Progress on Active Analgesic Components and Mechanisms of Commonly Used Traditional Chinese Medicines: A Comprehensive Review

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ABSTRACT - Many clinical diseases are accompanied by the symptoms of pain, and the degree of pain is closely related to the patients' suffering. Therefore, effectively relieving pain has become one of the vital concerns of clinical treatment and analgesic drug research. Non-opioid drugs are mainly used for the clinical treatment of mild to moderate pain, whereas opioid drugs are mainly used for treating moderate to severe pain. However, opioid drugs easily elicit adverse reactions, such as gastrointestinal discomfort, addiction, dependence, and so on. Traditional Chinese medicine and its active ingredients have unique advantages in the treatment of pain for quite a long time, and many analgesic drugs directly or indirectly were isolatiedfrom Chinese medicine or natural products, such as Liu Suan Yan Hu Suo Yi Su Pian and aspirin. With the development and modernization of research on herbal medicine more and more studies have been conducted on the active ingredients and mechanisms of traditional Chinese medicine analgesics. However, no review has been done on analgesic active components and their mechanisms. In this paper, 81 active components with clear chemical structure and definite analgesic effects *in vivo* and *in vitro* of traditional Chinese medicine and mechanisms of action reported in recent literatures are reviewed and summarized to provide reference for clinical analgesia and analgesics research.

INTRODUCTION

The International Association for the Study of Pain revised the definition of pain as follows: Pain is a mutually recognizable somatic experience that reflects a person's apprehension of threat to their bodily or existential integrity (1). Acute pain, which occurs as a response to a specific injury, has a biological importance and self-limiting character. By contrast, chronic pain is a disease state that may outlast the usual duration of recovery if accompanied with a disease or injury (2). Pain not only affects the quality of life and work efficiency, but also creates a huge financial burden, with a report showing that chronic pain alone costs as much as $635 billion a year in the United States (3). Pharmacotherapy is often used for pain relief.

Non-opioid drugs are used in the treatment of mild to moderate pain, whereas non-opioid drugs are used for moderate to severe pain treatment (4). However, for most patients with pain, the analgesic effect of opioid drugs is limited, and their long-term use can lead to abuse, addiction, and overuse, with the latest data showing that about 16,000 overdose deaths associated with prescription opioids are reported each year, and the incidence of iatrogenic opioid dependence or abuse was 4.7% of those prescribed with opioids for pain (5-7). Traditional Chinese medicine (TCM) has been used in the treatment of pain for more than one thousand years, and scientists studying herbal medicines have found more than 800 kinds of TCM to be effective in relieving pain, while also creating several monomeric compounds to develop novel analgesic drugs. TCM has the advantages of good efficacy, is non-addictive, has less adverse reactions, and has an abundant supply, which attracted the attention of clinicians in the field of pain treatment.

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With the increasingly progress of medicine and technology and the better understanding of natural medicine, the interest and acceptance of TCM have been increasing, and its role in health has been widely recognized in the world (8-10). In recent years, the exploration of TCM in analgesia has become one of the hotspots of modern Chinese medicine research.

In modern pharmacological study, plenty of compounds with significant analgesic activity were isolated from TCM, including alkaloids, flavonoids, terpenoids, aromatic compounds, coumarins, aliphaticnatural products, and lignans. In this paper, the analgesic effect and mechanism of these compounds are reviewed, to provide a reference for the development and utilization of TCM for analgesia.

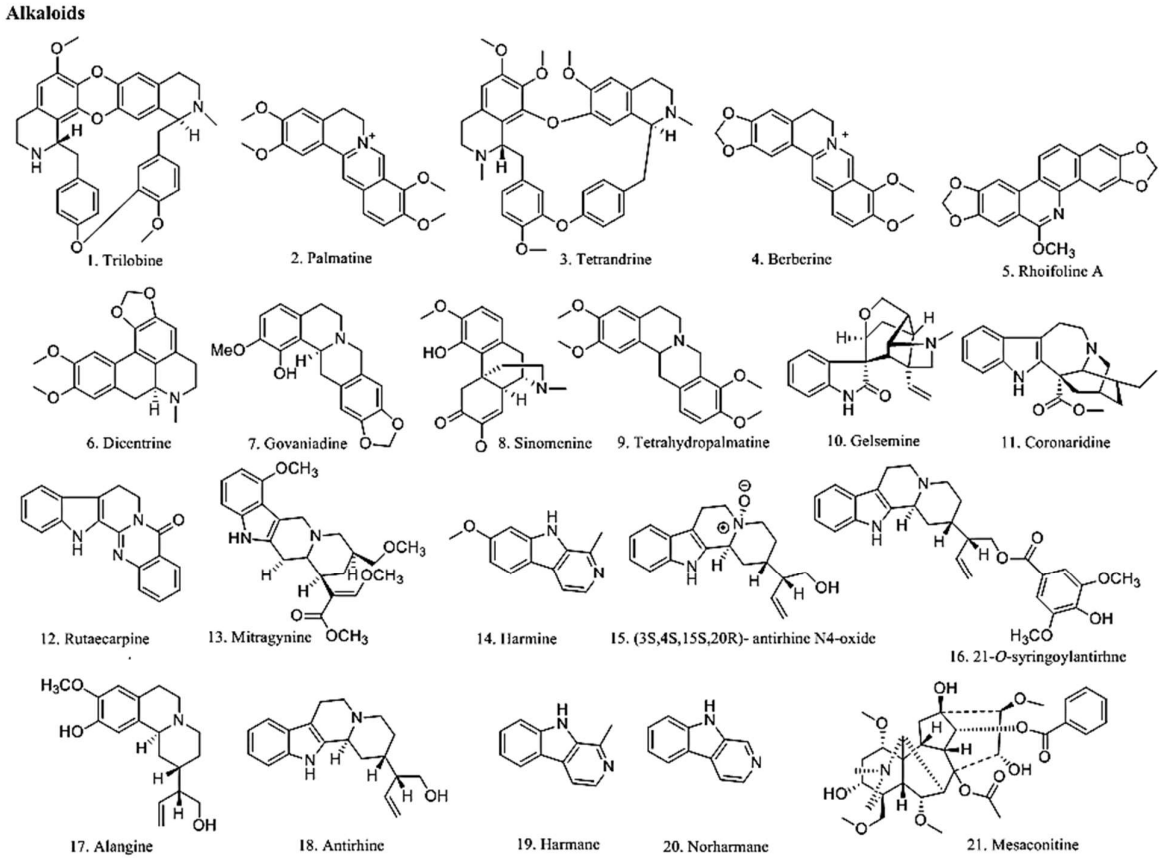
ANALGESICS BASED ON THE COMPOUNDS' PHYTOCHEMISTRY

Many classic analgesics, such as morphine, codeine, and aspirin are isolated from natural products. Therefore, the study on the analgesic effect and mechanisms of active components and the discoveries of new analgesic drugs from plants provide grounds for innovative research on analgesic drugs.

Upon a literature survey we identified a total of 81 compounds with significant analgesic activities, including 40 alkaloids, 15 flavonoids, 10 terpenoids, 5 aromatic compounds, 8 coumarins, 2 aliphaticnatural products, and 1 lignan. A compound may exist in a variety of herbal medicine, and we have summarized all its sources (Table 1). The structures of these compounds and their analgesic activities are shown in Figure. 1

Alkaloids

Alkaloids are a class of nitrogen heterocyclic compounds containing negative oxidized nitrogen atoms in biological organisms and are the most important analgesic compounds. Isoquinoline alkaloids ***(1-9)***, indole alkaloids ***(10-20)***, terpene alkaloids ***(21-29)***, pyridine and piperidine alkaloids ***(30-33)***, and amide alkaloids ***(34-40)*** were shown to have significant analgesic activity.



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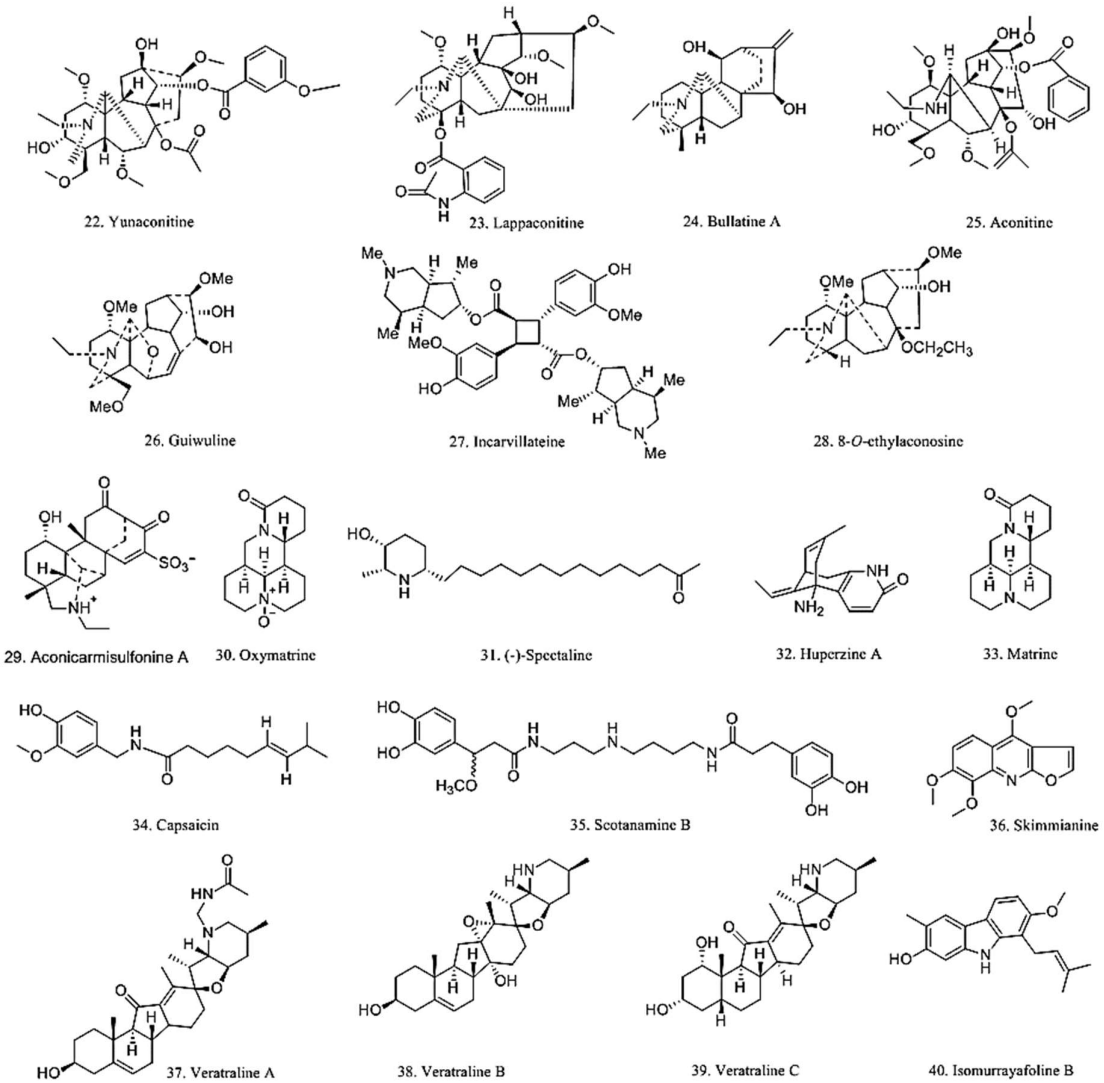
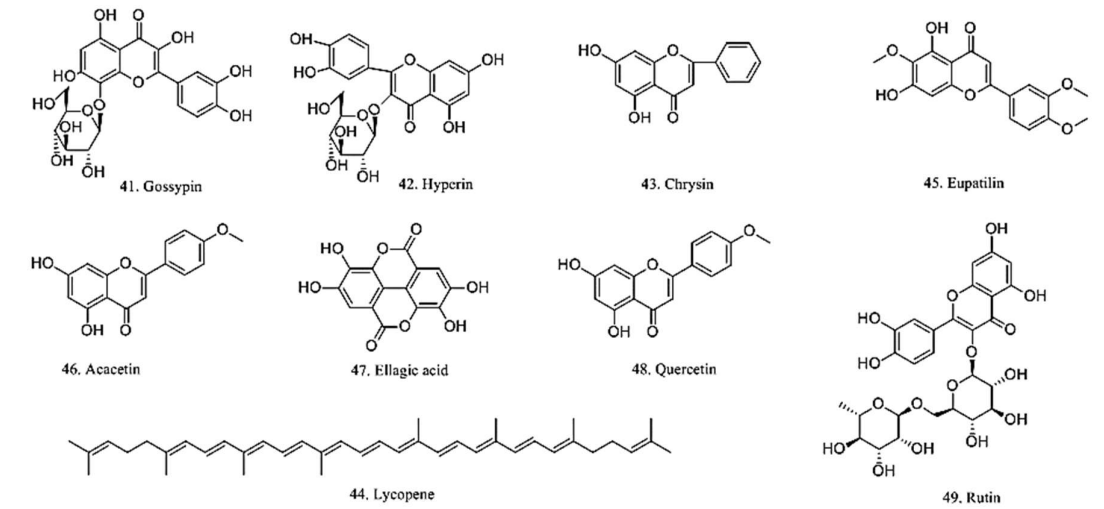


Flavonoids



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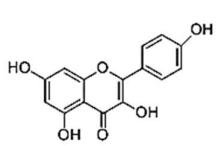
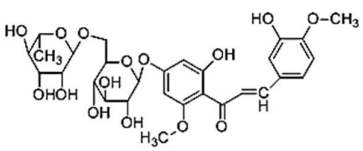
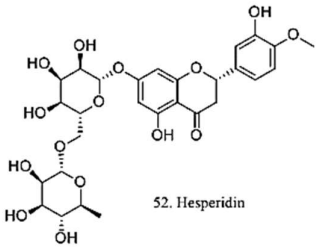


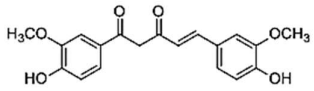
50. Kaempferol



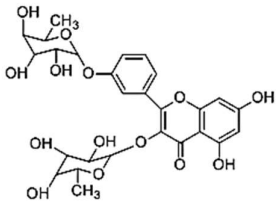
51. Hesperidin methyl chalcone



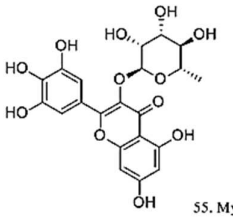
52. Hesperidin



53. Curcumin



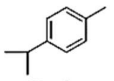
54. Kempferol-3,4′ -di-*O*- α -L-rhamnopyranoside



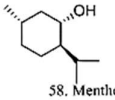
55. Myricitrin

Terpenes

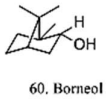
56. 1,8-Cineole



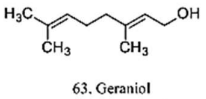
57. *p*-Cymene



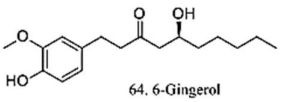
58. Menthol



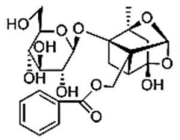
60. Borneol



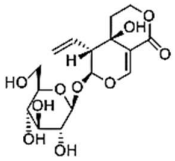
63. Geraniol



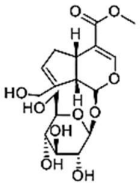
64. 6-Gingerol



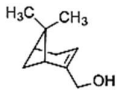
59. Paeoniflorin



61. Swertiamarin

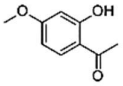


62. Geniposide

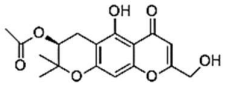


65. Myrtenol

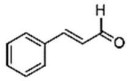
Aromatic compounds



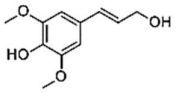
66. Paeonol



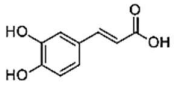
67. Divaricatol



68. Cinnamaldehyde

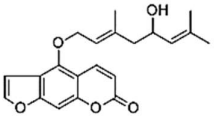


69. Sinapyl alcohol

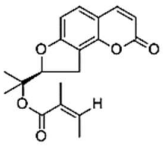


70. Caffeic acid

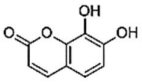
Coumarins



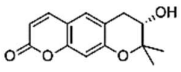
71. Notopterol



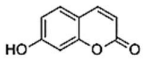
72. Columbianadin



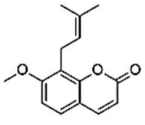
73. Daphnetin



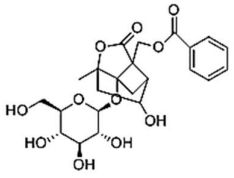
74. Decursinol



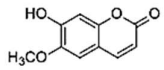
75. 7-Hydroxycoumarin



76. Osthole

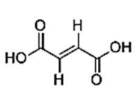


77. Albiflorin

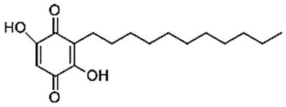


78. Scopoletin

Aliphaticnatural products



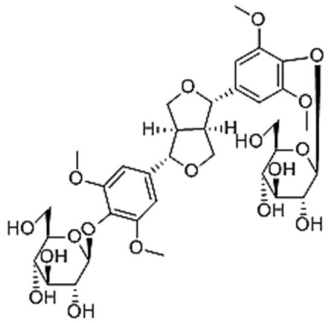
79. Fumaric acid



80. Embelin

Figure 1 continued…

Lignans



81. Liriodendrin

Figure 1 Structures of analgesic compounds in TCM

Flavonoids

Flavonoids are formed in plants from the aromatic amino acids phenylalanine and malonate. The basic structure of flavonoids is the flavonoid nucleus, which consists of 15 carbon atoms labeled as the three rings of A, B, and C (C_6–C_3–C_6). The various classes of flavonoids differ in the level of oxidation and the pattern of substitution of the C ring, whereas individual compounds within a class differ in the pattern of substitution of the A and B rings (11). Flavonoids ***(41-55)*** in TCM play an important role in analgesia, and have high application value and prospect.

