

EXPERIMENTAL MODELS AND PAIN

There are many variants of experimental models that use animal model and allow evaluation of the analgesic and antinociceptive properties of plant extracts and their natural compounds. (Figure 1). Acetic acid-induced writhing test is a widely accepted classical model to detect new agents with antinociceptive activity at the peripheral level.[32] The writhing response induced by acetic acid is mediated by the acid-sensitive ion channels of peritoneal mast cells and prostaglandin.[33]

However, abdominal constriction test is not a specific test as certain types of non-analgesics such as muscle relaxants can also give false positive results, which could lead to misinterpretation of the results. To confirm the possible antinociception mechanisms involved, more specific tests should be considered to determine participation of central and / or peripheral levels of antinociception.[34]

Formalin test evaluates the analgesic effects at peripheral and central levels of the nervous system. The injection of formalin produces two distinct phases: the first phase called neurogenic nociception is produced by the direct activation of the nociceptive fibers, which release substance P, glutamate and bradykinin; the late phase is mediated by the release of inflammatory mediators such as nitric oxide, excitatory amino acids (aspartate and glutamate), cyclins, prostaglandins (PGE2) and leukotrienes.[35]

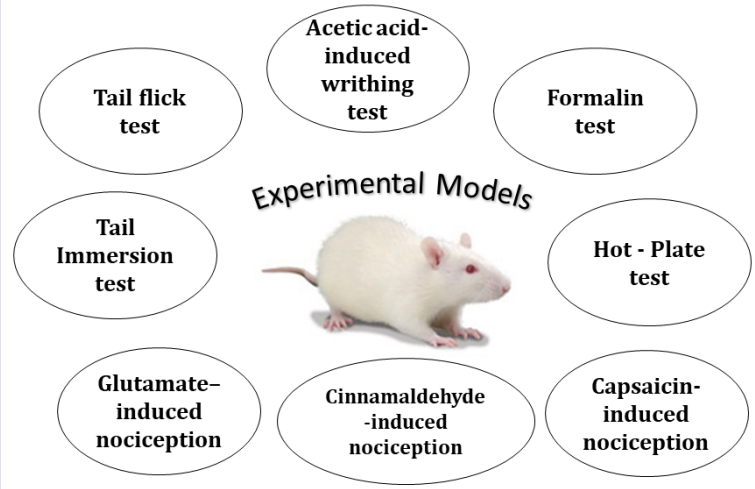

Figure 1: Experimental models to evaluate the analgesic potential.

Tail – flick test is predominantly based on the spinal reflex and is considered selective for centrally acting analgesic compounds. Tail immersion test evaluates peripheral and central activity, and is also considered a model of chronic pain.[36-37]

Hot plate test measures thermally induced nociception at the supraspinal level and spinal levels, it is a suitable model to evaluate the potential of any compound with antinociceptive activity at the central level. It has the advantage of being selective and sensitive only to analgesics of central action, but not peripheral; It is a selective test for opioid compounds.[7,34]

Glutamate test is used to show the activation of NMDA receptors, causing an increase in calcium intake with the activation of neuronal NO synthase and the formation of nitric oxide. Thus, glutamate participates in the processes involved in the perception and central sensitization of pain.[38]

Among experimental models for the study of acute pain, some natural irritants are used that cause pain by activating TRP channels, such as capsaicin that acts specifically on type C unmyelinated fibers through TRPV1 receptors and cinnamaldehyde that acts by TRPA1. The TRPV1 and TRPA1 channels are involved in the transduction and sensitization of primary afferent somatosensory neurons. Both TRPV1 and TRPA1 play a role in pain and neurogenic inflammation through activation of sensory nerves, both peripherally and centrally. Activation of the TRPA1 and TRPV1 channels can cause the release of vasoactive peptides, such as the calcitonin gene-related peptide and substance P from nerve terminals.[39-40]

MEDICINAL PLANTS WITH POTENTIAL ANALGESIC ACTIVITY

Due to possible side effects and low efficacy of conventional drugs, consumption of natural alternatives, such as medicinal plants, to control pain is currently increasing.[7] The effects of medicinal plant extracts have been studied using different experimental models, using in evaluation a variety of extracts, the most tested being the aqueous, ethanolic, aqueous-ethanolic and acetonic types, as well as the fractions obtained from these compounds.

The main natural compounds that modulate pain include flavonoids such as quercetin and Kaempferol, catechins, anthocyanins, saponins, sesquiterpenes, phenolic compounds such as gallic acid, alkaloids, monoterpenes, triterpenes among others. Some of the main medicinal plants that modulate pain are presented in Table 1.

ANALGESIC MECHANISMS OF NATURAL COMPOUNDS

There are a diversity of vegetale species that own a variety of promising compounds that act as pain modulators. The main phytoconstituents reported and that are related to analgesic activity are flavonoids, alkaloids, terpenes and saponins; many of them already identified with their chemical structures. These compounds intervene in the neurophysiological mechanisms of pain, previously described, modulating pain either by peripheral or central mechanisms. (Figures 2 and 3).

Flavonoids are a class of polyphenols that are consumed in the human diet through vegetables, fruits, cereals, spices and other products of plant origin. They are formed in plants from the aromatic amino acids phenylalanine and malonate.[5,105] The general analgesic effect of flavonoids is through the activation of the Nrf2 / HO-1 pathway. Flavonoids can act on 5-HT2 and 5-HT3 receptors, which may be involved in the mechanism of central analgesic activity. There are also studies on the role of flavonoids in analgesic activity mainly by acting by prostaglandins.[106-107]

Vitexin is a glucoside flavone, it produces analgesic effects mediated by mechanisms related to opioids, since antagonists of the opioid delta, mu and kappa receptors reverse the analgesic effects of this flavonoid.[106] The flavonoid quercetin suppresses the levels of protein kinase expression C (PKC) and TRPV1 receptor in the spinal cord and dorsal root ganglia, it also has other mechanisms, including nitric oxide production, activation of ɣ-aminobutyric acid (GABA) and serotonin receptors, similar effects of opioids.[108]