Terpenoids

Terpenoids are the most structurally diverse class of plant natural products biosynthesized from isoprene units with a general formula of $(C_5H_8)n$. Terpenecompounds are the main components of volatile oils, also known as essential oils, and have wide physiological activities, such as expectorant, relieving cough, transpiration and analgesia. A total of 10 terpenoids ***(56-65)*** have been reported to show analgesic activities.

Aromatic compounds

Aromatic compounds are often used in cosmetics, consumer goods, and in the medical field. These compounds are widely found in Chinese herbal medicines, such as *Paconia lactiflora*, *Saposhnikouia diuaricata*, *Cinnamomum japonicum*, and so on, and some aromatic compounds ***(66-70)*** in TCM show good analgesic effect.

Coumarins

Coumarin is one of the most important natural organic compounds in nature products. Moreover, it has many biological activities, such as anti-HIV, anti-cancer, antihypertensive, anti-arrhythmia, anti-osteoporosis, anti-asthmatic, antibacterial, and analgesic effects. Experiments showed that coumarin compounds, such as notopterol, columbianadin, daphnetin, decursinol, 7-hydroxycoumarin, and osthole ***(71–78)*** have good analgesic effects.

Aliphaticnatural products

Aliphatic naturalproducts are an important class of compounds in the organic chemistry industry. They can be used in spices and in the preparation of some drugs according to their properties. Two aliphatic natural products, such as fumaric acid ***(79)*** isolated from *Corydalis yanhusuo* and embelin ***(80)*** isolated from *Embelia oblongifolia*, *Ardisia crenata*, and *Embelia ribes*, also showed good analgesic activities.

Lignans

Lignan is a class of secondary metabolite that is usually in the form of a glycoside and consists of two phenyl-propanoid molecules connected by 8-8′carbon atoms. Liriodendrin ***(81)*** was the only lignan reported to have significant analgesic activity.

ANALGESIC ACTIVITIES

The analgesic activities of monomeric compounds isolated from TCM *in vivo* were studied. Experimental animal models of acute and chronic pains are the two major types of pain model for

studying analgesic effects. Studies of acute pain model include chemical stimuli, such as acetic acid, capsaicin, glutamate, acetylcholine, and *p*-benzoquinone-writhing test, formalin test, and physical stimulation, such as hot or cold-plate test, tail-flick test, electrical stimulation test, Randall-Selitto test, tail immersion test, Hargreaves test, and the mechanical von Frey test. Studies have shown that chronic pain are induced by chronic constriction injury (CCI), spared nerve injury(SNI), spinal cord injury (SCI), and partial sciatic nerve ligation (PSNL). Other types include paclitaxel-induced neuropathic pain, diabetic neuropathic pain, complete Freund's adjuvant (CFA)-induced pain, LPS-induced inflammation pain, and cancer pain. The experimental studies on the analgesia of active compounds are summarized in Table 2.

ANALGESIC MECHANISM

Modern studies have shown that compounds isolated from TCM play a key role in the regulation of pain-related signaling pathways (10). The mechanisms of analgesia could be roughly divided into the central nervous system to exert a central analgesic effect and through the peripheral nervous system to relieve pain by reducing the secretion of analgesic substance, alleviating the accumulation of local analgesic substances, increasing the release of peripheral endogenous analgesic matter, and regulating c-Fos genes. Moreover, some compounds relieve pain by inhibiting the process of inflammation.

Activate opiate receptors and increase opioid peptide levels

Opioid peptides (*β*-endorphin, encephalin, and dynorphin) are widely distributed in the hypothalamus, brain, and spinal cord. They bind to opioid receptors, μ (mu or MOP) receptor, δ (delta or DOP) receptor, and κ (kappa or KOP) receptor, and reduce the release of nociceptive substances and produce strong analgesic effects.

p-Cymene, an aromatic monocyclic monoterpene, could found in the volatile oils of more than 100 plants and naturally occurs in over 200 foods (12). The analgesic effects of *p*-cymene in tail-flick test was antagonized by naloxone (non-selective antagonist of opioid receptors), naltrindole (δ-opioid receptor antagonist), nor-BNI (κ-opioid receptor antagonist), and CTOP (μ-opioid receptor antagonist). These suggested that the anti-hyperalgesia of *p*-cymene maybe related to the opioid system (13). Naloxone and nor-NBI could antagonize the antinociceptive effect of menthol, which is a natural cooling product of peppermint and is widely used as an analgesic agent for pain conditions, such as sports injuries and arthritis, but CTOP, 7-benzylidenenal-trexone (δ_1 antagonist) and naltriben (δ_2 antagonist) could not. These suggest that menthol mediates analgesic properties through the selective activation of κ opioid receptors (14, 15).

Capsaicin, the main ingredient in hot pepper, has an analgesic action in humans. Capsaicin significantly could increase the proopiomelanocortin mRNA levels in the arcuate nucleus of rats, suggesting that the analgesic effect of capsaicin couldbe associated with the increased activities of cerebral opioid systems (16). Quercetin which could be widely found in flowers, leaves, and fruits of plants and found in more than 100 Chinese herbs, could relieve cancer pain and diabetic neuropathic pain via the opioid-dependent analgesic pathways (17). Curcumin, a yellow pigment extracted from zingiberaceous plants, has a wide range of therapeutic effects, such as anti-inflammatory, anti-bacterial, anti-viral, anti-fungal, anti-tumor, antispasmodic, and hepatoprotective effects. Curcumin could relieve diabetic peripheral neuropathic pain, and its mechanism could be related to the opioid system (18).

The analgesic effect of scotanamine B, an amide alkaloid from *Scopolia tangutica*, was recorded using the tail-flick assay and was reversed by naloxone. Scotanamine B displayed agonist activity at the μ receptor with an EC_{50} value of 7.3 Mm. Naloxone could also antagonize analgesic effects of govaniadine in the hot-plate test and the inhibition of paeoniflorin on bee venom-induced persistent spontaneous nociception (19-21). At the same time, naltrexone partially blocked analgesic effect in thehot-plate test of hesperidin (hesperetin-7-rhamnoglucoside), which is the main flavonoid in sweet oranges and lemons with anti-inflammatory, sedative, and analgesic effects. Although the analgesic effect of hesperidin is mediated through opioid mechanisms, it does not directly bind to and activate μ opioid receptors and has no effect on the inward GIRK1/2 currents (22, 23).

Bullatine A, a C_{20}-diterpenoid alkaloid, is one of the main active components of *Aconitum brachypodum*. Bullatine A could reduce pain hypersensitivity in the rat model of neuropathic pain, inflammatory pain, diabetic neuropathic pain, or bone cancer pain but could not block the acute nociceptive response effectively under normal conditions. This alkaloid specifically stimulates the expression of dynorphin A in spinal microglia *in*

vivo and in the cultured primary microglia *in vitro*. The stimulatory effect of bullatine A was completely inhibited by the microglial inhibitor minocycline, and its spinal anti-allodynic effects were completely blocked by intrathecal injection of minocycline, the specific dynorphin A antiserum, and the selective κ-opioid receptor antagonist. Thus, the expression of spinal microglial dynorphin A could be stimulated to mediate bullatine A anti-nociception under the pain hypersensitivity conditions (24).

Affect cholinergic nerve system

The two types of cholinergic receptors are muscarinic (M) receptors and nicotinic (N) receptors. M cholinergic receptors are divided into five subtypes, M_1-M_5 and M_2/M_4 receptors are involved in mediating muscarinic analgesia. In addition, the agonists of nicotinic and muscarinic acetylcholine receptors are being evaluated as candidate analgesics and may represent a new therapeutic strategy for the treatment of pain (25).

Matrine, along with lupinine, sparteine, and cytosine, is a typical lupine alkaloid that could be found in many leguminous plants, especially *Sophora*s pecies. Hot-plate test results showed that muscarinic receptor antagonists atropine (5 mg/kg i.p.) and pirenzepine (0.1 μg/mouse i.c.v.) and acetylcholine depletor hemicholinium-3 (1 μg/mouse i.c.v.) can attenuate the analgesic effect produced by (+)-matrine (10 mg/kg s.c.), whereas the opioid receptor antagonist naloxone (2 mg/kg i.p.), dopamine D_2 receptor agonist (-)-quinpirole (0.1 mg/kg i.p.), or catecholamine depletor reserpine (2.5 mg/kg i.p.) cannot. Meanwhile, radioligand binding assay results showed that (+)-matrine exhibits no affinity for μ, κ, and δ-opioid receptors. Hence, (+)-matrine exerted its analgesic effect by increasing cholinergic activation in the central nervous system rather than by acting on opioid receptors directly (26).

Previous studies suggested that huperzine A, a natural plant alkaloid isolated from *Huperzia serrata*, is a potent analgesic with few side effects. In 2015, results of the conditioned place preference behavioral assay showed that huperzine A could attenuate mechanical allodynia induced by peripheral nerve injury, and this effect was blocked by the M-receptor antagonist atropine. Furthermore, ambenonium chloride, a competitive inhibitor of acetylcholinesterase, also increased paw-withdrawal threshold, but failed to induce place preference in conditioned place preference. Therefore, acetylcholinesterase in both the peripheral and central nervous systems were involved in the regulation of mechanical allodynia by huperzine A (27).

Affect central catecholaminergic system

Central catecholaminergic systems mainly include norepinephrine (NE), adrenaline (Adr), dopamine (DA), and so on, which are not only neurotransmitters, but also can cause pain directly and participate in pain and analgesia. In the peripheral nervous system, they stimulate sensory nerve endings and cause pain as pronociceptives through second messenger action on the local and paracrine signaling. In the central nervous system, they have inhibitory and excitatory effects on the neurons. However, the inhibition effect is the main factor resulted in pain threshold is raised.

Mesaconitine is a principal alkaloid from *Aconitum carmichaeli* and *Aconitum kusnezoffii*. The analgesic effect of mesaconitine was decreased by α-methyl-p-tyrosine, 6-hydroxydopamine, diethyldithiocarbamate, disulfiram, and reserpine, and was increased by methamphetamine and norepinephrine. In addition, mesaconitine promoted the α-methyl-p-tyrosine-induced decrease in norepinephrine levels in hippocampus, medulla oblongata plus pons, and spinal cord. Thus, the analgesic activity mediated by mesaconitine is closely related to responses involving thecentral catecholaminergic system, in particular, the noradrenergic system (28). Mesaconitine increases the excitabilities in rat hippocampal pyramidal cells by enhancing the extraneuronal noradrenaline level through inhibition of noradrenaline uptake (29). Results of tail-immersion and hot-plate tests showed that pretreatment with 6-hydroxydopamine (50 μg, i.c.v. or 20 μg, i.t.) or 5,7-dihydroxytryptamine (80 μg, i.c.v. or 20 μg, i.t.) couldclearly reduce lappaconitine, an important bisnorditerpenoid alkaloid. Meanwhile, the analgesic effect of lappaconitine (i.c.v.) could be reduced by pretreatment with β-adrenergic antagonist timolol. The i.t. administration of lappaconitine induces a strong analgesic effect, which can be reduced by pretreatment with α-adrenergic antagonist phenoxybenzamine. These data suggested that central norepinephrine influences the analgesic effect of lappaconitine and these pathways are mediated by the expression of β-adrenoceptors and α-adrenoceptors in the spinal cord (30).

Paeoniflorin and albiflorin have obvious analgesic effect in tail-pressure test in diabetic mice shown by measuring the struggling behavior as an

index of threshold. Yohimbine, an α_2-adrenoceptor antagonist, could abolish completely the antinociceptive effect of paeoniflorin, and albiflorin increased noradrenaline release and activatedα_2-adrenoceptor to modulate spinal nociceptive transmission in diabetic neuropathy (31).

Moreover, levo-tetrahydropalmatine, a tetrahydroprotoberberine isoquinoline alkaloid, is a primary active constituent from the genus *Corydalis*. Levo-tetrahydropalmatine does not influence motor function but exerts antihyperalgesic effects that can be abolished by a dopamine D_1 receptor antagonist SCH23390 (0.02 mg/kg). Thus, this alkaloid improves mechanical hyperalgesia by enhancing dopaminergic transmission mediated by dopamine D_1 receptor (32).

Increase the content of 5-hydroxytryptamine (5-HT)

5-HT is one of the main neurotransmitters involved in the descending control of pain or emotion in the central nervous system and it works by binding with specific 5-HT receptors (33). The analgesic effect of lappaconitine was reduced by pretreatment with ketanserin, a 5-HT_2 antagonist, and mianserin, a 5-HT_1 antagonist. Thus, the analgesic mechanism of lappaconitine may be related to the 5-HT_2 receptor in the brain and the 5-HT_1 receptor in the spinal cord (30).

Acacetin (5, 7-dihydroxy-4-methoxyflavone), a bioflavonoid compound, was reported to possess antiperoxidative, anti-inflammatory, and antiplasmodial activities. WAY100635, a selective 5-HT_{1A} receptor antagonist, partially reduced the antinociceptive response of acacetin in the acetic acid-induced writhing test. 5-HT_{1A} seems to be involved in the mechanism of acacetin analgesia (34). Besides, quercetin also could alleviate arthritis pain by mediating by serotonin 5-HT_{1A} receptors (35).

Inhibite neurotransmitter γ-aminobutyric acid (GABA)

GABA, the major inhibitory neurotransmitter in the central nervous system, has three types of receptors, namely, $GABA_A$, $GABA_B$, and $GABA_C$. The dysfunction or deficiency of GABAergic system is associated with epilepsy, pain, and anxiety (36). Recent studies have demonstrated in a rat model of neuropathic pain that the $GABA_A$ receptor antagonist bicuculine dose-dependently blocked the antinociceptive effects of sinomenine, a main bioactive ingredient in *Sinomenium acutum*, which is well known to have anti-rheumatism and immunomodulatory effects (37).

Chrysin (5, 7-dihydroxyflavone) is a natural flavone commonly found in many plants with a wide range of biological activities, including antioxidant, anti-allergic, anxiolytic, and vasorelaxant activities. Tail-immersion tests also show that chrysin has significant analgesic activity, which can be significantly and dose-dependently suppressed by pretreatment with flumazenil, a specific antagonist for benzodiazepine sites associated with $GABA_A$ receptors and with bicuculline, a $GABA_A$ receptor antagonist. These results indicate that the analgesic effect of chrysin is acted on $GABA_A$ receptors (38).

Another study showed that the oxymatrine-carbenoxolone sodium inclusion compound had obvious analgesic effect in the hot-plate test, tail immersion test, acetic acid induced abdominal constriction, and formalin-induced pain, and simultaneously increased the $GABA_A$ α_1 receptor expression in the spinal cord, the cerebral cortex, and the hippocampal region of mice (39).

Regulate ion channels

Calcium ion (Ca^{2+}) overload and Na^+ currents are instrumental in the etiology of pain and neuropathy. Ca^{2+} enters into cells by different ways including cation channels, chemical channels, and voltage gated calcium channels. Furthermore, the two types of neuronal voltage-gated Na^+ channels are tetrodotoxin-sensitive and tetrodotoxin-resistant. Studies show that Na^+ channels have demonstrated a great involvement in inflammatory pain and in pain sensation (36,40).

Rhoifoline A, a benzodihydropyridine alkaloid obtained from *Zanthoxylum nitidum*, could inhibit the chemical nociception induced by acetic acid and formalin, the thermal nociception in the hot-plate test and tail-flick test. The analgesic effect of rhoifoline A was significantly antagonized by nimodipine, a blocker of L-type Ca^{2+} channels in the hot-plate test. Therefore, the analgesic mechanism of rhoifoline A possibly involved L-type Ca^{2+} channels (41).

Hyperin, an important natural product, has anti-inflammatory, antispasmodic, diuretic, antitussive, antihypertensive, cholesterol-lowering, central analgesic, cardio-cerebral vascular protection, and other physiological activities. Low or high-calcium can significantly strengthen or antagonize the inhibitory effect of hyperin on nerve discharge-induced histamine and potassium chloride. A_{23187}, which promotes the influx of Ca^{2+}, could antagonize

the effect of hyperin. These findings suggest that the analgesia of hyperin is closely related to the reduction of Ca^{2+} influx of sensory nerve endings (42). Sinomenine suppressed formalin-induced pain behavior only in the first phase, but not the second phase. Sinomenine also significantly reduced voltage gated sodium currents in a dose-dependent manner (IC_{50}=2.3±0.2 mM), suggesting that sinomenine has a peripheral analgesic effect (43).

Oxymatrine, a natural quinolizidine alkaloid, is the main basic constituent derived from the root of *Sophora flavescens* and the seeds of *Sophora alopecuroides*. The inhibition of voltage-activated K^+ channel plays an important role in the analgesic effect of oxymatrine. Meanwhile, oxymatrine could decrease Ca_2^+ in cultured dorsal root ganalia neurons, decrease protein expression levels of Cav2.2 in the brain tissue, and increase protein expression levels of Cav2.2 in dorsal root ganalia tissues (44, 45).

Tetrandrine is a bisbenzylisoquinoline alkaloid, which mainly exists in Menispermaceae. Previous studies have shown that it possessed antiarrhythmic, antihypertensive, cardioprotective, antitumorigenic, anti-inflammatory, and analgesic effects (47). The analgesic effect of tetrandrine could be significantly antagonized by $CaCl_2$ through intracerebroventricular or intraperitoneal administration. On the contrary, EGTA could enhance the analgesic effect of tetrandrine, suggesting that the analgesic mechanism of tetrandrine might be related to calcium antagonists (47).

A study showed that menthol decreased inflammatory pain induced by CFA in a dose-dependent manner, and formalin-induced spontaneous nocifensive behavior. Menthol blocked voltage-gated sodium channels and voltage-gated calcium channels in a voltage-, state-, and use-dependent manner. Furthermore, repetitive firing, action potential amplitude, and neuronal excitability were decreased by menthol. At the same time, spontaneous synaptic transmission of cultured superficial dorsal horn neurons was blocked by menthol. Menthol has central analgesic effect on inflammatory pain, which may be related to the blocking of voltage-gated Na^+/Ca^{2+} (48).

Studies showed that the natural coumarin osthole has a variety of pharmacological effects, such as anti-tumor, anti-convulsant, anti-inflammatory, osteogenic, anti-hepatitis, neuroprotective, and analgesic activities, and has a obvious effect on nucleus pulposus-evoked pain by inhibiting overexpression of acid-sensitive ion channel 3 in rat dorsal root ganglion and inhibiting the activation of extracellular signal-regulated kinase in rats (49, 50)

Inhibit of glutamate receptor

Glutamate receptors, which are the major excitatory neurotransmitter receptors in the brain and play an important role in analgesia, has different subtypes of glutamate receptors each of which can be divided into several subtypes, such as NMDA receptors (GluN1 to GluN3), AMPA receptors (GluA1 to GluA4), kainate receptors (GluK1 to GluK5), and mGlu receptors (mGluR1 to mGluR8). Almost all types of glutamate receptors are involved in the formation of hyperalgesia (51).

Gelsemine is the main active ingredient of *Gelsemium elegans* and shows significant analgesic activity in various chronic pains models, such as formalin-induced tonic pain, spinal nerve ligation-induced painful neuropathy, and bone cancer-induced mechanical allodynia. Strychnine, the glycine receptor (GlyR) antagonist, could relieve the analgesic effect of gelsemine with an apparent ID_{50} value of 3.8 μg (52). The analgesic action of gelsemine in neuropathic pain was prevented by gene ablation of the GlyR α3 subunitnearly and completely, but not GlyR α1, indicating that gelsemine generates analgesic effect via spinal α3 glycine receptors. Gelsemine directly regulates recombinant and native glycine receptors and play conformational specificity and subunit selectivity effects (53).

Paeonol, a micromolecular phenolic compound, has been proven to have a variety of pharmacological and physiological effects, such as sedation, hypnosis, antipyresis, antioxidation, anti-inflammation, antibacteria, immunoregulation, anti-tumor, and analgesia (54). Paeonol could relieve inflammatory pain and reverse the upregulated levels of NR2B, CaMKIIα, GluR1, p-GluR1-Ser831, ERK/CREB, and mTOR pathway proteins in anterior cingulate cortex in CFA mice, but has no effect on NR2A, p-GluR1-Ser845, and $GABA_A$-α_2 (55).

Oxymatrine could lower the threshold of CCI mice in mechanical allodynia and thermal hyperalgesia test. At the same time, the mean IOD of NR2B in the dorsal horn and expression levels of NR2B, p-ERK, and p-CREB protein in the chronic neuropathic pain model were decreased by oxymatrine. Thus, the regulation of NMDA NR2B receptor-ERK/CREB signaling may be the targets for the antinociceptive effects of oxymatrine (56).

In addition, recent reports confirmed that paeoniflorin exerted central analgesic effect through adenosine A_1 receptor by inhibiting colorectal distention-evoked glutamate release and the NMDA receptor dependent extracellular signal-regulated protein kinase (p-ERK) signaling in rats with neonatal maternal separation-induced visceral hyperalgesia (57).

Affect transient receptor potential (TRP)

Transient Receptor Potential (TRP) family of ion channels expressed on nociceptors, the TRP superfamily contains 28 channels with 7 different subgroups, and TRPA1, TRPV1 and TRPV4 have been associated with pain transmission of sensory neurons, including DRG (40).

Hyperpolarization-activated inward currents are blocked by capsaicin via TRPV1 in the rat dorsal root ganglion neurons. The analgesic effects of capsaicin reportedly cause the densensitization of nociceptive neurons owing to depletion of pain-related substances (58). Apart from this, studies have shown that the aporphinic alkaloid dicentrine could attenuate spontaneous nociception and mechanical cold hypersensitivity in inflammation pain model probably via a TRPA1-dependent pathway (59).

Borneol, also known as *bingpian* or *longnao* in Chinese, is a bicyclic monoterpene compound and a time-honored herb from *Cinnamomum* tree in TCM, has been used for more than 2,000 years in clinical applications. The TRPM8 channel was identified as a molecular target for borneol in the pain mouse models induced by CFA, capsaicin, and formalin, showing that topical borneol-induced analgesia was almost exclusively mediated by TRPM8 (60).

1, 8-cineole, a terpene oxide and a TRPM8 agonist, is the main component of most eucalyptus oil (75%), rosemary (40%), and many other essential oils. The sensory irritation tests i*n vivo* showed that 1, 8-cineole conferred an analgesic effect due to its inhibition of TRPA1 (61).

Additionally, L-menthol could effectively alleviate pain behavior in many pain models, such as chemical stimuli (capsaicin, acrolein, acetic acid), noxious heat and inflammation pain induced by CFA. The genetic deletion of TRPM8 completely abolished the analgesia caused by L-menthol in all these models, while other analgesics (acetaminophen) remained effective. When mice were treated with AMG2850, a selective TRPM8 inhibitor, the analgesia effect of L-menthol disappeared. Consequently, TRPM8 is the principal mediator of menthol-induced analgesia of acute and inflammatory pain (14). TRPV1 receptor was reported to be involved in the analgesic effect of hesperidin and curcuminoid in inflammatory pain model (62, 63).

Influence adenosine system

The adenosine receptor system is promising for pain treatment. Adenosine receptors are widely distributed not only in the spinal cord and brain areas involved in pain transmission but also in peripheral sensory afferents or adjacent cells.

Incarvillateine mainly exists in *Incarvillea sinensis*, a traditional Chinese medicine used to treat rheumatism and bruises and is very effective for pain and inflammation. Incarvillateine dose-dependently attenuated acetic acid-induced writhing, thermal hyperalgesia of CFA inflammatory pain, and mechanical allodynia of SNI or paclitaxel-induced neuropathic pain. Incarvillateine-induced analgesia was attenuated by theophylline (nonselective adenosine antagonist), 1, 3-dipropyl-8-cyclopentylxanthine (A_1 agonist), and 3, 7-dimethyl-1-propargylxanthine (A_2 agonist). These findings showed that the analgesic mechanism of incarvillateine may be related to the adenosine system in inflammatory and neuropathic pain models (64).

Levo-tetrahydropalmatine has remarkable analgesic effect and as an analgesic has been used clinically for more than 40 years. Treatment with levo-tetrahydropalmatine suppressed the increase of mechanical allodynia and spinal phosphorylation of the NMDA receptor NR1 subunit expression in CCI mice model. Intrathecal treatment with levo-tetrahydropalmatine combined with the Sig-1R antagonist, BD1047, synergistically blocked mechanical allodynia. Intrathecal pretreatment with naloxone, a non-selective opioid receptor antagonist, did not affect levo-tetrahydropalmatine. These results show that analgesic effect of levo-tetrahydropalmatine modulates spinal Sig-1R activation (65).

Paeoniflorin significantly attenuates paclitaxel-induced allodynia, suppresses saphenous nerve firing, and inhibits demyelination in the plantar nerve. Moreover, paeoniflorin down-regulates the paclitaxel-induced expression of CHOP in cultured Schwann cells, thereby inhibits ER stress. Adenosine A_1 receptor antagonist 8-cyclopentyl-1, 3-diprooylxanrhine could inhibit attenuation of mechanical allodynia caused by paclitaxel and down-regulate CHOP levels in cell cultures induced by paeoniflorin. Hence, adenosine A_1 receptor plays

an important role in the analgesic effect of paeoniflorin (66).

Affect purinergic receptors

Adenosine triphosphate is thought to play a critical role in nociceptive transmission or pain signals. Adenosine triphosphate is implicated in peripheral pain signaling by acting on P2X receptors. The seven P2X subtypes are widely expressed in many tissues (67).

P2X7 receptors have an important role in immune and pain response, and bullatine A as a potent P2X7 antagonist could dose-dependently inhibit ATP-induced upregulation of P2X7 mRNA, but had no obvious effect on P2X4 mRNA level in BV-2 cells. P2X pathways may be a possible mechanism for the analgesia of bullatine A (68).

Inhibit c-Fos gene expression

c-Fos has been the subject of study in relation to the pathophysiology of pain as a possible tool to aid in its understanding. In recent years, c-Fos has been used as a useful instrument for studying natural products with analgesic profile (69).

Gelsemine is effective for the treatment of neuropathic pain. After treatment with gelsemine, the mechanical thresholds and thermal latencies were prolonged in PSNL mice. A previous immunohistochemical study had shown that PSNL upregulated c-Fos expression in the neurons of the anterior cingulate cortex while gelsemine decreasedc-Fos expression by 58% (70). Besides, intrathecal pretreatment of paeoniflorin was effective in the management of bee venom-induced pain via suppression of spinal c-Fos expression in both superficial (lamina I–II) and deep (lamina IV–VI) layers of the $L_{4–5}$ dorsal spine (21).

Inhibit cyclooxygenase (COX) activity and reduce the secretion of pain-causing substances

Some compounds can reduce production of cytokine substances, including interleukin (IL), tumor necrosis factor (TNF), prostaglandins, and other peripheral pain-causing substances to produce an analgesic effect. NO is a kind of important information transmitting substance and neurotransmitter. Increasing the level of cyclic guanosine monophosphate (cGMP) in target cells by NO-cGMP pathway is one of the ways in which NO participates in analgesia. Nitric oxide synthase (NOS) is a key enzyme in the synthesis of NO, and its activity changes directly regulate the amount and biological effects of NO. Berberine has significant analgesic effect, and findings on visceral hypersensitivity in rats show that berberine decrease visceral hypersensitivity by increasing NO levels. In addition, quercetin could attenuate oxaliplatin-induced chronic painful peripheral neuropathy, and the mechanism is related to NO and peroxynitrite (71, 72). Lycopene, a natural pigment is recognized by the Food and Agriculture Organization of the United Nations and the World Health Organization as a class A nutrient, and it is also the hotspot in the functional food, medicine, and cosmetics industries. Lycopene can reduce diabetic neuropathic pain by inhibiting the release of NO and TNF-α (73,74).

Tetrandrine exerted strong antinociceptive effects on LPS-induced hyperalgesia in mice by inhibiting IKKβ phosphorylation, which reduced the production of important pain mediators, such as PGE_2 and COX-2, via the IKKβ/IκB/NF-κB pathway (46). Meanwhile, the analgesic mechanism of tetrandrine may be through the inhibition of IL-6 production in blood and reduction of TNF-α level in plasma of endotoxin-induced mice (75).

Gelsemine, also known as koumine, possesses analgesic, anti-inflammatory, and neurosteroid modulating activities. Gelsemine inhibited microglial and astroglial activation in the spinal dorsal horn post-incision, and suppressed expression of pro-inflammatory cytokines IL-1β, IL-6, TNF-α (76). Levo-tetrahydropalmatine has similar mechanism, which could inhibit the activation of microglia and increase pro-inflammatory cytokines to alleviate bone cancer pain (65).

Paeoniflorin and albiflorin could attenuate neuropathic pain by inhibiting the activation of p38 mitogen-activated protein kinase (p38 MAPK) pathway in spinal microglia and subsequently up-regulating pro-inflammatory cytokines IL-1β and TNF-α in rats model induced by CCI (77).

Myrtenol is the main component of aromatic plant essential oil, and research shows that it could inhibit the writhing reaction of mice induced by acetic acid, but it had no significant effect on the licking time of mice in hot-plate test. The analgesic effect is also shown in the formalin experiment, but only in the second stage. Myrtenol reduces nociception in mice by inhibiting the release of inflammatory mediators, cell migration, and receptor signaling pathways involved in pain transmission (78).

Paeonol inhibits the production of NO, PGE_2, and IL-6 induced by LPS via prevention of ERK activation in RAW264.7 macrophages. Meanwhile, paeonol decreased protein expression of iNOS and

COX-2 and production of pro-inflammatory cytokines, such as TNF-α and IL-1β, NO and PGE_2, and increased production of IL-10 in rat paw exudates of rat model of carrageenan-evoked thermal hyperalgesia (50, 79).