Naringenin is a flavanone found primarily in citrus fruits such as lemon, orange, tangerine, and grapefruit. It stimulates Nrf2 at the macrophage level and inhibits the activation of NF-κB induced by LPS, which contributes to the inhibition of the production IL-33, TNFα, IL-1β and IL-6 and the expression of 2-cyclooxygenase-mRNA. Naringenin regulates TRP channels expressed by nociceptor neurons such as TRPV1, TRPM3, and TRPM8 to induce analgesia and sodium entry, inhibiting Nav1.8 channels, which contributes to its analgesic effect.[106,109]

Astragalin and eupatilin are derivatives of flavones that have an analgesic effect through their action on the TRPA1 receptors in the sensory terminals of the C fiber and produce the reduction of the nociception induced by formalin.[47]

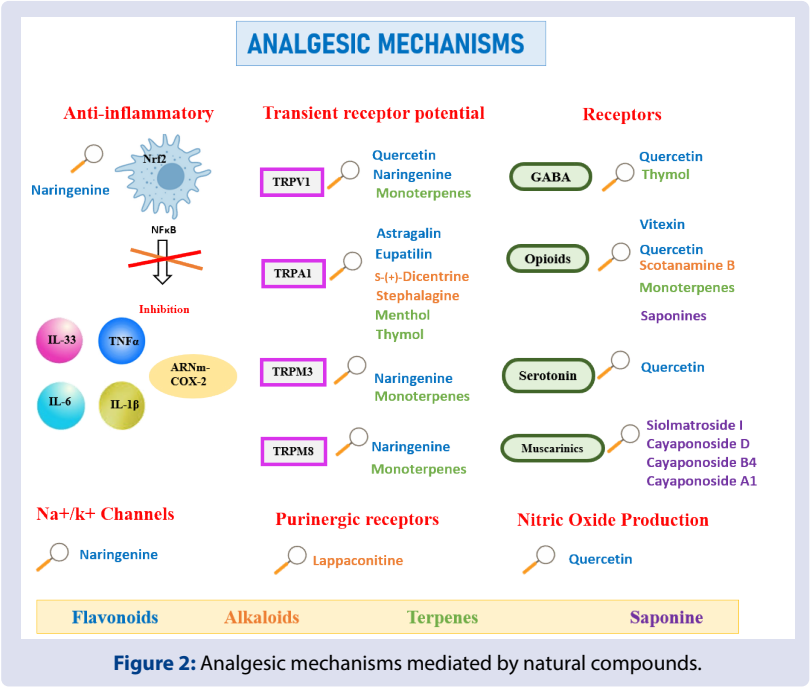

Figure 2: Analgesic mechanisms mediated by natural compounds.

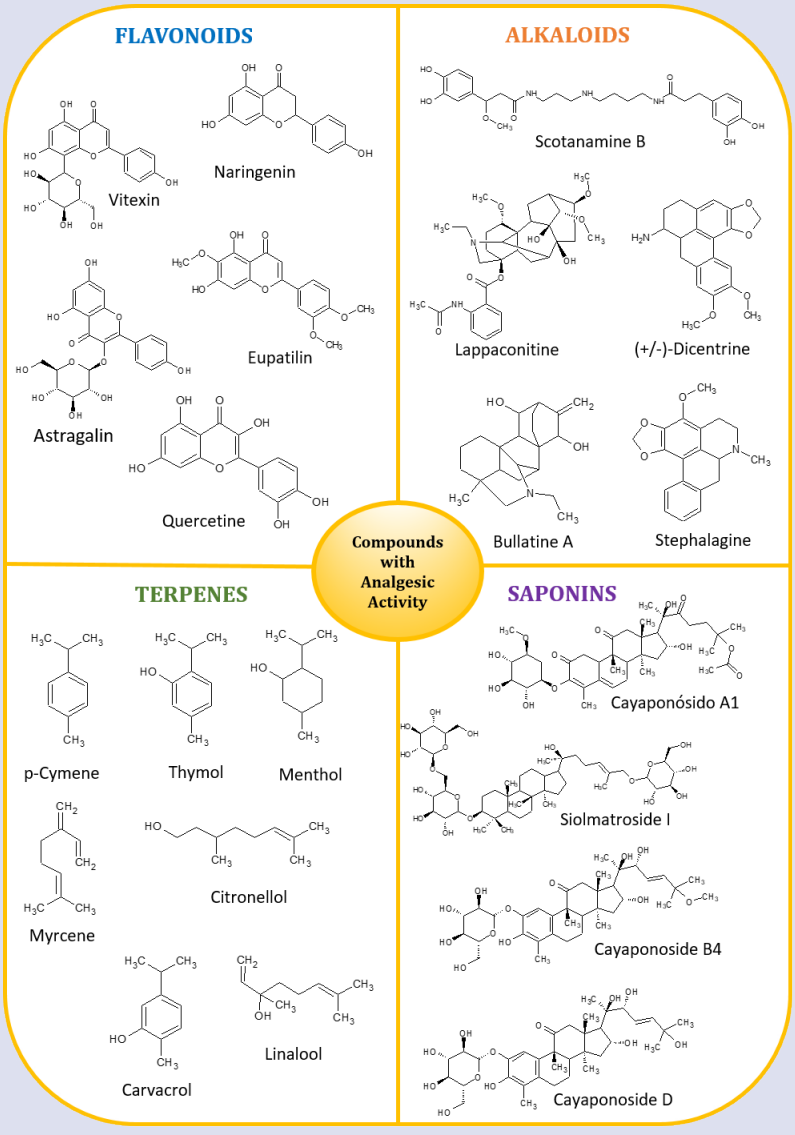

Figure 3: Chemical structure of the main natural compounds with analgesic activity.

Table 1: Some important medicinal plants with antinociceptive activity.