Caffeic acid, a main representative of natural phenolic compounds, is widely distributed in medicinal plants, such as *Polygonum aviculare*, *Mentha canadaensis*, *Ligusticum chuanxiong*, *Slauia miltiorrhiza*, *Taraxacum mongolicum*, and *Artemisia capillaris* (80, 81). Caffeic acid reduced neutrophil, free radical, and nitric oxide-mediated hypernociception as evident from the reduction in myeloperoxidase, malondialdehyde, and nitrite levels, respectively, in rat model induced by carrageenan and lipopolysaccharide (LPS)-induced mechanical hyperalgesia (80).

7-Hydroxycoumarin, also known as umbelliferone, is a coumarin found in a variety of edible fruits and plants. 7-Hydroxycoumarin has obvious analgesic effect in animal models of CFA-induced hyperalgesia by inhibiting release of TNF-α and IL-1$\beta$and the production of PGE_2, directly acting as hyperalgesic mediator (82).

Quercetin alleviates TiO_2-induced chronic arthritis pain in mice by inhibiting TiO_2-induced neutrophil and macrophage recruitment, proteoglycan degradation, oxidative stress, cytokine production (TNF-α, IL-1β, IL-6, and IL-10), COX-2 mRNA expression, bone resorption, and activation of the Nrf2/HO-1 signaling pathway (83).

Other analgesic mechanisms

Geniposide, an acyclic enone glycoside compound, is one of the main active ingredients of dumplings of *Gardenia jasminoides* and *Eucommia ulmoides.* Geniposide completely protects against hydrogen peroxide-induced oxidative damage in PC12 and HEK293 cells that express rat and human GLP-1Rs but not in HEK293T cells that do not express GLP-1Rs. The orthosteric GLP-1R antagonist exendin *(9-39*) right-shifts the concentration response curve of geniposide without changing the maximal protection, with identical pA2 values in both cell lines. Subcutaneous and oral administration of geniposide blocks the formalin-induced tonic response, with respective maximum inhibitory rates of 72% and 68% and ED_{50} values of 13.1 and 52.7 mg/kg. Intrathecal geniposide induces dose-dependent antinociception, which is completely blocked by spinal exendin *(9-39)*, siRNA/GLP-1R, and cyclic AMP/PKA pathway inhibitors. These data illustrate that geniposide exerts its analgesic effect via the spinal GLP-1 receptors (84).

Caffeic acid potent anti-hyperglycemic inhibits thiobarbituric acid reactive substances and elevates antioxidant enzyme and attenuates alpha-amylase and alpha-glucosidase in alloxan-induced diabetic mice (85). Its elevation in serum insulin levels and its antioxidant potential might be responsible for its analgesic effect properties. Lycopene weakened neuropathic pain in mice with partial sciatic nerve ligation by up-regulating the expression of spinal astrocytic connexin 43 (86).

Pre-administration (i.t.) of PK11195, an antagonist of translocator protein (18 kDa) partly reversed the analgesic effects of gelsemine. The analgesic mechanism of gelsemine might involve inhibition of spinal neuroinflammation and activation of translocator protein on postoperative pain rat model. Gelsemine could also regulate the biosynthesis of iso-leucine neurosteroids, which are potential therapeutic drugs that play a key role in analgesia in the spinal cord (76, 87).

Ellagic acid is widely distributed in in fruits and nuts, such as blueberries, blackberries, raspberries, strawberries, pomegranates, and walnuts. It has anti-tumor, anti-inflammatory, anti-oxidative, anti-diabetic neuropathy effects, and it can inhibit PGE_2 synthesis and has other pharmacological effects. Ellagic acid has peripheral and central analgesic effects, which involve the opioid receptors in the systemic and peripheral and $_L$-arginine-NO-cGMP-ATP-sensitive K^+ channel pathway (88-90).

DISCUSSION

In spite of traditional Chinese medicine has a long history in pain treatment, its active ingredients and mechanism of analgesic action is not clear. However, monomeric compounds in traditional Chinese medicine have potential applications in pain treatment. Among the compounds reviewed in this paper, some alkaloids: trilobine, palmatine, tertrandrine, berberine, govaniadine, sinomenine, gelsemine, tetrahydropalmatine, and various aconitines showed significant analgesic activities, and analgesic mechanism of them have been deeply investigated, which may be the candidate compounds for new analgesics. Then, of the 81 compounds, only tetrahydropalmatine is used as an analgesic in clinical practice. The analgesic effects of the remaining compounds were studied by animal experiments. The purpose of animal experiments is to replicate various human pains on other animals to reveal the activity of the compounds, but the

exploration of their clinical effects cannot be limited to animal experiments. Therefore, we deem that research on clinical trials of these analgesic compounds should be strengthened to develop new analgesics.

In addition, the analgesic mechanisms of most compounds are related to glutamate receptor, central catecholaminergic system, the transient receptor potential family of ion channels, and the NO-cGMP and NF-κB pathway are also focus on the research of anti-inflammatory and analgesic drugs.

Through literature investigation, we found that only positive results of some experiments have been reported and the negative results were simply mentioned or omitted directly, so we can't summarize the negative results very well in this paper. Here, we strongly appeal to the researchers to show the negative results to the readers bravely, because the negative results are also valuable for scientific research. Sharing negative results can reduce the likelihood of peer-researcher repetition, and encourage other researchers to explore new research methods.

CONCLUSION

All in all, the study on analgesic activity of traditional Chinese medicine and natural products is more in-depth, but further researches are needed in the development of these compounds into new drugs with significant analgesic activity, which are more efficient and less toxic. Besides, there are abundant supplies of medicinal herbs from a variety of plants in China, in this case, how to use these plant resources sustainably and develop anti-inflammatory and analgesic drugs with remarkable activity is one of the directions worthy of efforts in the future.

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REFERENCES

1. Cohen; Milton; Quintner; John; Rysewyk, V.; Simon. Reconsidering the international association for the study of pain definition of pain. *Pain Reports* **2018**, *latest articles* (2): 1.
2. Forouzanfar, F.; Hosseinzadeh, H. Medicinal herbs in the treatment of neuropathic pain: a review. *Iranian Journal of Basic Medical Sciences* **2018**, *21*, 347-358.
3. Lutz, B.M.; Nia, S.; Xiong, M.; Tao, Y.X.; Bekker, A. Mtor, a new potential target for chronic pain and opioid-induced tolerance and hyperalgesia. *Molecular Pain* **2015**, *11*, 32.
4. Park, H.J.; Moon, D.E. Pharmacologic management of chronic pain. *Korean Journal of Pain* **2010**, *23*, 99-108.
5. Garland, E.L. Treating chronic pain: The need for non-opioid options. *Expert Review of Clinical Pharmacology* **2014**, *7*, 1-6.
6. Salsitz, E.A. Chronic pain, chronic opioid addiction: A complex nexus. *Journal of Medical Toxicology* **2016**, *12*, 1-4.
7. Higgins, C.; Smith, B.H.; Matthews, K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. *Br J Anaesth* **2018**, *120*, 1335-1344.
8. Wang Y. Advances in pharmacy and pharmacology of analgesic Chinese medicine. *Chin J of Clinical Rational Drug Use* **2015**, 171-172.
9. Lin, A.X.; Chan, G.; Hu, Y.; Ouyang, D.; Ung, C.; Shi, L.; Hu, H. Internationalization of traditional chinese medicine: current international market, internationalization challenges and prospective suggestions. *Chinese Medicine* **2018**, *13*, 9.
10. Du, G.H.; Yuan, T.Y.; Du, L.D.; Zhang, Y.X. The potential of traditional chinese medicine in the treatment and modulation of pain. *Advances in Pharmacology* **2016**, *75*, 325.
11. Jr, W.A.V.; Vicentini; Dagger, F.T.M.C.; Baracat; Dagger, M.M.; Geor, S.R. Flavonoids as anti-inflammatory and analgesic drugs: mechanisms of action and perspectives in the development of pharmaceutical forms. 2012; 297-330.
12. Bonjardim, L.R.; Cunha, E.S.; Guimarães, A.G.; Santana, M.F.; Oliveira, M.G.; Serafini, M.R.; Araújo, A.A.; Antoniolli, A.R.; Cavalcanti, S.C.; Santos, M.R. Evaluation of the anti-inflammatory and antinociceptive properties of *p*-cymene in mice. *Zeitschrift Für Naturforschung C* **2012**, *67*, 15-21.
13. de Santana, M.F.; Guimarães, A.G.; Chaves, D.O.; Silva, J.C.; Bonjardim, L.R.; De, L.J.W.; Ferro, J.N.; Barreto, E.O.; dos Santos, F.E.; Soares, M.B. The anti-hyperalgesic and anti-inflammatory profiles of *p*-cymene: evidence for the involvement of opioid system and cytokines. *Pharmaceutical Biology* **2015**, *53*, 1583-1590.

14. Liu, B.; Fan, L.; Balakrishna, S.; Sui, A.; Morris, J.B.; Jordt, S.E. TRPM8 is the principal mediator of menthol-induced analgesia of acute and inflammatory pain. *Pain* **2013**, *154*, 2169.
15. Galeotti, N.; Mannelli, L.D.C.; Mazzanti, G.; Bartolini, A.; Ghelardini, C. Menthol: A natural analgesic compound. *Neuroscience Letters* **2002**, *322*, 145-148.
16. Kwak, J. Acute Effects of Capsaicin on Proopioimelanocortin mRNA Levels in the Arcuate Nucleus of Sprague-Dawley Rats. *Psychiatry Investigation* **2012, 9***(2)*: 187-190.
17. Sun, J.; Yu, S. Research progress of quercetin. *Chin Med J Res Prac* **2011**, 85-88.
18. Mittal, N.; Joshi, R.; Hota, D.; Chakrabarti, A. Evaluation of antihyperalgesic effect of curcumin on formalin-induced orofacial pain in rat. *Phytotherapy Research Ptr* **2009**, *23*, 507-512.
19. Muhammad, N.; Shrestha, R.L.; Adhikari, A.; Wadood, A.; Khan, H.; Khan, A.Z.; Maione, F.; Mascolo, N.; De, F.V. First evidence of the analgesic activity of govaniadine, an alkaloid isolated from *Corydalis govaniana* wall. *Natural Product Research* **2015**, *29*, 430-437.
20. Long, Z.; Zhang, Y.; Guo, Z.; Wang, L.; Xue, X.; Zhang, X.; Wang, S.; Wang, Z.; Civelli, O.; Liang, X. Amide alkaloids from *Scopolia tangutica*. *Planta Medica* **2014**, *80*, 1124-1130.
21. Yu, H.Y.; Mu, D.; Chen, J.; Yin, W. Suppressive effects of intrathecal paeoniflorin on bee venom-induced pain-related behaviors and spinal neuronal activation. *Pharmacology* **2011**, *88*, 159-166.
22. Loscalzo, L.M.; Wasowski, C.; Paladini, A.C.; Marder, M. Opioid receptors are involved in the sedative and antinociceptive effects of hesperidin as well as in its potentiation with benzodiazepines. *European Journal of Pharmacology* **2008**, *580*, 306-313.
23. Loscalzo, L.M.; Yow, T.T.; Wasowski, C.; Chebib, M.; Marder, M. Hesperidin induces antinociceptive effect in mice and its aglycone, hesperetin, binds to μ-opioid receptor and inhibits GIRK1/2 currents. *Pharmacology Biochemistry & Behavior* **2011**, *99*, 333-341.
24. Huang, Q.; Mao, X.F.; Wu, H.Y.; Li, T.F.; Sun, M.L.; Liu, H.; Wang, Y.X. Bullatine A stimulates spinal microglial dynorphin A expression to produce anti-hypersensitivity in a variety of rat pain models. *Journal of Neuroinflammation* **2016**, *13*, 214.
25. Rigo, F.K.; Rossato, M.F.; Trevisan, G.; De Prá, S.D.; Ineu, R.P.; Duarte, M.B.; Cj, D.C.J.; Ferreira, J.; Gomez, M.V. PhKv a toxin isolated from the spider venom induces antinociception by inhibition of cholinesterase activating cholinergic system. *Scandinavian Journal of Pain* **2017**, *17*, 203.
26. Yin, L.L.; Zhu, X.Z. The involvement of central cholinergic system in (+)-matrine-induced antinociception in mice. *Pharmacology Biochemistry & Behavior* **2005**, *80*, 419-425.
27. Zuo, Z.X.; Wang, Y.J.; Li, L.; Wang, Y.; Mei, S.H.; Feng, Z.H.; Wang, M.; Li, X.Y. Huperzine A alleviates mechanical allodynia but not spontaneous pain via muscarinic acetylcholine receptors in mice. *Neural Plasticity,2015,(2015-12-1)* **2015**, *2015*, 1-11.
28. Murayama, M.; Ito, T.; Konno, C.; Hikino, H. Mechanism of analgesic action of mesaconitine. Relationship between analgesic effect and central monoamines or opiate receptors. *European Journal of Pharmacology* **1984**, *101*, 29-36.
29. Ameri, A.; Seitz, U. Effects of mesaconitine on [3H]noradrenaline uptake and neuronal excitability in rat hippocampus. *Experimental Brain Research.experimentelle Hirnforschung.expérimentation Cérébrale* **1998**, *121*, 451-456.
30. Ono, M.; Satoh, T. Pharmacological studies on lappaconitine: Possible interaction with endogenous noradrenergic and serotonergic pathways to induce antinociception. *Japanese Journal of Pharmacology* **1992**, *58*, 251-257.
31. Leeab, K.K.; Yuzurihara, M.; Kase, Y.; Kobayashi, H. Antinociceptive effect of paeoniflorin via spinal α-adrenoceptor activation in diabetic mice. *European Journal of Pain* **2011**, *15*, 1035-1039.
32. Zhou, H.H.; Wu, D.L.; Gao, L.Y.; Fang, Y.; Ge, W.H. L-tetrahydropalmatine alleviates mechanical hyperalgesia in models of chronic inflammatory and neuropathic pain in mice. *Neuroreport* **2016**, *27*, 476-480.
33. Wu, Y.Y.; Jiang, Y.L.; He, X.F.; Zhao, X.Y.; Shao, X.M.; Sun, J.; Shen, Z.; Shou, S.Y.; Wei, J.J.; Ye, J.Y., *et al.* 5-HT in the dorsal raphe nucleus is involved in the effects of 100-Hz electro-acupuncture on the pain-depression dyad in rats. *Exp Ther Med* **2017**, *14*, 107-114.
34. Carballo-Villalobos, A.I.; González-Trujano, M.E.; López-Muñoz, F.J. Evidence of mechanism of action of anti-inflammatory/antinociceptive activities of acacetin. *European Journal of Pain* **2014**, *18*, 396–405.
35. Martínez, A.L.; González-Trujano, M.E.; Aguirre-Hernández, E.; Moreno, J.; Soto-Hernández, M.; López-Muñoz, F.J. Antinociceptive activity of Tilia americana var. mexicana inflorescences and quercetin in the formalin test and in an arthritic pain model in rats. *Neuropharmacology* **2009**, *56*, 564-571.
36. Wang, Z.J.; Heinbockel, T. Essential oils and their constituents targeting the gabaergic system and sodium channels as treatment of neurological diseases. *Molecules* **2018**, *23*, 1061.
37. Zhu, Q.; Sun, Y.; Zhu, J.; Fang, T.; Zhang, W.; Li, J.X. Antinociceptive effects of sinomenine in a rat model of neuropathic pain. *Scientific Reports* **2014**, *4*, 7270.

38. Zhai, K.; Hu, L.; Chen, J.; Fu, C.Y.; Chen, Q. Chrysin induces hyperalgesia via the GABAA receptor in mice. *Planta Medica* **2008**, *74*, 1229-1234.
39. Zhou, J.; Yang, G.; Jin, S.; Tao, L.; Yu, J.; Jiang, Y. Oxymatrine-carbenoxolone sodium inclusion compound induces antinociception and increases the expression of GABA(A)alpha1 receptors in mice. *European Journal of Pharmacology* **2010**, *626*, 244-249.
40. Nazıroğlu, M.; Braidy, N. Thermo-sensitive TRP channels: novel targets for treating chemotherapy-induced peripheral pain. *Frontiers in Physiology* **2017**, *8*.
41. Hu, J.; Shi, X.; Mao, X.; Chen, J.; Zhu, L.; Zhao, Q. Antinociceptive activity of Rhoifoline A from the ethanol extract of Zanthoxylum nitidum in mice. *Journal of Ethnopharmacology* **2013**, *150*, 828-834.
42. Chen, Z.; Ma, C.; Xu, S. Analgesic mechanism of hyperin.*Acta Pharmaceutica Sinica* **1989**, 326-330.
43. Lee, J.Y.; Yoon, S.Y.; Won, J.; Kim, H.B.; Kang, Y.; Oh, S.B. Sinomenine produces peripheral analgesic effects via inhibition of voltage-gated sodium currents. *Neuroscience* **2017**, *358*, 28-36.
44. Wu, S.; Yang, L.; Lv, X. Study on analgesia of oxymatrine and its relation to calcium channels.*Chinese Journal of Integrated Traditional and Western* **2015**, *35*, 461-465.
45. Wang, Y.; Yuan, J.; Yuan, X.; Wang, W.; Pei, X.; Zhao, Q.; Cao, H.; Xu, M.; Liu, Z. Observation of antinociceptive effects of oxymatrine and its effect on delayed rectifier K currents (IK) in PC12 cells. *Neurochemical Research* **2012**, *37*, 2143-2149.
46. Zhao, H.; Luo, F.; Li, H.; Li, Z.; Yi, Y.; Wan, J. Antinociceptive effect of tetrandrine on LPS-induced hyperalgesia via the inhibition of IKKβ phosphorylation and the COX-2/PGE_2 pathway in mice. *Plos One* **2014**, *9*, 94586.
47. Song, B.; Zhang, J.; Chen, Z.; Ma, C.;Xu, S.; Fang, M.; Zhang, Y. Effect of calcium ion on analgesic effect of tetrandrine. *Acta Universitatis Medicinalis Anhui* **1995**, 1-3.
48. Pan, R.; Tian, Y.; Gao, R.; Li, H.; Zhao, X.; Barrett, J.E.; Hu, H. Central mechanisms of menthol-induced analgesia. *Journal of Pharmacology & Experimental Therapeutics* **2012**, *343*, 661-672.
49. He, Q.L.; Chen, Y.; Jian, Q.; Mo, S.L.; Ming, W.; Zhang, J.J.; Li, M.N.; Zou, X.N.; Zhou, S.F.; Chen, X.W. Osthole, a herbal compound, alleviates nucleus pulposus-evoked nociceptive responses through the suppression of overexpression of acid-sensing ion channel 3 (ASIC3) in rat dorsal root ganglion. *Medical Science Monitor International Medical Journal of Experimental & Clinical Research* **2012**, *18*, BR229-BR236.
50. Wu, H.X.; Wang, Y.M.; Xu, H.; Wei, M.; He, Q.L.; Li, M.N.; Sun, L.B.; Cao, M.H. Osthole, a coumadin analog from *Cnidium monnieri* (L.) cusson, ameliorates nucleus pulposus-induced radicular inflammatory pain by inhibiting the activation of extracellular signal-regulated kinase in rats. *Pharmacology* **2017**, *100*, 74-82.
51. Kantamneni, S. Cross-talk and regulation between glutamate and GABAB receptors. *Frontiers in Cellular Neuroscience* **2015**, *9*, 135.
52. Zhang, J.Y.; Gong, N.; Huang, J.L.; Guo, L.C.; Wang, Y.X. Gelsemine, a principal alkaloid from *Gelsemium sempervirens* Ait., exhibits potent and specific antinociception in chronic pain by acting at spinal α3 glycine receptors. *Pain®* **2013**, *154*, 2452.
53. Lara, C.O.; Murath, P.; Muñoz, B.; Marileo, A.M.; Martín, L.S.; San Martín, V.P.; Burgos, C.F.; Mariqueo, T.A.; Aguayo, L.G.; Fuentealba, J. Functional modulation of glycine receptors by the alkaloid gelsemine. *British Journal of Pharmacology* **2016**, *173*, 2263-2277.
54. Sun, G.P.; Wang, H.; Xu, S.P.; Shen, Y.X.; Wu, Q.; Chen, Z.D.; Wei, W. Anti-tumor effects of paeonol in a HepA-hepatoma bearing mouse model via induction of tumor cell apoptosis and stimulation of IL-2 and TNF-alpha production. *European Journal of Pharmacology* **2008**, *584*, 246-252.
55. Wang, D. The effects and mechanisms of peaonol and ZBD-2 in chronic inflammatory pain induced by complete Freund's adjuvant in mice. The Second Military medical university 2016.
56. Wang, H.; Li, Y.; Dun, L.; Xu, Y.; Jin, S.; Du, J.; Ma, L.; Li, J.; Zhou, R.; He, X. Antinociceptive effects of oxymatrine from *Sophora flavescens*, through regulation of NR2B-containing NMDA receptor-ERK/CREB signaling in a mice model of neuropathic pain. *Phytomedicine International Journal of Phytotherapy & Phytopharmacology* **2013**, *20*, 1039-1045.
57. Zhang, X.J.; Chen, H.L.; Li, Z.; Zhang, H.Q.; Xu, H.X.; Sung, J.J.; Bian, Z.X. Analgesic effect of paeoniflorin in rats with neonatal maternal separation-induced visceral hyperalgesia is mediated through adenosine A_1 receptor by inhibiting the extracellular signal-regulated protein kinase (ERK) pathway. *Pharmacology Biochemistry & Behavior* **2009**, *94*, 88-97.
58. Jin-Seong, L.; Sung-Gon, K.; Hyeun-Kyeung, K.; Sun-Yong, B.; Cheol-Min, K. Acute effects of capsaicin on proopioimelanocortin mRNA levels in the arcuate nucleus of Sprague-Dawley rats. *Psychiatry Investigation* **2012**, *9*, 187-190.
59. Montrucchio, D.P.; Córdova, M.M.; Santos, A.R.S. Plant derived aporphinic alkaloid S-(+)-dicentrine induces antinociceptive effect in both acute and chronic inflammatory pain models: evidence for a role of TRPA1 channels. *Plos One* **2013**, *8*, 88-91.
60. Wang, S.; Zhang, D.; Hu, J.; Jia, Q.; Xu, W.; Su, D.; Song, H.; Xu, Z.; Cui, J.; Zhou, M. A clinical and mechanistic study of topical borneol-induced

analgesia. *EMBO Molecular Medicine,9,6(2017-04-10)* **2017**, *9*, 802-815.
61. Takaishi, M.; Fujita, F.; Uchida, K.; Yamamoto, S.; Sawada, M.; Hatai, C.; Shimizu, M.; Tominaga, M. 1,8-cineole, a TRPM8 agonist, is a novel natural antagonist of human TRPA1. *Molecular Pain* **2012**, *8*.
62. Pinhoribeiro, F.A.; Hohmann, M.S.; Borghi, S.M.; Zarpelon, A.C.; Guazelli, C.F.; Manchope, M.F.; Casagrande, R.; Jr, V.W. Protective effects of the flavonoid hesperidin methyl chalcone in inflammation and pain in mice: Role of TRPV1, oxidative stress, cytokines and NF-κB. *Chemico-Biological Interactions* **2015**, *228*, 88-99.
63. Lee, J.Y.; Shin, T.J.; Choi, J.M.; Seo, K.S.; Kim, H.J.; Yoon, T.G.; Lee, Y.S.; Han, H.; Chung, H.J.; Oh, Y. Antinociceptive curcuminoid, KMS4034, effects on inflammatory and neuropathic pain likely via modulating TRPV1 in mice. *Br J Anaesth* **2013**, *111*, 667-672.
64. Wang, M.L.; Yu, G.; Yi, S.P.; Zhang, F.Y.; Wang, Z.T.; Huang, B.; Su, R.B.; Jia, Y.X.; Gong, Z.H. Antinociceptive effects of incarvillateine, a monoterpene alkaloid from *Incarvillea sinensis*, and possible involvement of the adenosine system. *Scientific Reports* **2015**, *5*, 16107.
65. Zhang, M.; Liu, Y.; Zhang, L.; Yue, D.; Qi, D.; Liu, G.; Liu, S. Levo-tetrahydropalmatine attenuates bone cancer pain by inhibiting microglial cells activation. *Mediators of Inflammation* **2015**, *2015*, 752512.
66. Andoh, T.; Kobayashi, N.; Uta, D.; Kuraishi, Y. Prophylactic topical paeoniflorin prevents mechanical allodynia caused by paclitaxel in mice through adenosine A_1 receptors. *Phytomedicine International Journal of Phytotherapy & Phytopharmacology* **2017**, *25*, 1.
67. Liang, S.; Xu, C.; Li, G.; Gao, Y. P2X receptors and modulation of pain transmission: focus on effects of drugs and compounds used in traditional chinese medicine. *Neurochemistry International* **2010**, *57*, 705-712.
68. Li, J.; Ren, W.; Huang, X.J.; Zou, D.J.; Hu, X. Bullatine A, a diterpenoid alkaloid of the genus Aconitum, could attenuate ATP-induced BV-2 microglia death/apoptosis via P2X receptor pathways. *Brain Research Bulletin* **2013**, *97*, 81-85.
69. Santos, P.L.; Brito, R.G.; Jpscf, M.; Jss, Q.; Quintansjúnior, L.J. Fos protein as a marker of neuronal activity: a useful tool in the study of the mechanism of action of natural products with analgesic activity. *Molecular Neurobiology* **2017**, *2017*, 1-20.
70. Wu, Y.; Li, Y.; Luo, Y.; Wang, T.; Wang, H.; Chen, S.; Qu, W.; Huang, Z. Gelsemine alleviates both neuropathic pain and sleep disturbance in partial sciatic nerve ligation mice. *Acta Pharmacologica Sinica* **2015**, *36*, 1308-1317.
71. Tang, Q.L.; Lai, M.L.; Zhong, Y.F.; Wang, A.M.; Su, J.K.; Zhang, M.Q. Antinociceptive effect of berberine on visceral hypersensitivity in rats. *World Journal of Gastroenterology* **2013**, *19*, 4582-4589.
72. Azevedo, M.I.; Pereira, A.F.; Nogueira, R.B.; Rolim, F.E.; Brito, G.A.; Wong, D.V.; Limajúnior, R.C.; De, A.R.R.; Vale, M.L. The antioxidant effects of the flavonoids rutin and quercetin inhibit oxaliplatin-induced chronic painful peripheral neuropathy. *Molecular Pain* **2013**, *9*, 53.
73. Liu, Y.; Li, J.; Yan, W.; Hao, L.; Zhao, E. Study on the ultrasonic-assisted extraction and antioxidant activities oflycopene from cherry tomatoes. *Storage and Process* **2017**, 73-77.
74. Kuhad, A.; Sharma, S.; Chopra, K. Lycopene attenuates thermal hyperalgesia in a diabetic mouse model of neuropathic pain. *European Journal of Pain* **2008**, *12*, 624–632.
75. Dai, X; Luo, F.; Zhang, Z.; Li, H.; Zhang, L.; Wan, J. Studies on analgesic effect and mechanism of tetrandrine on lipopolysaccharide-induced hyperalgsia in mice. *Lishizhen Medicine and Materia Medica Research***2010**, *21*, 1049-1050.
76. Xiong, B.J.; Xu, Y.; Jin, G.L.; Liu, M.; Yang, J.; Yu, C.X. Analgesic effects and pharmacologic mechanisms of the gelsemium alkaloid koumine on a rat model of postoperative pain. *Sci Rep* **2017**, *7*, 14269.
77. Zhou, J.; Wang, L.; Wang, J.; Wang, C.; Yang, Z.; Wang, C.; Zhu, Y.; Zhang, J. Paeoniflorin and albiflorin attenuate neuropathic pain via mapk pathway in chronic constriction injury rats. *Evidence-Based Complementray and Alternative Medicine,* **2016**, *2016*, 1-11.
78. Silva, R.O.; Salvadori, M.S.; Sousa, F.B.M.; Santos, M.S.; Carvalho, N.S.; Sousa, D.P.; Gomes, B.S.; Oliveira, F.A.; Barbosa, A.L.R.; Freitas, R.M. Evaluation of the anti-inflammatory and antinociceptive effects of myrtenol, a plant-derived monoterpene alcohol, in mice. *Flavour & Fragrance Journal* **2014**, *29*, 184-192.
79. Tosun, A.; Akkol, E.K.; Yeşilada, E. Anti-inflammatory and antinociceptive activity of coumarins from *Seseli gummiferum* subsp. corymbosum (Apiaceae). *Zeitschrift Fur Naturforschung Section C-a Journal of Biosciences* **2009**, *64*, 56-62.
80. Mehrotra, A.; Shanbhag, R.; Chamallamudi, M.R.; Singh, V.P.; Mudgal, J. Ameliorative effect of caffeic acid against inflammatory pain in rodents. *European Journal of Pharmacology* **2011**, *666*, 80.
81. Editorial boardo of State Administration of Traditional Chinese Medicine. *Zhonghuabencao*. The Press of Science and technology of Shanghai: 2009.
82. de Lima, F.O.; Nonato, F.R.; Couto, R.D.; Barbosa Filho, J.M.; Nunes, X.P.; Ribeiro, d.S.R.; Soares,