Medicinal Plant	Part of the plant	Model of study	Extract and dose	Majority compounds	Positive Control	Ref.
Ageratum fastigiatum	branches and leaves	−Acetic acid-induced writhing −Formalin test −Hot-Plate test −Tail Immersion test	Ethanolic extract (50, 100, 200, 250 and 500 mg/kg)	Flavonoids, tannins, coumarins, terpenes, sterols and saponins.	Acetylsalicylic acid (200 mg/kg p.o.), Morphine (5 mg/kg s.c.), diclofenac sodium (25 mg/kg)	41, 42
Agrimonia eupatoria L.	aerial parts	−Hot-Plate test −Acetic acid-induced writhing −Formalin test	Aqueous extract (199.18 and 398.26 mg/Kg), Ethyl acetate fraction (36.24 and 72.48 mg/Kg)	Quercetin, apigenin, isoquercetin, luteolin, agrimoniin, *p*-coumaric acid tiliroside, kaempferol O-acetyl-hexosyl-O-rhamnoside	Morphine (10mg/kg i.p.), Diclofenac (10mg/kg i.p.)	43
Alchornea laxiflora	root	− Acetic acid induced writhing − Formalin test − Hot-Plate test	Ethanolic extract and fractions (75, 150 and 225 mg/kg i.p.)	Quercetin, quercetrin, rutin, taxifolin, quercetin 3,4-diacetate,Triterpenes, capsaicin and dihydrocapsaicin	Acetyl salicylic acid (100 mg/kg i.p.)	44
Annona crassiflora	Fruit	−Formalin test −Cinnamaldehyde-induced nociception −Capsaicin-induced nociception	Methanolic extract and alkaloidal fraction ((30, 100 and 300 mg/kg p.o.), alkaloid stephalagine (0.1, 0.3 and 1 mg/kg p.o.)	Alkaloids as stephalagine		39
Arctium lappa L	root	−Acetic acid-induced writhing	Hydro-glycero-ethanolic extract (125, 250 and 500 mg/kg p.o)	Chlorogenic acid, Quercitrin	Diclofenac (20 mg/kg p.o.)	45
Artemisia annua	aerial parts	−Acetic acid-induced writhing −Hot-Plate test −Tail Immersion test	Ethanolic extract (200 mg/kg p.o.)	Sesquiterpene lactones, flavonoids, polyalkynes and coumarins	Diclofenac (6 mg/kg p.o.)	46
Artemisia Herba-Alba	aerial parts	−Hot-Plate test	Aqueous extract (10, 31.6, 100, 316, and 1000 mg/kg i.p.), astragalin and eupatilin (0.316, 1, 3.16, 10, 31.6, and 100 mg/kg i.p.)	Astragalin, eupatilin	Morphine (5 mg/kg i.p.)	47
Artemisia macrocephala Jacquem	aerial parts	−Acetic acid-induced writhing −Formalin test −Tail Immersion test	Methanolic extract (150 and 300 mg/kg p.o.), Sub-fractions (100 and 200 mg/kg p.o.)	Flavonoids	Diclofenac (50 mg/kg i.p.), Indomethacin (10 mg/kg i.p.)	48
Artocarpus lacucha Buch-ham	bark	−Hot-Plate test −Tail Immersion test −Acetic acid-induced writhing −Formalin test	Hydro-alcoholic extract (50, 100, 200mg/Kg)	Catechin	Morphine (5 mg/Kg) Diclofenac (10 mg/Kg i.p.)	49
Aspidospermacuspa (Kunth) Blake	bark	−Acetylsalicylic acid induced writhing test −Tail Flick test	Aqueous extract (69, 138 and 276 mg/kg)	Aspidocarpine, 11-Methoxytubotaiwine, Picraline, tubotaiwine, apparicine, akuammidine, akuammine, akuammicine, akuammigine and pseudoakuammigine	Acetylsalicylic acid (200mg/kg p.o.), tramadol (40mg/kg i.p)	50
Bauhinia glauca subsp. *hupehana*	aerial parts	−Acetic acid-induced writhing −Tail Flick test −Hot-Plate test −Glutamate-induced nociception	Ethanol extract (50, 100, 200 and 800 mg/kg p.o.)	Gallic acid, peperomin B, quercetin, fisitin, luteolin, farrerol and racemate	Aspirin (200 mg/kg p.o.) morphine (10 mg/kg s.c.)	36
Bauhinia purpurea	leaves	−Acetic acid-induced writhing −Hot-Plate test −Formalin test	Aqueous extract 10%, 50%, 100%	Flavonoids, saponins, steroids and triterpenes	Morphine (5 mg/kg) Acetylsalicylic acid (100 mg/kg)	51