M.B.; Villarreal, C.F. Mechanisms involved in the antinociceptive effects of 7-hydroxycoumarin. *Journal of Natural Products* **2011**, *74*, 596.
83. Borghi, S.M.; Mizokami, S.S.; Pinhoribeiro, F.A.; Fattori, V.; Crespigio, J.; Clementenapimoga, J.T.; Napimoga, M.H.; Pitol, D.L.; Issa, J.; Fukada, S.Y. The flavonoid quercetin inhibits titanium dioxide (TIO2)-induced chronic arthritis in mice. *Journal of Nutritional Biochemistry* **2018**, *53*, 81-95.
84. Gong, N.; Fan, H.; Ma, A.N.; Xiao, Q.; Wang, Y.X. Geniposide and its iridoid analogs exhibit antinociception by acting at the spinal GLP-1 receptors. *Neuropharmacology* **2014**, *84*, 31-45.
85. Raafat, K.; Wurglics, M.; Schubert-Zsilavecz, M. Prunella vulgaris L. active components and their hypoglycemic and antinociceptive effects in alloxan-induced diabetic mice. *Biomedicine & Pharmacotherapy* **2016**, *84*, 1008-1018.
86. Zhang, F.F.; Morioka, N.; Kitamura, T.; Fujii, S.; Miyauchi, K.; Nakamura, Y.; Hisaoka-Nakashima, K.; Nakata, Y. Lycopene ameliorates neuropathic pain by upregulating spinal astrocytic connexin 43 expression. *Life Sciences* **2016**, *155*, 116-122.
87. Venard, C.; Boujedaini, N.; Belon, P.; Mensah-Nyagan, A.G.; Patte-Mensah, C. Regulation of neurosteroid allopregnanolone biosynthesis in the rat spinal cord by glycine and the alkaloidal analogs strychnine and gelsemine. *Neuroscience* **2008**, *153*, 154-161.
88. Taghi, M.M.; Naghizadeh, B.; Ghorbanzadeh, B.; Farbood, Y. Central and peripheral antinociceptive effects of ellagic acid in different animal models of pain. *European Journal of Pharmacology* **2013**, *707*, 46-53.
89. Mansouri, M.T.; Naghizadeh, B.; Ghorbanzadeh, B. Involvement of opioid receptors in the systemic and peripheral antinociceptive actions of ellagic acid in the rat formalin test. *Pharmacology Biochemistry & Behavior* **2014**, *120*, 43-49.
90. Ghorbanzadeh, B.; Mansouri, M.T.; Hemmati, A.A.; Naghizadeh, B.; Mard, S.A.; Rezaie, A. Involvement of L-arginine/NO/cGMP/K(ATP) channel pathway in the peripheral antinociceptive actions of ellagic acid in the rat formalin test. *Pharmacology Biochemistry & Behavior* **2014**, *126*, 116-121.
91. Sun, W. Brief manual for natural active ingredients.China Medical Science Press: 1998.
92. Chao, J.; Liao, J.W.; Peng, W.H.; Lee, M.S.; Pao, L.H.; Cheng, H.Y. Antioxidant, analgesic, anti-inflammatory, and hepatoprotective effects of the ethanol extract of *Mahonia oiwakensis* stem. *International Journal of Molecular Sciences* **2013**, *14*, 2928.
93. Liu, X.; Hu, Z.; Shi, Q.; Zeng, H.; Shen, Y.; Jin, H.; Zhang, W. Anti-inflammatory and anti-nociceptive activities of compounds from *Tinospora sagittata* (Oliv.) Gagnep. *Archives of Pharmacal Research* **2010**, *33*, 981.
94. Chen, F. Determination of active ingredients in traditional Chinese medicine. People's Medical Publishing House: 2008.
95. Wang, L. Experimental study on the analgesie effect and mechanism of propofol. Soochow University, 2002.
96. Deng, Z.; Yu, S.; Ke, F.; Chen, J.; Huang, Yu.; Huang, D. Dicentrine, a natural vascular α_1-adrenoceptor antagonist, isolated form *Lindera megaphylla*. *British Journal of Pharmacology* **1991**, *v.104*.
97. Tsai, T.H.; Wang, G.J.; Lin, L.C. Vasorelaxing alkaloids and flavonoids from *Cassytha filiformis*. *Journal of Natural Products* **2008**, *71*, 289-291.
98. Shamima, A.R.; Fakurazi, S.; Hidayat, M.T.; Hairuszah, I.; Moklas, M.A.; Arulselvan, P. Antinociceptive action of isolated mitragynine from *Mitragyna speciosa* through activation of opioid receptor system. *International Journal of Molecular Sciences* **2012**, *13*, 11427-11442.
99. Farzin, D.; Kalantari, P.; Zaer, H. Effects of harmane, norharman and harmine on the hot–plate and formalin-induced nociceptions in mice. *Journal of Mazandaran University of Medical Sciences* **2012**.
100. Jiang, H.; Liu, Y.B.; Li, Y.; Li, L.; Ma, S.G.; Qu, J.; Yu, S.S. Analgesic corynanthe-type alkaloids from *Strychnos angustiflora*. *Tetrahedron* **2016**, *72*, 1276-1284.
101. Ma, X.; Jiang, S. Diterpenoid alkaloids from *Aconitum bulleyanum* Diels. *China Journal of Chinese Materia Medica* **1998**, *23*, 679-680.
102. Guo, Z. A preliminary research on the quality control of the processed products of radix aconitum vilmoriniani. Yunnan University of TCM, 2015.
103. Wang, D.P.; Lou, H.Y.; Huang, L.; Hao, X.J.; Liang, G.Y.; Yang, Z.C.; Pan, W.D. A novel franchetine type norditerpenoid isolated from the roots of *Aconitum carmichaeli* Debx. with potential analgesic activity and less toxicity. *Cheminform* **2012**, *22*, 4444-4446.
104. Zhao, D.K.; Ai, H.L.; Zi, S.H.; Zhang, L.M.; Yang, S.C.; Guo, H.C.; Shen, Y.; Chen, Y.P.; Chen, J.J. Four new C_{18}-diterpenoid alkaloids with analgesic activity from *Aconitum weixiense*. *Fitoterapia* **2013**, *91*, 280-283.
105. Guo, Q.; Xia, H.; Shi, G.; Zhang, T.; Shi, J. Aconicarmisulfonine a, a Sulfonated C_{20}-diterpenoid alkaloid from the Lateral roots of *Aconitum carmichaelii*. *Organic Letters* **2018**, 816-819.
106. Alexandre-Moreira, M.S.; Jr, V.C.; Al, P.D.M.; Bolzani, V.S.; Barreiro, E.J. Antinociceptive profile of (-)-spectaline: a piperidine alkaloid from *Cassia leptophylla*. *Planta Medica* **2003**, *69*, 795-799.
107. Jr, V.C.; Alexandremoreira, M.S.; Fraga, C.A.; Barreiro, E.J.; Bolzani, V.S.; de Miranda, A.L. Antinociceptive profile of 2,3,6-trisubstituted piperidine alkaloids: 3-O-acetyl-spectaline and semi-synthetic derivatives of (-)-spectaline. *Chemical &*

Pharmaceutical Bulletin **2008**, *56*, 407-412.
108. Li, Q.; Yang, K.X.; Zhao, Y.L.; Qin, X.J.; Yang, X.W.; Liu, L.; Liu, Y.P.; Luo, X.D. Potent anti-inflammatory and analgesic steroidal alkaloids from *Veratrum taliense*. *Journal of Ethnopharmacology* **2015**, *179*, 274-279.
109. Fazal-ur-Rehman; Khan, M.F.; Khan, I.; Shareef, H.; Marwat, S.K. Analgesic activity of carbazole alkaloid from *Murraya paniculata* Linn. (Rutaceae). *World Applied Sciences Journal* **2014**.
110. Rauf, A.; Khan, R.; Raza, M.; Khan, H.; Pervez, S.; De, F.V.; Maione, F.; Mascolo, N. Suppression of inflammatory response by chrysin, a flavone isolated from *Potentilla evestita* Th. Wolf. *In silico* predictive study on its mechanistic effect. *Fitoterapia* **2015**, *103*, 129-135.
111. Jeong, J.H.; Moon, S.J.; Jhun, J.Y.; Yang, E.J.; Cho, M.L.; Min, J.K. Eupatilin exerts antinociceptive and chondroprotective properties in a rat model of osteoarthritis by downregulating oxidative damage and catabolic activity in chondrocytes. *Plos One* **2015**, *10*, e0130882.
112. Rauf, A.; Khan, R.; Khan, H.; Ullah, B.; Pervez, S. Antipyretic and antinociceptive potential of extract/fractions of *Potentilla evestita* and its isolated compound, acacetin. *Bmc Complementary & Alternative Medicine* **2014**, *14*, 448.
113. Raafat, K.; Ellakany, A. Acute and subchronic in-vivo effects of *Ferula hermonis* L. and sambucus nigra L. and their potential active isolates in a diabetic mouse model of neuropathic pain. *Bmc Complementary & Alternative Medicine* **2015**, *15*, 1-14.
114. Parveen, Z.; Deng, Y.; Saeed, M.K.; Dai, R.; Ahamad, W.; Yu, Y.H. Antiinflammatory and analgesic activities of *Thesium chinense* Turcz extracts and its major flavonoids, kaempferol and kaempferol-3-O-glucoside. *Yakugaku Zasshi-journal of the Pharmaceutical Society of Japan* **2007**, *127*, 1275-1279.
115. Ali, M.; Khan, S.A.; Rauf, A.; Khan, H.; Shah, M.R.; Ahmad, M.; Mubarak, M.S.; Hadda, T.B. Characterization and antinociceptive activity (in vivo) of kempferol-3, 4′-di-O-α-L-rhamnopyranoside isolated from *Dryopteris cycadina*. *Medicinal Chemistry Research* **2015**, *24*, 3218-3229.
116. Meotti, F.C.; Luiz, A.P.; Pizzolatti, M.G.; Kassuya, C.A.; Calixto, J.B.; Santos, A.R. Analysis of the antinociceptive effect of the flavonoid myricitrin: evidence for a role of the L-arginine-nitric oxide and protein kinase C pathways. *Journal of Pharmacology & Experimental Therapeutics* **2006**, *316*, 789-796.
117. Chandra, M.; Prakash, O.; Kumar, R.; Bachheti, R.K.; Bhushan, B.; Kumar, M.; Pant, A.K. β-Selinene-rich essential oils from the parts of *Callicarpa macrophylla* and their antioxidant and pharmacological activities. *Medicines* **2017**, *4*, 52.
118. Masoumiardakani, Y.; Mandegary, A.; Esmaeilpour, K.; Najafipour, H.; Sharififar, F.; Pakravanan, M.; Ghazvini, H. Chemical composition, anticonvulsant activity, and toxicity of essential oil and methanolic extract of *elettaria cardamomum*. *Planta Medica* **2016**, *82*, 1482-1486.
119. La Rocca, V.; Fonsêca, D.V.D.; Silva-Alves, K.S.; Santos, P.L. Geraniol induces antinociceptive effect in mice evaluated in behavioural and electrophysiological models. *Basic & Clinical Pharmacology & Toxicology* **2016**, *120*.
120. Young, H.Y.; Luo, Y.L.; Cheng, H.Y.; Hsieh, W.C.; Liao, J.C.; Peng, W.H. Analgesic and anti-inflammatory activities of [6]-gingerol. *Journal of Ethnopharmacology* **2005**, *96*, 207-210.
121. Choi, J.; Shin, K.M.; Park, H.J.; Jung, H.J.; Kim, H.J.; Lee, Y.S.; Rew, J.H.; Lee, K.T. Anti-inflammatory and antinociceptive effects of sinapyl alcohol and its glucoside syringin. *Planta Medica* **2004**, *70*, 1027-1032.
122. Liao, J.C.; Deng, J.S.; Lin, Y.C.; Lee, C.Y.; Lee, M.M.; Hou, W.C.; Huang, S.S.; Huang, G.J. Antioxidant, antinociceptive, and anti-inflammatory activities from *Actinidia callosa* var. callosa in vitro and in vivo. *Evid Based Complement Alternat Med* **2012**, *2012*, 1325-1325.
123. Chen, Y.F.; Tsai, H.Y.; Wu, T.S. Anti-inflammatory and analgesic activities from roots of *Angelica pubescens*. *Planta Medica* **1995**, *61*, 2.
124. Ye, H.; Xiong, X.; Qiu, W.; Wang, Z.; Xiao, H.; He, W.; Liu, J.; Zeng, J. Analgesic effect of daphnetin in mice with pain due to acetic acid, hot board and electric stimulation.*Chinese Journal of Clinical Rehabilitation* **2005**, *9*, 174-176.
125. Choi, S.S.; Han, K.J.; Lee, J.K.; Lee, H.K.; Han, E.J.; Kim, D.H.; Suh, H.W. Antinociceptive mechanisms of orally administered decursinol in the mouse. *Life Sciences* **2003**, *73*, 471-485.
126. Wu, L.; Li, P.; Wang, X.; Zhuang, Z.; Farzaneh, F.; Xu, R. Evaluation of anti-inflammatory and antinociceptive activities of *Murraya exotica*. *Pharm Biol* **2010**, *48*, 1344-1353.
127. Li, R.; Zhao, C.; Yao, M.; Song, Y.; Wu, Y.; Wen, A. Analgesic effect of coumarins from Radix angelicae pubescentis is mediated by inflammatory factors and TRPV1 in a spared nerve injury model of neuropathic pain. *Journal of Ethnopharmacology* **2016**, *195*, 81-88.
128. Chang, T.N.; Deng, J.S.; Chang, Y.C.; Lee, C.Y.; Liao, J.C.; Lee, M.M.; Peng, W.H.; Huang, S.S.; Huang, G.J. Ameliorative effects of scopoletin from *Crossostephium chinensis* against inflammation pain and its mechanisms in mice. *Evidence-Based Complementray and Alternative Medicine,2012,(2012-9-6)* **2012**, *2012*, 595603.
129. Mahendran, S.; Badami, S.; Ravi, S.; Thippeswamy, B.S.; Veerapur, V.P. Synthesis and evaluation of

analgesic and anti-inflammatory activities of most active free radical scavenging derivatives of embelin-a structure-activity relationship. *Chemical & Pharmaceutical Bulletin* **2011**, *59*, 913-919.

130. Zheng, L; Tan,J.; Tang, X. Analgesic,antipyretic effects and no addictive of Tetrandrine. *Academic Journal of Second Military Medical University* **1984**.
131. Küpeli, E.; Koşar, M.; Yeşilada, E.; Hüsnü, K.; Başer, C. A comparative study on the anti-inflammatory, antinociceptive and antipyretic effects of isoquinoline alkaloids from the roots of Turkish *berberis* species. *Life Sciences* **2002**, *72*, 645.
132. Zhao, H.; Luo, F.; Li, H.; Zhang, L.; Yi, Y.; Wan, J. Antinociceptive effect of tetrandrine on LPS-induced hyperalgesia via the inhibition of IKKβ phosphorylation and the COX-2/PGE_2 pathway in mice. *Plos One* **2014**, *9*, e94586.
133. Zhang, M. Pharmacological effects of sinomenine. *Shaanxi Medical Journal* **1981**.
134. Zhu, Q.; Sun, Y.; Mao, L.; Liu, C.; Jiang, B.; Zhang, W.; Li, J.X. Antinociceptive effects of sinomenine in a rat model of postoperative pain. *British Journal of Pharmacology* **2016**, *173*, 1693.
135. Gao, T.; Hao, J.; Wiesenfeld-Hallin, Z.; Wang, D.Q.; Xu, X.J. Analgesic effect of sinomenine in rodents after inflammation and nerve injury. *European Journal of Pharmacology* **2013**, *721*, 5-11.
136. Kang, D.W.; Moon, J.Y.; Choi, J.G.; Kang, S.Y.; Ryu, Y.; Jin, B.P.; Lee, J.H.; Kim, H.W. Antinociceptive profile of levo-tetrahydropalmatine in acute and chronic pain mice models: role of spinal sigma-1 receptor. *Sci Rep* **2016**, *6*, 37850.
137. Cao, F.L.; Shang, G.W.; Wang, Y.; Yang, F.; Li, C.L.; Chen, J. Antinociceptive effects of intragastric DL-tetrahydropalmatine on visceral and somatic persistent nociception and pain hypersensitivity in rats. *Pharmacology Biochemistry & Behavior* **2011**, *100*, 199.
138. Tan, J.; Qiu, C.; Zheng, L. Analgesic effect and no tolerance of gelsemide, *Pharmacology and Clinics of Chinese Materia Medica* **1988**.
139. Xu, Y.; Qiu, H.Q.; Liu, H.; Liu, M.; Huang, Z.Y.; Yang, J.; Su, Y.P.; Yu, C.X. Effects of koumine, an alkaloid of Gelsemium elegans Benth., on inflammatory and neuropathic pain models and possible mechanism with allopregnanolone. *Pharmacology Biochemistry & Behavior* **2012**, *101*, 504-514.
140. Ling, Q.; Liu, M.; Wu, M.X.; Xu, Y.; Yang, J.; Huang, H. H.; Yu, C.X. Anti-allodynic and neuroprotective effects of koumine, a benth alkaloid, in a rat model of diabetic neuropathy. *Biological & Pharmaceutical Bulletin* **2014**, *37*, 858-864.
141. Okuyama, E.; Gao, L.H.; Yamazaki, M. Analgesic components from bornean medicinal plants, *Tabernaemontana pauciflora* blume and *Tabernaemontana pandacaqui* poir. *Chemical & Pharmaceutical Bulletin* **1992**, *40*, 2075-2079.
142. Matsuda, H.; Wu, J.X.; Tanaka, T.; Iinuma, M.; Kubo, M. Antinociceptive activities of 70% methanol extract of evodiae fructus (fruit of *Evodia rutaecarpa* var. *bodinieri*) and its alkaloidal components. *Biological & Pharmaceutical Bulletin* **1997**, *20*, 243-248.
143. Zhao, D.; Shi, Y.; Zhu, X.; Liu, L.; Ji, P.; Long, C.; Shen, Y.; Kennelly, E.J. Identification of potential biomarkers from *Aconitum carmichaelii*, a traditional chinese medicine, using a metabolomic approach. *Planta Medica* **2017**.
144. Suzuki, Y.; Oyama, T.; Ishige, A.; Isono, T.; Asami, A.; Ikeda, Y.; Noguchi, M.; Omiya, Y. Antinociceptive mechanism of the aconitine alkaloids mesaconitine and benzoylmesaconine. *Planta Medica* **1994**, *60*, 391-394.
145. Oyama, T.; Isono, T.; Suzuki, Y.; Hayakawa, Y. Anti-nociceptive effects of aconiti tuber and its alkaloids. *American Journal of Chinese Medicine* **1994**, *22*, 175-182.
146. Nesterova, Y.V.; Povet'Yeva, T.N.; Suslov, N.I.; Zyuz'Kov, G.N.; Pushkarskii, S.V.; Aksinenko, S.G.; Schultz, E.E.; Kravtsova, S.S.; Krapivin, A.V. Analgesic activity of diterpene alkaloids from *Aconitum Baikalensis*. *Bulletin of Experimental Biology & Medicine* **2014**, *157*, 488-491.
147. Lin, Z.; Cai, W.; Tang, X. Anti-inflammatory and analgesic effects of yunaeonitine. *Chinese Journal of Pharmacology and Toxicology* **1987**.
148. Gutser, U.T.; Friese, J.; Heubach, J.F.; Matthiesen, T.; Selve, N.; Wilffert, B.; Gleitz, J. Mode of antinociceptive and toxic action of alkaloids of *Aconitum* spec. *Naunyn-Schmiedeberg's Archives of Pharmacology* **1997**, *357*, 39-48.
149. Ono, M.; Satoh, T. Pharmacological studies of lappaconitine. Analgesia produced by intracerebroventricular, intracisternal and intrathecal injections. *Journal of pharmacobio-dynamics* **1990**, *13*, 374.
150. Bello Ramirez, A.M.; Nava Ocampo, A. A. A QSAR analysis of toxicity of *Aconitum* alkaloids. *Fundamental & Clinical Pharmacology* **2004**, *18*, 699-704.
151. Zhu, L.; Wu, J.; Zhao, M.; Song, W.; Qi, X.; Wang, Y.; Lu, L.; Liu, Z. Mdr1a plays a crucial role in regulating the analgesic effect and toxicity of aconitine by altering its pharmacokinetic characteristics. *Toxicology & Applied Pharmacology* **2017**, *320*, 32-39.
152. Haiyan, W.; Yuxiang, L.; Linglu, D.; Tingting, X.; Yinju, H.; Hongyan, L.; Lin, M.; Yuanxu, J.; Yanrong, W.; Jianqiang, Y. Antinociceptive effects of matrine on neuropathic pain induced by chronic constriction injury. *Pharmaceutical Biology* **2013**, *51*, 844-850.
153. Linglu, D.; Yuxiang, L.; Yaqiong, X.; Ru, Z.; Lin, M.; Shaoju, J.; Juan, D.; Tao, S.; Jianqiang, Y.