Bidens odorata Cav.	leaves	−Acetic acid-induced writhing −Formalin test	Ethanolic Extract (50–200 mg/kg)	Phenolic compounds (benzoic acid and caffeic acid), phytosterols (stigmasterol and β-Sitosterol), glycol ethers (α-tocopherol), fatty acids (linolenic acid and linoleic acid), and terpenes (squalene, caryophyllene, and β-amyrin).	Naproxen (100 mg/kg), ketorolac (10 mg/kg)	52
Calliandra umbellifera Benth	aerial parts	−Acetic acid-induced writhing −Formalin test −Glutamate-induced nociception	Methanol Extract (100, 200 and 300 mg/kg p.o.)	Phenolic compounds, Flavonoids	Morphine (6 mg/kg i.p.)	38
Capparis erythrocarpus	root bark, stem and leaves	−Hot-Plate test −Acetic acid-induced writhing	Ethanolic Extract (200 mg/kg p.o.)	Saponins, triterpenes, phytosterols and alkaloids	Morphine (5 mg/kg i.m.), Diclofenac (10 mg/kg p.o.)	53
Carissa Spinarum	leaves	−Formalin test −Acetic acid-induced writhing	Acetone extract (50, 100 mg/kg)	Flavonoids, Alkaloids, terpenoids	Diclofenac (15 mg/kg)	54
Chiliotrichum diffusum	Flowers	−Acetic acid-induced writhing −Hot-Plate test	Aqueous extract (10, 30, 100, 300 mg/kg i.p.; 100, 300, 1000 mg/kg p.o. and 125, 250, 500 mg/kg i.p.)	Chlorogenic acid; caffeic acid; quercetin-3-*O*-β-D-galactoside (hyperoside); Quercetin-3-*O*-β-D-glucoside (isoquercitrin); quercetin-3-*O*-β-D-rhamnoside (quercitrin); kaempferol-3-*O*-α-L-rhamnoside (afzelin); quercetin; Apigenin; Kaempferol	Indomethacin (10 mg/kg i.p.) Morphine (10 mg/kg i.p.)	55
Cistus laurifolius L.	leaves	−p-Benzoquinone-induced writhing	Aqueous and Ethanolic Extract (250, 500 mg/kg)	3-*O*methylquercetin, 3,7-*O*-dimethylquercetin and 3,7-*O*-dimethylkaempferol	Acetylsalicylic acid (200 mg/kg)	56
Clutia abyssinica	root	−Acetic acid-induced writhing	Dichloromethanolic Extract (50, 100 and 150 mg/kg)	Flavonoids, saponins and alkaloids	Diclofenac (15 mg/kg)	57
Cnicus arvensis (L.) Roth	aerial parts	−Acetic acid-induced writhing −Formalin test	Methanol Extract (100, 150, 200, 300 mg/kg)	Alkaloids, tannins, terpenoids, flavonoids	Diclofenac (10 mg/kg i.p.)	58
Cordia myxa L.	leaves	−Hot-Plate test	Ethanol extract and fractions (350 mg/kg)	Pyrrolizidine alkaloids. phenyl propanoids.	Paracetamol (100 mg/kg p.o.)	59
Crassocephalum bauchiense Hutch	leaves	−Acetic acid-induced writhing −Formalin-induced nociception −Capsaicin-induced nociception −Glutamate-induced nociception −Hot-Plate test	Aqueous extract (20, 40, 80 and 160 mg/kg p.o.) and the alkaloid fraction (40 mg/kg p.o.),	Alkaloids compounds	Morphine (5 mg/kg s.c.)	60
Croton blanchetianus	leaves	−Acetic acid-induced writhing −Tail Immersion test −Formalin test	Ethanolic extract (50, 100, 200 mg/kg)	Alkaloids, reducing sugars, cinnamic derivatives, flavonoids, saponins, condensed tannins, terpenes, and steroids	Morphine (10 mg/kg i.p.), Indomethacin (20 mg/kg i.p.)	61
Cucumis ficifolius	root	−Acetic acid-induced writhing −Hot-Plate test −Formalin test	Methanolic extract (200, 400, and 800 mg/kg), Fractions (AQ100, aqueous fraction 100 mg/kg; AQ200, aqueous fraction 200 mg/kg; B100, butanol fraction 100 mg/kg; B200, butanol fraction 200 mg/kg)	Phenols, tannins, saponins, terpenoids, and flavonoids	Acetylsalicylic acid (150 mg/kg), Morphine (20 mg/kg)	62

Dysphania graveolens	aerial parts	−Formalin test −Hot-Plate test	Dichloromethane–Methanolic extract, infusion and essential oil (31, 100,316 mg/kg)	Pinostrobin, pinocembrin and chrysin	Morphine (5 mg/kg p. o.) Metamizol (100 mg/kg p.o.)	63
Echinodorus grandiflorus	aerial parts	−Acetic acid-induced writhing	Hydroalcoholic extract (10 and 50 mg/kg p.o.)	Diterpenes, flavonoids and caffeic acid derivative	Indomethacin (5 mg/kg p.o.)	64
Echinodorus scaber	aerial parts	−Acetic acid-induced writhing	Hydroalcoholic extract (10 or 50 mg/kg p.o.)	Diterpenes, flavonoids and caffeic acid derivative	Indomethacin (5 mg/kg p.o.)	64
Euphorbia retusa	leaves	−Hot-Plate test −Acetic acid-induced writhing	Methanol extract (200 mg/kg p.o.)	Rutin, quercetin, and kaempferol	Paracetamol (100 mg/kg)	65
Ferulago angulata	aerial parts	−Acetic acid-induced writhing −Formalin test −Hot-Plate test	Hydro-alcoholic extract (100, 200 and 400 mg/kg i.p.), Essential oil (50, 100 and 200 µL/kg i.p.)	Thymol, spathulenol, trans-anethol, myristicin, alpha-pinene, flavonoids and polyphenolic compounds	Indomethacin (10 mg/kg i.p.), Morphine (10 mg/kg i.p.)	66
Globimetular brounii Van Tieghem	leaves	−Acetic acid-induced writhing −Hot-Plate test	Ethanolic Extract (12.5, 25 and 50 mg/kg i.p.)	Flavonoids, tannins, alkaloid or saponins	Piroxicam (10 mg/kg i.p.), Pentazocine (20 mg/kg i.p.)	67
Hamelia patens	leaves	−Hot-Plate test −Formalin test −Acetic acid-induced writhing	Ethanolic extracts 50, 100 and 200 mg/kg p.o.).	Polyphenol (catechin),hydroxycinnamic acid (caffeic acid), cyclohexane carboxylic acids acids(shikimic acid and quinic acid), diterpene (phytol), phytosterol(_-sitosterol), triterpenes (squalene, oleanolic acid, ursolic acid),tocopherols and alkaloid (mitraphylline)	Buprenorphine (1mg/kg)	68
Ipomoea involucrata	leaves	−Acetic acid-induced writhing	Ethanolic Extract (25, 50 and 100 mg/kg)	Flavonoids, tannins, terpenoids, saponins and alkaloids	Aspirin (2 mg/kg)	69
Juniperus sabina	leaves	−Acetic acid-induced writhing −Hot-Plate Test −Formalin test	Total Flavonoids Extract (125,250,500 mg/kg)	Rutin, quercitrin, and isoquercitrin	Aspirin (200 mg/kg)	70
Lavandula officinalis	flowers and head branches	−Formalin test −Hot-Plate test	Hydro-alcoholic extract (100, 200, 250, 300, 400 and 800 mg/kg i.p.)	Linalool, acetate linalool, monotril,cezcoiterpen, luteolin, ursolic acid, coumarin, and umbelliferone	Morphine (10 mg/kg s.c.), Indomethacin (10 mg/kg i.p.) Dexamethasone (10 mg/kg i.p.)	71
Lecythis pisonis Camb.	leaves	−Acetic acid-induced writhing −Formalin test −Capsaicin test	Ethanol extract and fractions (6.25, 12.5, 25, 50, 100 and 200 mg/kg p.o.)	Triterpenoids, ursolic acid and oleanolic acids	Morphine (2.5 mg/kg s.c.)	40
Libidibia ferrea	bark	−Hot-Plate test −Acetic acid-induced writhing	Aqueous and Acetone-Water extracts (50, 100, 200 mg/kg p.o.)	Gallic acid, Catechin	Morphine (10mg/kg i.p.) Indomethacin (10 mg/kg p.o.)	72
Linum usitatissimum	leaves	−Hot-Plate test	Ethanolic Extract 500 mg/kg	Alkaloid, flavonoid, and triterpenoids compounds	Morphine (2.5 mg/kg)	73
Litsea glutinosa	leaves	−Hot-Plate test −Acetic acid-induced writhing	n-hexane, Ethyl acetate, Chloroform and Methanolic extracts (250 and 500 mg/kg)	Saponin, alkaloids and tannin	Ketorolac (10 mg/kg)	74
Masua ferrea Linn	fruit	−Acetic acid-induced writhing −Tail Immersion test −Hot-Plate test	Methanolic extract (100, 200 mg/kg i.p. and 200, 400 mg/kg p.o.)	Mesuaxanthone-A, mesuaxanthone-B, 1,5-dihydroxyxanthone (II), euxanthone 7-methyl ether (IV), β-sitosterol, Ferrol-A, 1,3-dimethoxy-5,6-dihydroxyxanthone (E), α-bisabolene, α-selinene, α-copaen, β-caryophyllen, α-copaene, germacrene D.	Diclofenac (10 mg/kg i. p.) Nalbuphine (10 mg/kg, i. p.)	75
Melastoma malabathricum	leaves	−Acetic acid-induced writhing −Hot-Plate test −Formalin test	Methanol extract (100, 250, and 500 mg/kg)	Quercitrin 9-octadecenamide	Morphine (5 mg/kg), Acetylsalicylic acid (100 mg/kg)	34

Mentha rotundifolia L.	leaves	−Acetic acid-induced writhing	Hydro-methanolic extract (200, 400 and 600 mg/kg p.o.)	Rutin, quercetin, luteolin, hesperidin	Aspirin (150 mg/kg p.o.)	76
Moringa oleifera	leaves	−Acetic acid-induced writhing −Formalin test −Hot-Plate test	Methanolic extract (50, 100 and 200 mg/kg p.o.), Aqueous Extract (10, 30, and 100 mg/kg i.p.)	Phenolic compounds and Flavonoids as kaempferol, rutin, and quercetin	Indomethacin (10 mg/kg p.o.), Acetylsalicylic acid (100 mg/kg i.p.), Morphine (5 mg/kg)	77 78
Muntingia calabura	leaves	−Acetic acid-induced writhing −Hot-Plate test −Formalin test	Petroleum ether fraction (100, 250 and 500 mg/kg p.o.)	Pinostrobin and flavanones as 5-hydroxy-3,7,8-trimethoxyflavone, 3,7-dimethoxy-5-hydroyflavone, 2_,4_-dihydroxy-3_-methoxychalcone, and8-hydroxy-6-methoxyflavone (calaburone).	Acetylsalicylic acid (100 mg/kg p.o.), Morphine (5 mg/kg p.o.)	79
Nepeta depauperata Benth	aerial parts	−Formalin Test −Hot-Plate test	Methanol Extract (50, 80, 160 and 250 mg/kg i.p.)	Spathulenol, beta caryophyllene, caryophyllene oxide	Morphine (2 mg/kg i.p.)	80
Nigella sativa	seeds	−Acetic acid-induced writhing −Formalin test −Tail Flick test	Polyphenol-rich extract, (1.25, 2.5, 5 g/kg p.o.; 0.625, 1.25, 5 g/kg i.p and 500, 1000 mg/kg i.p)	Quercetin	Indomethacin (10 mg/kg p.o.), Morphine (10 mg/kg, i.p.)	81
Nyctanthes arbortristis	leaves	−Tail Flick test −Acetic acid-induced writhing	Ethanolic extract (100, 200, 300, 400 mg/kg p.o.)	Tannic acid, methyl salicylate, amorphous glucosider, mannitol, amorphous resin, ascorbic acid, Flavonoids	Aspirin (100mg/kg p.o)	82
Passiflora leschenaultii	leaves	−Acetic acid-induced writhing −Formalin test −Hot-Plate test	Acetone extracts (200 and 400 mg/kg p.o.)	Hyperin, Chlorogenic acid, Caffeic acid and Rutin	Morphine (10 mg/kg i.p.)	83
Passiflora subpeltata	leaves	−Acetic acid-induced writhing −Formalin test	Acetone extract (200 and 400 mg/kg)	Withcyanogenic glycosides apigenin and luteolin	Morphine (10 mg/kg p.o.)	84
Parapiptadenia rigida	bark	−Hot-Plate test −Acetic acid-induced writhing	Aqueous and Acetone-Water extracts (50, 100, 200 mg/kg p.o.)	Gallic acid, Catechin	Morphine (10mg/kg i.p.), Indomethacin (10 mg/kg p.o.)	72
Pereskia bleo Kunth	leaves	−Hot-Plate test −Capsaicin- induced nociception −Glutamate-induced nociception	Ethanol extract and fractions 30, 50, and 100 mg/kg	Vitexin, Sitosterol	Morphine (5mg/kg p.o)	85
Persicaria glabra (Wild)	leaves	−Hot-Plate test −Acetic acid-induced writhing	Methanol extract 100 and 200 mg/kg p.o.	Quercetin, Isorhamnetin, avicularin, isorhamnetin-3-O-α-l-(6″-*E*-*p*-coumaroyl)-rhamnoside	Morphine (5 mg/kg i.p.) Aspirin (50 mg/kg p.o.)	33
Phyllanthus muellerianus	leaves	−Hot-Plate test	Essential Oil (100, 200, and 400 mg/kg p.o.)	bis(2-ethyloctyl) phthalate, bis(2-ethylicosyl)phthalate, 3-friedelanone, β-sitosterol and methyl gallate, geraniin, corilagin, furosin, quercetin-3-*O*-β-d-glucoside (isoquercitrin), kaempferol-3-*O*-β-d-glucoside (astragalin), quercetin-3-*O*-d-rutinoside (rutin), gallic acid, methyl gallate, caffeic acid, chlorogenic acid, 3,5-dicaffeoylquinic acid, and caffeoylmalic acid.	Acetylsalicylic acid (100 mg/kg p.o.)	86
Phyllanthus reticulatus	aerial parts	− Acetic acid-induced writhing − Radiant heat Tail-Flick test	Petroleum ether extract, ethyl acetate extract and Methanol extract (150,300 mg/kg p.o.	flavonoids and glycosides	Aminopyrine (50 mg/kg p.o.) Morphine (2 mg/kg s.c.)	32