Antinociceptive effect of matrine on vincristine-induced neuropathic pain model in mice. *Neurological Sciences Official Journal of the Italian Neurological Society & of the Italian Society of Clinical Neurophysiology* **2014**, *35*, 815-821.
154. Kamei, J.; Xiao, P.; Ohsawa, M.; Kubo, H.; Higashiyama, K.; Takahashi, H.; Li, J.; Nagase, H.; Ohmiya, S. Antinociceptive effects of (+)-matrine in mice. *European Journal of Pharmacology* **1997**, *337*, 223-226.
155. Menéndez, L.; Lastra, A.; Hidalgo, A.N.; Baamonde, A. The analgesic effect induced by capsaicin is enhanced in inflammatory states. *Life Sciences* **2004**, *74*, 3235-3244.
156. Ma, X.L.; Zhang, F.X.; Dong, F.; Bao, L.; Zhang, X. Experimental evidence for alleviating nociceptive hypersensitivity by single application of capsaicin. *Molecular Pain* **2015**, *11*, 22.
157. Chang, Z.Q.; Wang, S.L.; Hao, C.Y.; Liu, F.; Bian, C.F.; Chen, J.M. Analgesic, antispastic and sedative effects of skimmianine. *Zhongguo Yao Li Xue Bao* **1982**, *3*, 163-165.
158. Viswanathan, S.; Sambantham, P.T.; Reddy, K.; Kameswaran, L. Gossypin-induced analgesia in mice. *Eur J Pharmacol* **1984**, *98*, 289-291.
159. Déciga-Campos, M.; Mata, R.; Rivero-Cruz, I. Antinociceptive pharmacological profile of *Dysphania graveolens* in mouse. *Biomedicine & pharmacotherapy* **2017**, *89*, 933.
160. Velázquez-González, C.; Cariño-Cortés, R.; Lucio, J.A.G.D.; Ortiz, M.I.; Arciniega, M.D.L.O.; Altamirano-Báez, D.A.; Jiménez-Ángeles, L.; Bautista-Ávila, M. Antinociceptive and anti-inflammatory activities of *Geranium bellum* and its isolated compounds. *Bmc Complementary & Alternative Medicine* **2014**, *14*, 506.
161. Kaur, R.; Singh, D.; Chopra, K. Participation of alpha2 receptors in the antinociceptive activity of quercetin. *Journal of Medicinal Food* **2005**, *8*, 529.
162. Calixtocampos, C.; Corrêa, M.P.; Carvalho, T.T.; Zarpelon, A.C.; Hohmann, M.S.N.; Rossaneis, A.C.; Coelhosilva, L.; Pavanelli, W.R.; Pingefilho, P.; Crespigio, J. Quercetin reduces ehrlich tumor-induced cancer pain in mice. *Analytical Cellular Pathology,2015,(2015-8-13)* **2015**, *2015*, 285708.
163. Anjaneyulu, M.; Chopra, K. Quercetin, a bioflavonoid, attenuates thermal hyperalgesia in a mouse model of diabetic neuropathic pain. *Prog Neuropsychopharmacol Biol Psychiatry* **2003**, *27*, 1001-1005.
164. Filho, A.W.; Filho, V.C.; Olinger, L.; de Souza, M.M. Quercetin: further investigation of its antinociceptive properties and mechanisms of action. *Archives of Pharmacal Research* **2008**, *31*, 713-721.
165. Guazelli, C.; Staurengoferrari, L.; Zarpelon, A.C.; Pinhoribeiro, F.A.; Ruizmiyazawa, K.W.; Vicentini, F.; Vignoli, J.A.; Camiliosneto, D.; Georgetti, S.R.; Baracat, M.M. Quercetin attenuates zymosan-induced arthritis in mice. *Biomedicine & pharmacotherapy* **2018**, *102*, 175.
166. Ruiz-Miyazawa, K.W.; Staurengo-Ferrari, L.; Mizokami, S.S.; Domiciano, T.P.; Vicentini, F.T.M.C.; Camilios-Neto, D.; Pavanelli, W.R.; Pinge-Filho, P.; Amaral, F.A.; Teixeira, M.M. Quercetin inhibits gout arthritis in mice: induction of an opioid-dependent regulation of inflammasome. *Inflammopharmacology* **2017**, 1-16.
167. Hernandez-Leon, A.; Fernández-Guasti, A.; González-Trujano, M.E. Rutin antinociception involves opioidergic mechanism and descending modulation of ventrolateral periaqueductal grey matter in rats. *European Journal of Pain* **2016**, *20*, 274.
168. Alonso-Castro, A.J.; Isiordia-Espinoza, M.A.; Aragon-Martinez, O.H. Synergism between naproxen and rutin in a mouse model of visceral pain. *Drug Development Research* **2017**, *78*, 184.
169. Kim, S.H.; Park, J.G.; Sung, G.H.; Yang, S.; Yang, W.S.; Kim, E.; Kim, J.H.; Ha, V.T.; Kim, H.G.; Yi, Y.S. Kaempferol, a dietary flavonoid, ameliorates acute inflammatory and nociceptive symptoms in gastritis, pancreatitis, and abdominal pain. *Molecular Nutrition & Food Research* **2015**, *59*, 1400.
170. Martínez, A.L.; González-Trujano, M.E.; Chávez, M.; Pellicer, F.; Moreno, J.; López-Muñoz, F.J. Hesperidin produces antinociceptive response and synergistic interaction with ketorolac in an arthritic gout-type pain in rats. *Pharmacology Biochemistry & Behavior* **2011**, *97*, 683-689.
171. Carballo-Villalobos, A.I.; González-Trujano, M.E.; Pellicer, F.; López-Muñoz, F.J. Antihyperalgesic effect of hesperidin improves with diosmin in experimental neuropathic pain. *Biomed Res Int* **2016**, *2016*, 8263463.
172. Banafshe, H.R.; Hamidi, G.A.; Noureddini, M.; Mirhashemi, S.M.; Mokhtari, R.; Shoferpour, M. Effect of curcumin on diabetic peripheral neuropathic pain: possible involvement of opioid system. *European Journal of Pharmacology* **2014**, *723*, 202-206.
173. Nurullahoglu, K.E.; Okudan, N.; Belviranli, M.; Oz, M. The comparison of preemptive analgesic effects of curcumin and diclofenac. *Bratisl Lek Listy* **2014**, *115*, 757-760.
174. Sahbaie, P.; Sun, Y.; Liang, D.Y.; Shi, X.Y.; Clark, J.D. Curcumin treatment attenuates pain and enhances functional recovery after incision. *Anesthesia & Analgesia* **2014**, *118*, 1336-1344.
175. Córdova, M.M.; Werner, M.F.D.P.; Silva, M.D.D.; Ruani, A.P.; Pizzolatti, M.G.; Santos, A.R.S. Further antinociceptive effects of myricitrin in chemical models of overt nociception in mice. *Neuroscience Letters* **2011**, *495*, 173-177.
176. Meotti, F.C.; Missau, F.C.; Ferreira, J.; Pizzolatti,

M.G.; Mizuzaki, C.; Nogueira, C.W.; Santos, A.R. Anti-allodynic property of flavonoid myricitrin in models of persistent inflammatory and neuropathic pain in mice. *Biochemical Pharmacology* **2006**, *72*, 1707-1713.

177. Santos, F.A.; Rao, V.S. Antiinflammatory and antinociceptive effects of 1,8-cineole a terpenoid oxide present in many plant essential oils. *Phytotherapy Research Ptr* **2000**, *14*, 240.
178. Almeida, J.R.; Souza, G.R.; Silva, J.C.; Saraiva, S.R.; Quintans, J.S.; Barreto, R.S.; Bonjardim, L.R.; Cavalcanti, S.C.; Jr, Q.L. Borneol, a bicyclic monoterpene alcohol, reduces nociceptive behavior and inflammatory response in mice. *Thescientificworldjournal* **2013**, *2013*, 808460.
179. Jaishree, V.; Badami, S.; Rupesh, K.M.; Tamizhmani, T. Antinociceptive activity of swertiamarin isolated from *Enicostemma axillare*. *Phytomedicine* **2009**, *16*, 227-232.
180. Heesung, C.; Kang, O.H.; Youngseob, L.; Janggi, C.; Youchang, O.; Hyejin, J.; Minsan, K.; Jonghak, K.; Seungil, J.; Dongyeul, K. Inhibition of LPS-induced iNOS, COX-2 and inflammatory mediator expression by paeonol through the mapks inactivation in RAW 264.7 cells. *American Journal of Chinese Medicine* **2009**, *37*, 181.
181. Chou, T.C.; Chang, L.P.; Li, C.Y.; Wong, C.S.; Yang, S.P. The antiinflammatory and analgesic effects of baicalin in carrageenan-evoked thermal hyperalgesia. *British Journal of Pharmacology* **2003**, *139*, 1724-1729.
182. Okuyama, E.; Hasegawa, T.; Matsushita, T.; Fujimoto, H.; Ishibashi, M.; Yamazaki, M. Analgesic components of *Saposhnikovia* root (*Saposhnikovia divaricata*). *Chemical & Pharmaceutical Bulletin* **2001**, *49*, 154-160.
183. Ma, Y.; Li, C.; Li, L.; Zhao, B.; Guo, S.; Huo, H. Experimental study on antipyretic, analgesic and anti-inflammatory actions of cinnamaldehyde. *Chinese Journal of Clinical Pharmacology and Therapeutics*，**2006**, *11*, 1336-1339.
184. Okuyama, E.; Nishimura, S.; Ohmori, S.; Ozaki, Y.; Satake, M.; Yamazaki, M. Analgesic component of *Notopterygium incisum* Ting. *Chemical & Pharmaceutical Bulletin* **1993**, *41*, 926.
185. Barros, T.A.; de Freitas, L.A.; Filho, J.M.; Nunes, X.P.; Giulietti, A.M.; de Souza, G.E.; dos Santos, R.R.; Soares, M.B.; Villarreal, C.F. Antinociceptive and anti-inflammatory properties of 7-hydroxycoumarin in experimental animal models: potential therapeutic for the control of inflammatory chronic pain. *Journal of Pharmacy & Pharmacology* **2010**, *62*, 205-213.
186. Singh, G.; Bhatti, R.; Mannan, R.; Singh, D.; Kesavan, A.; Singh, P. Osthole ameliorates neurogenic and inflammatory hyperalgesia by modulation of iNOS, COX-2, and inflammatory cytokines in mice. **2018**.
187. Shakya, A.; Singh, G.K.; Chatterjee, S.S.; Kumar, V. Role of fumaric acid in anti-inflammatory and analgesic activities of a *Fumaria indica* extracts. *Journal of Intercultural Ethnopharmacology* **2014**, *3*, 173-178.
188. Jung, H.J.; Park, H.J.; Kim, R.G.; Shin, K.M.; Ha, J.; Choi, J.W.; Kim, H.J.; Lee, Y.S.; Lee, K.T. In vivo anti-inflammatory and antinociceptive effects of liriodendrin isolated from the stem bark of *Acanthopanax senticosus*. *Planta Med* **2003**, *69*, 610-616.

Table 1 Compounds with analgesic activity isolated from TCM

No.	Compounds	CAS	Molecular formula	Sources[1]	Latin name[2]	Family	Medical Part[3]	Ref
	Alkaloids							
1	Trilobine	6138-73-4	$C_{35}H_{34}N_2O_5$	Baiyaozi	*Stephania cepharantha*	Menispermaceae	Root tubers	[81]
				Mufangji	*Cocculus orbiculatus*	Menispermaceae	Roots	[81
2	Palmatine	3486-67-7	$C_{21}H_{22}NO_4^+$	Banruitangsongcao	*Thalictrum petaloideum*	Ranunculaceae	Roost and rhizomes	[91]
				Yanguocao	*Thalictrum minus*	Ranunculaceae	Roots and rhizomes	[91]
				Huangbai	*Phellodendron amurense*	Rutaceae	Barks	[91]
				Huanglian	*Coptis chinensis*	Ranunculaceae	Rhizomes	[91]
				Haisongzi	*Pinus koraiensis*	Pinaceae	Seeds	[91]
				Maweilian	*Thalictrum foliolosum*	Ranunculaceae	Roots and rhizomes	[91]
				Shidagonglaogen	*Mahonia japonica*	Berberidaceae	Roots	[91]
				Shidagonglaoye	*Mahonia fortune*	Berberidaceae	leaves	[91]
				Xiatianwu	*Corydalis decumbens*	Papaveraceae	Tubers	[91]
				Xiaobo	*Berberis silvataroucan*	Berberidaceae	Roots/stems/branches	[91]
				Huanglian	*Coptis teetoides*	Ranunculaceae	Rhizomes	[91]
				Yanhusuo	*Corydalis yanhusuo*	Papaveraceae	Tubers	[91]
				Alishanshidagonglao	*Mahonia oiwakensis*	Berberidaceae	Stems	[-92]
				Qingniudan	*Tinospora sagittata*	Berberidaceae	Roots	[93]
3	Tetrandrine	2086-83-1	$C_{20}H_{18}N_2O_4^+$	Baiyaozi	*Stephania cepharantha*	Menispermaceae	Root tubers	[91]
				Bianfugegen	*Menispermum*	Menispermaceae	Rhizomes	[-91]
				Fenfangji	*Stephania tetrandra*	Menispermaceae	Tubers	[-91]
				Yinbuhuan	*Cyclea barbata*	Menispermaceae	Roots and stems	[-91]
				Hangfangji	*Aristolochia heterophylla*	Menispermaceae	Tubers	[-91]
				Qingmuxiang	*Aristolochia debilis*	Aristolochiaceae	Roots	[-91]
4	Berberine	2086-83-1	$C_{20}H_{18}N_2O_4^+$	Baiqucai	*Chelidonium majus*	Papaveraceae	Whole grass	[94]
				Baiyaozi	*Stephania cepharantha*	Menispermaceae	Root tubers	[-94]