Pimenta racemosa	leaves	−Acetic acid-induced writhing −Hot-Plate test	Aqueous methanol extract (125, 250 and 500 mg/kg p.o.)	Gallic acid, methyl gallate, avicularin, quercetin 3-O-β-D-arbinopyranoside, quercetin 3-O-β-Dglucopyranoside, quercetrin, cynaroside, strictinin, castalagin, grandinin, quercetin, ellagic acid	Aspirin (200 mg/kg p.o.), Tramadol (20 mg/kg p.o.)	87
Psidium brownianum Mart *ex* DC.	leaves	−Acetic acid-induced writhing −Formalin test −Capsaicin-induced nociception −Hot-Plate test	Essential oil (100 and 200 mg/kg p.o.)	α-terpineol, β-eudesmol, β-pinene, cineole,	Diclofenac (10 mg/kg p.o.), Morphine (7.5 mg/kg i.p.)	88
Psidium guajava	leaves	−Hot-Plate test −Acetic acid-induced writhing	Aqueous and Acetone-Water extracts (50, 100, 200 mg/kg p.o.)	Gallic acid, Catechin	Morphine (10mg/kg i.p.), Indomethacin (10 mg/kg p.o.)	72
Ricinus communis L.	leaves	−Acetic acid-induced writhing −Formalin test −Tail Immersion test	Methanol extract (100, 125 and 150 mg/kg)	Kaemferol-3-*O*-*β*-drutinoside, kaemferol-3-*O*-*β*-d-xylo pyranoid, tannins, gallic acid, and Quercetin, steroids and alkaloids, sesquiterpenes as ricinusoids A, ricinusoids B	Aspirin and diclofenac (50 mg/kg.)	37, 89
Salsola grandis	aerial parts	− p-Benzoquinone - induced writhing	Ethanol extract and subextract (100 mg/kg)	Isorhamnetin-3-*O*-rutinoside, Quercetin-3-*O*-rutinoside, Quercetin-3-*O*-metylether, Tiliroside, Isorhamnetin-3-glucuronide, Isorhamnetin-3-*O*-glucoside, Quercetin-3-*O*-galactoside, Quercetin-3-*O*-rhamnoside, Quercetin, Manghaslin, Momordin II, Momordin II	Acetylsalicylic acid (100 mg/kg)	90
Salvia circinata	aerial parts	−Acetic acid-induced writhing	Aqueous extract (1, 10, 30, 100 and 300 mg/kg), Amarisolide and pedalitin (1, 5 and 10 mg/kg i.p.)	Amarisolide, pedalitin	Ketorolac (1 mg/kg i.p.)	91
Satureja hortensis	seed	−Acetic acid-induced writhing −Formalin test	Essential Oil (100, 200 and 400 µl/kg p.o.), Hydroalcoholic and Polyphenolic Extract (50, 100 and 200 mg/kg i.p.)	α-thujen, α-pinene, β- pinene, myrcene, α- terpinen, ρ-cymene, Y-terpinene, thymol, carvacrol acetate, β-caryophyllene	Morphine (10 mg/kg i.p.), Indomethacin 10 mg/kg (i.p.)	92
Sideritis brevibracteata	aerial parts	−p-Benzoquinone-induced writhing	Methanol, Chloroform and N-butanol extracts (100 mg/kg)	Hypolaetin, Isoscutellarein, 30-hydroxy-40-O-methylisoscutellarein, Verbascoside	Aspirin (100 mg/kg)	93
Siolmatra brasiliensis (Cogn.) Baill	stems	−Hot-Plate test	Hydroethanolextract and ethyl acetate fraction 10,30,100 mg/kg	Saponins cayaponoside A1, cayaponoside B4, cayaponoside D, and siolmatroside	Morphine (2.5 mg/kg)	94
Tamarindus indica Linn	root	−Hot-Plate test −Acetic acid-induced writhing	Ethanol extracts (100 and 200 mg/kg)	Tannins, alkaloids, saponins, flavonoids, phenol, steroids	Pentazocine (30 mg/kg p.o), Aspirin (100mg/kg p.o.)	95

Terminalia ivorensis A. Chev	stem bark and root bark	−Hot-Plate test	Methanol Extract (100, 200 and 400 mg/kg p.o.)	Ivorengenin A (3-oxo-2α,19α,24-trihydroxyolean-12-en-28-oic acid) and ivorengenin B (4-oxo-19α-hydroxy-3,24-dinor-2,4-secoolean-12-ene-2,28-dioic acid), arjungenin, arjunic acid, betulinic acid, sericic acid, and oleanolic acid, sericic acid and lonchoterpene (28-hydroxy-18α-glycirrhetinic acid)	Aspirin (100 mg/kg p.o.)	96
Teucrium stocksianum	whole	−Acetic acid-induced writhing −Formalin test	Aqueous extract (100, 200 and 300 mg/kg i.p.), Methanol Extract (50, 100 and 200 mg/kg i.p.)	Flavonoids, saponins, terpenoides, tannins	Aspirin (100 mg/kg i.p.), Tramadol (30 mg/kg i.p.)	97, 98
Tribulus terrestris L.	leaves	−Acetic acid-induced writhing	Flavonoids fraction (12.5, 25 and 50 g raw medicinal materials (RMM)/kg p.o.)	Quercetin-3,7 diglucoside, Quercetin-3-O-sophoroside-7- O-glucoside, Quercetin-3-O-arabinosyl galactoside, Isorhamnetin-3-glucoside, Quercetin-3,7 diglucoside, Quercetin-3-O-(2,6-α-L-dirhamnopyranosyl-β-D-glucopyranoside, Kaempferol-glucosyl-(1→2) –rhamnoside, Quercetin-3-O-β-(2(G)-O-β-xylopyranosyl-6(G)-O-α-rhamnopyranosyl) Glucopyranoside, Quercetin3- gentiobioside, Kaempferol-3- gentiobioside, Isoquercitrin, 26-O-β-D-glucopyranosyl-(25R)-5α-furostan-12-one-3β,22α,26-triol-3-O-β-Dglucopyranosyl-(1→4)-β-D-galactopyranoside, Luteolin-7-O-β-D-glucoside, Apigenin-6,8 glucoside	Aspirin (200 mg/kg p.o.)	99
Vaccinium ashei	fruit	−Formalin test −Acetic acid-induced writhing −Hot-Plate test −Tail Flick test	Lyophilized extract (3.2 and 6.4 mg/kg p.o.)	Anthocyanins	Diclofenac (5mg/kg) Morphine (10 mg/kg)	100
Varronia multispicata (Cham.) Borhidi	leaves	−Acetic Acid-Induced Writhing −Hot-Plate test	Aqueous Extract (25, 75, 200, 400 mg/kg p.o.)	Quercetin, Quercetin 3-O-robinobioside, Kaempferol, Kaempferol 7-O-glucoside, Kaempferol 3-O-rutinoside, 3,7-Dimethoxy-5,3', 4'-trihydroxyflavone, 5,6'-Dihydroxy-7,2',4',5'-tetramethoxyflavone, 5,3'-Dihydroxy-3,7,4'-trimethoxyflavone, 5-Hydroxy-3,7,3',4'-tetramethoxyflavone	Indomethacin (10 mg/kg p.o.)	101
Viscum orientale	leaves	−Acetic acid-induced writhing −Formalin test	Methanol Extract (300, 500 mg/kg p.o.)	Gallic acid, vanillic acid, caffeic acid, ellagic acid, quercetin	Diclofenac (25mg/kg p.o.)	102
Zea mays	stigmata	−Formalin test	Hydro-ethanolic extract (500 mg/kg i.p.)	Flavonoids, leucoanthocyans, heterosid sterodic, coumarins, alkaloids, cardiac glycosides, anthocyanins and tannins.	Tramadol (10 mg/kg i.p.)	103
Zornia brasiliensis	aerial parts	−Acetic acid-induced writhing −Hot-Plate test −Formalin Test	7-methoxyflavone (7MF) (30, 50, 100 and 300 µmol/kg, i.p.)	7-methoxyflavone (7MF)	Dipyrone (100 µmol/kg p.o.), Morphine (15 µmol/kg i.p.), Indomethacin (100 mmol/kg i.p.)	104

Alkaloids are a class of heterocyclic nitrogen compounds and are the most important analgesic compounds. Isoquinoline alkaloids, indole alkaloids, terpenic alkaloids, pyridine and piperidine alkaloids, and amide alkaloids have been shown to have significant analgesic activity.[5]

Scotanamine B, an amide alkaloid, exhibited agonist activity at the mu receptor; bullatine A, a diterpenoid alkaloid, could reduce hypersensitivity to pain as it specifically stimulates the expression of dynorphin A (endogenous opioid) in the spinal microglia.[5] The aporphinic alkaloid S-(+)-dicentrine reduces spontaneous cinnamaldehyde-induced nociception through modulation of TRPA1, either orally or intraplantarly, while the alkaloid stephalagine prevents cinnamaldehyde-induced pain when administered orally.[39,110]

The alkaloid lappaconitine is a compound reported in the Aconitum gender, its analgesic mechanism is related to its effect on purinergic receptors that are key in microglial activation and its interaction with neurons. Lappaconitine produces downregulated expression of the P2X3, P2X7 receptor in neurons of the dorsal root ganglion when evaluated in a rat model.[111,112]

Terpenoids are the most structurally diverse class of natural plant products biosynthesized from isoprene units, are the main components of volatile oils, also known as essential oils, and have broad physiological activities, such as expectorant, cough relief, perspiration and analgesia. The monoterpene p-cymene is found in the volatile oils of more than 100 plants and is found naturally in more than 200 foods. The analgesic effects of p-cymene were antagonized by naloxone (a non-selective opioid receptor antagonist) suggesting that p-cymene antihyperalgesia may be related to the opioid system.[5,113]

Thymol partially blocks voltage-gated Na+ and K+ channels and directly activates GABAA receptors for aminobutyric acid; it also reversibly inhibits prostaglandin synthesis, which is probably related to the analgesic effect of thymol in endodontic therapy.[114] Menthol reverses cinnamaldehyde-induced heat hyperalgesia, an effect that may have been a consequence of blockade of TRPA1 by this compound.[113] Citronellol, myrcene, carvacrol, linalool have potential antinociceptive activity with the participation of the opioid system, similar to the mechanism of sesquiterpenlactones.[115-117]

Monoterpenes act as partial agonists of transient vanilloid receptor 1 (TRPV1), transient vanilloid receptor 3 (TRPV3), TRPM8, and TRPA1. Being the prolonged inhibition of TRPV1-3 and TRPM8 after activation, the most important effect for pain control.[118-119]

The isolated saponins siolmatroside I, cayaponoside D, cayaponoside B4 and cayaponoside A1 have important antinociceptive effects, mainly due to the opioidergic pathways that seem to be involved in their mechanism of action. In addition, these saponins also cause the activation of cholinergic pathways through stimulation of muscarinic receptors M2 and M4 in the dorsal horn of the spinal cord, contributing to the analgesic effect through the activation of inhibitory interneurons, which reduces nociceptive transmission.[94]

FUTURE PERSPECTIVES IN THE TREATMENT OF PAIN

The review suggests that natural compounds have great potential for pain control and may in the future offer a new possibility for more appropriate pain management. There is a limitation in its future application, because most of the studies analyzed are in a preclinical stage using animal models, so they are not yet directly related to the possible clinical applicability. Therefore, pharmacokinetic studies, the incorporation into pharmaceutical formulations and the development of biotechnological products should be carried out to complement these selected studies.

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The evidence found in the studies shows a probable use of natural compounds in pain management, complemented with the analysis of the possible mechanisms involved in pain modulation; however, new studies are needed to test its mechanisms at molecular level and clinical investigations in the near future. However, the use of mixtures of natural compounds with various mechanisms of action could generate enhancements between them, reducing their dose and the probable appearance of side effects, eventually becoming more widely used than the current analgesics found. in the market; therefore, the realization of tests with mixtures of natural compounds is imperative.

CONCLUSIONS

The use of medicinal plants is a potential alternative to pain treatment, due to their natural compounds such as flavonoids, alkaloids, terpenoids and saponins with proven analgesic activity in preclinical stages; It is recommended to carry out studies of mixtures of natural compounds with the intention of reducing the dose, its probable side effects and enhancing the effects found by presenting probable different mechanisms of action.

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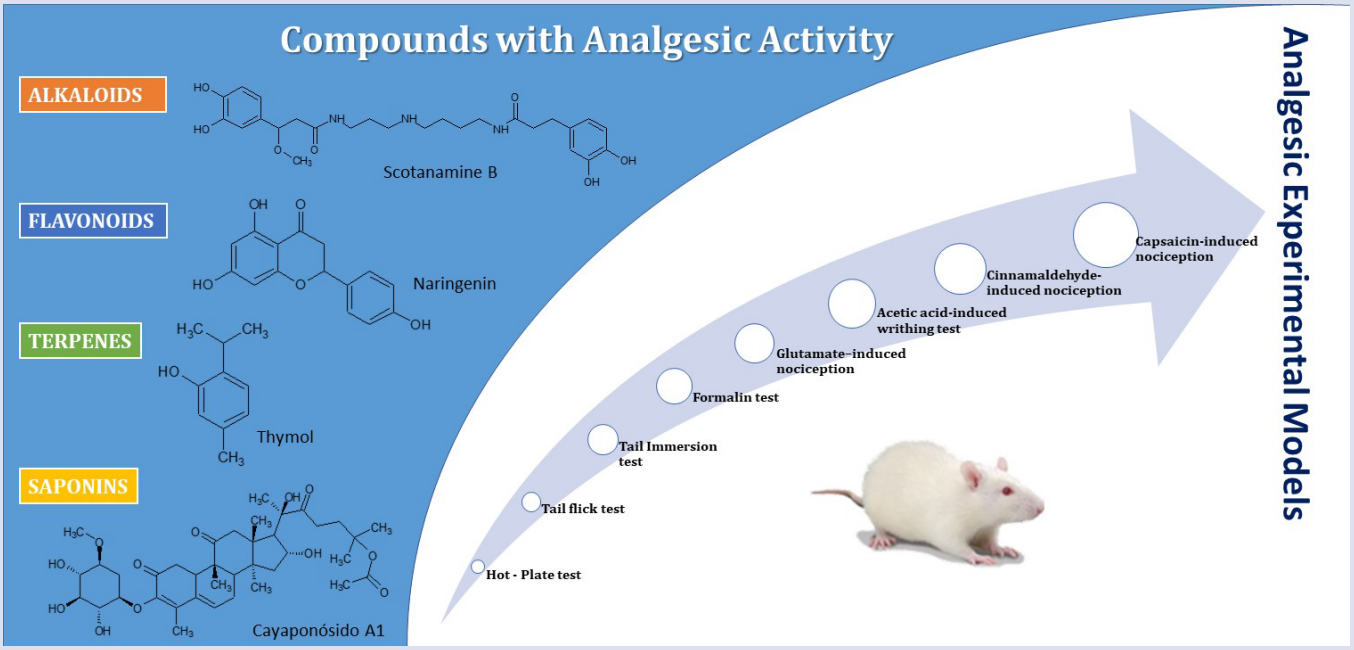
GRAPHICAL ABSTRACT



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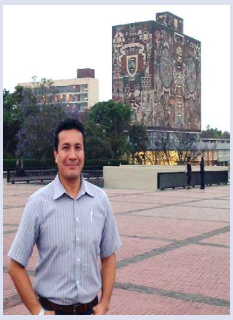

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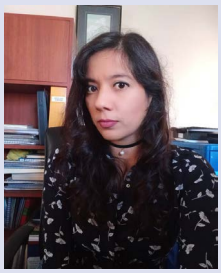

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