				Banruitangsongcao	*Thalictrum petaloideum*	Ranunculaceae	Roots and rhizomes	[-94]
				Huangbai	*Phellodendron amurense*	Rutaceae	Barks	[-94]
				Huanglian	*Coptis chinensis*	Ranunculaceae	Rhizomes	[-94]
				Maweilian	*Thalictrum foliolosum*	Ranunculaceae	Roots and rhizomes	[94]
				Yanguocao	*Thalictrum minus*	Ranunculaceae	Roots and rhizomes	[94]
				Yanhusuo	*Corydalis yanhusuo*	Papaveraceae	Tubers	[-94]
				Kuoyeshidagonglao	*Mahonia bealei*	Berberidaceae	Roots	[-94]
				Huananshidagonglao	*Mahonia japonica*	Berberidaceae	Roots	[-94]
5	Rhoifoline A		$C_{20}H_{13}NO_5$	Liangmianzhen	*Zanthoxylum nitidum*	Rutaceae	Roots/Root barks	[41]
6	Dicentrine	517-66-8	$C_{20}H_{21}NO_4$	Wugenteng	*Cassytha filiformis*	Lauraceae	Whole grass	[-95]
				Heikenan	*Lindera megaphylla*	Lauraceae	Roots/barks/branches	[96]
7	Govaniadine		$C_{24}H_{37}NO_6$	Kumanghuangjin	*Corydalis govaniana*	Papaveraceae	Whole grass	[19]
8	Sinomenine	115-53-7	$C_{19}H_{23}NO_4$	Bianfugegen	*Menispermum dauricum*	Menispermaceae	Rhizomes	[-94]
				Qingfengteng	*Sinomenium aeutum*	Menispermaceae	Stems	[-94]
9	Tetrahydropalmatine	2934-97-6	$C_{21}H_{25}NO_4$	Yanhusuo	*Corydalis yanhusuo*	Papaveraceae	Tubers	[-81]
				Xiatianwu	*Corydalis decumbens*	Papaveraceae	Tubers	[81]
				Juhuahuanglian	*Corydalis pallida*	Papaveraceae	Roots	[81]
				-	-	-	-	-
				Chibanyanhusuo	*Corydalis remota*	Papaveraceae	Tubers	[-91]
10	Gelsemine	509-15-9	$C_{20}H_{22}N_2O_2$	Gouwen	*Gelsemium elegans*	Loganiaceae	Whole plant	[-52]
11	Coronaridine	2752-64-9	$C_{33}H_{45}NO_{11}$	Changchunhua	*Catharanthus roseus*	Apocynaceae	Whole grass	[-81]
				Gouyahua	*Ervatamia divaricata*	Apocynaceae	Roots and leaves	[-81]
12	Rutaecarpine	84-26-4	$C_{18}H_{13}N_3O$	Wuzhuyu	*Evodia rutaecarpa*	Rutaceae	Immature fruits	[-81]
				Shihu	*Evodia rutaecarpa*	Rutaceae	Immature fruits	[81]
13	Mitragynine	4098-40-2	$C_{23}H_{30}N_2O_4$	Meilimaozhumu	*Mitragyna speciosa*	Rubiaceae	Leaves	[-98]
14	Harmine	442-51-3	$C_{13}H_{12}N_2O$	Luotuopeng	*Peganum harmala*	Zygophyllaceae	Whole grass	[-99]
15	(3*S*,4*S*,15*S*,20*R*)-		$C_{19}H_{24}N_2O_2$	Niuyanmaqian	*Strychnos angustiflora*	Loganiaceae	Seeds	[-100]

	antirhine N_4-oxide							
16	21-*O*-syringoylantirhne		$C_{28}H_{32}N_2O_5$	Niuyanmaqian	*Strychnos angustiflora*	Loganiaceae	Seeds	[100]
17	Alangine		$C_{19}H_{27}NO_2$	Niuyanmaqian	*Strychnos angustiflora*	Loganiaceae	Seeds	[-100]
18	Antirhine	16049-28-8	$C_{19}H_{24}N_2O$	Niuyanmaqian	*Strychnos angustiflora*	Loganiaceae	Seeds	[-100]
19	Harmane	486-84-0	$C_{12}H_{10}N_2$	Luotuopeng	*Peganum harmala*	Zygophyllaceae	Whole grass	[-99]
20	Norharmane	244-63-3	$C_{11}H_8N_2$	Luotuopeng	*Peganum harmala*	Zygophyllaceae	Whole grass	[-99]
21	Mesaconitine	70578-24-4	$C_{35}H_{49}NO_{11}$	Fuzi	*Aconitum carmichaeli*	Ranunculaceae	Daughter roots	[-81]
				Beiwutou	*Aconitum kusnezoffii*	Ranunculaceae	Root tubers	[-94]
				Wutou	*Aconitum carmichaeli*	Ranunculaceae	Root tubers	[-94]
22	Yunaconitine	518-34-3	$C_{38}H_{42}N_2O_6$	Beiwutou	*Aconitum kusnezoffii*	Ranunculaceae	Root tubers	[101]
				Dianxiwutou	*Aconitum bulleyanum*	Ranunculaceae	Roots	[101]
				Dongchuanwutou	*Aconitum geniculatum*	Ranunculaceae	Root tubers	[101]
				Huangcaowu	*Aconitum vilmorinianum*	Ranunculaceae	Root tubers	[102]
23	Lappaconitine	32854-75-4	$C_{32}H_{44}N_2O_8$	Ganwanwutou	*Aconitum finetianum*	Ranunculaceae	Tubers	[81]
				Gaowutou	*Aconitum sinomontanum*	Ranunculaceae	Roots	[81]
				Niubian	*Aconitum barbatum*	Ranunculaceae	Roots	[81]
24	Bullatine A	1354-84-3	$C_{22}H_{33}NO_2$	Xueshangyizhihao	*Aconitum brachypodum*	Ranunculaceae	Roots	[24]
25	Aconitine	302-27-2	$C_{34}H_{47}NO_{11}$	Wutou	*Aconitum carmichaeli*	Ranunculaceae	Root tubers	[-81]
				Beiwutou	*Aconitum kusnezoffii*	Ranunculaceae	Root tubers	[-81]
				Fuzi	*Aconitum carmichaeli*	Ranunculaceae	Roots	[-81]
				Xueshangyizhihao	*Aconitum brachypodum*	Ranunculaceae	Roots	[-81]
26	Guiwuline	1358-76-5	$C_{20}H_{22}N_2O$	Wutou	*Aconitum carmichaeli*	Ranunculaceae	Root tubers	[103]
27	Incarvillateine	129748-10-3	$C_{42}H_{58}N_2O_8$	Jiaohao	*Incarvillea sinensis*	Bignoniaceae	Aerial part	[-64]
28	8-*O*-ethylaconosine		$C_{24}H_{39}NO_4$	Weixiwutou	*Aconitum weixiense*	Ranunculaceae	Roots	[104]
29	Aconicarmisulfonine A		$C_{22}H_{29}NO_6S$	Wutou	*Aconitum carmichaelii*	Ranunculaceae	Roots	[-105]
30	Oxymatrine	6837-52-8	$C_{15}H_{24}N_2O_2$	Baicihua	*Sophora davidii*	Leguminosae	Flowers	[-81]
				Kudouzi	*Sophora alopecuroides*	Leguminosae	Seeds	[-81]
				Kushen	*Sophora flavescens*	Leguminosae	Roots	[=81]

				Shashenhuai	*Sophora moorcroftiana*	Leguminosae	Seeds	[-81]
				Shandougen	*Sophora subprostrata*	Leguminosae	Roots	[-81]
31	(-)-Spectaline	96614-54-9	$C_{20}H_{39}NO_2$	Xiayejueming	*Cassia leptophylla*	Leguminosae	Flowers	[-106]
				Meilijueming	*Cassia spectabilis*	Leguminosae	Seeds	[107]
32	Huperzine A	102518-79-6	$C_{15}H_{18}N_2O$	Shezushisha	*Huperzia serrata*	Huperziaceae	Whole grass	[27]
33	Matrine	519-02-8	$C_{15}H_{24}N_2O$	Baicihua	*Sophora davidii*	Leguminosae	Flowers	[-81]
				Kudouzi	*Sophora alopecuroides*	Leguminosae	Seeds	[81]
				Kushen	*Sophora flavescens*	Leguminosae	Roots	[81]
				Shandougen	*Sophora subprostrata*	Leguminosae	Roots	[81]
34	Capsaicin	404-86-4	$C_{18}H_{27}NO_3$	Lajiao	*Capsicum annuum*	Solanaceae	Fruits	[91]
35	Scotanamine B		$C_{26}H_{37}N_3O_7$	Shanlangdanag	*Scopolia tangutica*	Solanaceae	Roots	[20]
36	Skimmianine	83-95-4	$C_{14}H_{13}NO_4$	Baixianpi	*Dictamnus dasycarpus*	Rutaceae	Root barks	[91]
				Choucao	*Ruta guaveolens*	Rutaceae	Whole grass	[91]
				Feilongzhangxue	*Toddalia asiatica*	Rutaceae	Roots or root barks	[91]
				Gouju	*Poncirus tuifoliata*	Rutaceae	Young fruits	[91]
				Huajiao	*Zanthoxylum bungeanum*	Rutaceae	Peels	[91]
				Yinyu	*Skimmia reevesiana*	Rutaceae	Stems and leaves	[91]
37	Veratraline A		$C_{30}H_{45}N_2O_2$	Dalililu	*Veratrum taliense*	Liliaceae	Roots and rhizomes	[108]
38	Veratraline B		$C_{27}H_{42}NO_4$	Dalililu	*Veratrum taliense*	Liliaceae	Roots and rhizomes	[=108]
39	Veratraline C		$C_{27}H_{42}NO_4$	Dalililu	*Veratrum taliense*	Liliaceae	Roots and rhizomes	[-108]
40	Isomurrayafoline B	107903-15-1	$C_{19}H_{21}NO_2$	Qianlixiang	*Murraya paniculata*	Rutaceae	Leaves	[109]
Flavonoids								
41	Gossypin	652-78-8	$C_{21}H_{20}O_{13}$	Mopancao	*Abutilon indicum*	Malvaceae	Whole grass	158
42	Hyperin	482-36-0	$C_{21}H_{20}O_{12}$	Biandijin	*Hypericum wightianum*	Guttiferae	Whole grass	[-94]
				Gouteng	*Uncaria rhynchophylla*	Rubiaceae	Branches	[=94]
				Jinsimei	*Hypericum patulum*	Guttiferae	Whole grass	[-94]
				Laoguancao	*Erodium stephanianum*	Geraniaceae	Whole grass	[=94]
				Luxiancao	*Pyrola calliantha*	Pyrolaceae	Whole grass	[-94]

				Manshanhong	*Folium Rhododendri*	Ericaceae	Leaves	[-94]
				Luobuma	*Apocynum venetum*	Apocynaceae	Leaves	[-94]
				Maoyancao	*Euphorbia lunulata*	Euphorbiaceae	Whole grass	[-94]
				Tusizi	*Cuscuta chinensis*	Convolvulaceae	Seeds	[-94]
				Xiakucao	*Prunella vulgaris*	Labiatae	Ear	[-94]
				Xianhecao	*Agrimonia pilosa*	Rosaceae	Aerial part	[-94]
				Yinchenhao	*Artemisia capillaris*	compositae	Aerial part	[-94]
				Yuxingcao	*Houttuynia cordata*	saururaceae	Aerial part	[-94]
				Yuanbaocao	*Hypericum sampsonii*	Guttiferae	Whole grass	[-94]
43	Chrysin	480-40-0	$C_{15}H_{10}O_4$	Tuorongweilingcai	*Potentilla evestita*	Rosaceae	Whole grass	[-110]
				Xifanlian	*Passiflora coerulea*	Passifloraceae	Whole grass	[38]
44	Lycopene	502-65-8	$C_{40}H_{56}$	Fanqie	*Lycopersicon esculentum*	Solanaceae	Fruits	[-86]
45	Eupatilin	22368-21-4	$C_{18}H_{16}O_7$	Aiye	*Artemisia argyi*	Compositae	Leaves	[81]
				Qihao	*Artemisia anomala*	Compositae	Whole grass	[81]
				Kuihao	*Artemisia princeps*	Compositae	Whole grass	[111]
46	Acacetin	480-44-4	$C_{16}H_{12}O_5$	Fengchaocao	*Leucas aspera*	Labiatae	Whole grass	[34]
				Tuorongweilingcao	*Potentilla evestita*	Rosaceae	Whole grass	[112]
47	Ellagic acid	476-66-4	$C_{14}H_6O_8$	Shiliu	*Punica granatum*	Punicaceae	Peels	[88]
				Caomei	*Fragaria × ananassa*	Rosaceae	Fruits	[-88]
48	Quercetin	117-39-5	$C_{15}H_{10}O_7$	Chuanbajiaolian	*Dysosma veitchii*	Berberidaceae	Whole grass	[17]
				Huanghaitang	*Hypericum ascyron*	Guttiferae	Whole grass	[17]
				Huaihua	*Sophora japonica*	Leguminosae	Flowers	[17]
				Huaimi	*Sophora japonica*	Leguminosae	Flower buds	[17]
				Danpi	*Paeonia suffruticosa*	Ranunculaceae	Root bark	[17]
				Juhua	*Dendranthema morifolium*	Compositae	Flowers	[17]
				Tianjihuang	*Hypericum japonicum*	Guttiferae	Whole grass	[17]
				Cheqianzi	*Plantago asiatica*	Plantaginaceae	Seeds	[17]
				Sangjisheng	*Taxillus sutchuenensis*	Loranthaceae	Branch leaves	[17]

				Xianhecao	*Agrimonia pilosa*	Rosaceae	Aerial part	[17]
				Jiaogulan	*Gynostemma pentaphyllum*	Cucurbitaceae	Whole grass	[17]
				Shanzha	*Crataegus pinnatifida*	Rosaceae	Fruits	[17]
				Guanyelianqiao	*Hypericum perforatum*	Guttiferae	Whole grass	[17]
				Tusizi	*Cuscuta chinensis*	Convolvulaceae	Seeds	[17]
				Ciwujia	*Acanthopanax senticosus*	Araliaceae	Root bark	[17]
				Jiguanhua	*Celosia cristata*	Amaranthaceae	Inflorescence	[17]
				Yuxingcao	*Houttuynia cordata*	Saururaceae	Whole grass	[17]
				Yuganzi	*Phyllanthus emblica*	Euphorbiaceae	Fruits	[17]
				Sanbaicao	*Saururus chinensis*	Saururaceae	Aerial part	[17]
				Chuipencao	*Sedum sarmentosum*	Crassulaceae	Whole grass	[17]
49	Rutin	153-18-4	$C_{27}H_{30}O_{16}$	Huaimi	*Sophora japonica*	Leguminosae	Flower buds	[-81]
				Kuqiaomai	*Fagopyrum tataricum*	Polygonaceae	Seeds	[-81]
				Pugongying	*Taraxacum mongolicum*	Compositae	Whole grass	[-81]
50	Kaempferol	520-18-3	$C_{15}H_{10}O_6$	Xiyangjiegumu	*Sambucus nigra*	Caprifoliaceae	Inflorescence	[113]
				Bairuicai	*Thesium chinense*	Santalaceae	Whole grass	[114]
51	Hesperidin methyl chalcone	24292-52-2	$C_{29}H_{36}O_{15}$	Chenzi	*Citrus junos*	Rutaceae	Fruits	[62]
52	Hesperidin	520-26-3	$C_{28}H_{34}O_{15}$	Qingpi	*Citrus reticulate*	Rutaceae	Young fruits or peels	[81]
				Zhishi	*Citrus aura*	Rutaceae	Young fruits	[81]
				Chenzipi	*Citrus junos*	Rutaceae	Peels	[81]
				Chenzi	*Citrus junos*	Rutaceae	Fruits	[81]
				Midiexiang	*Rosmarinus officinalis*	Labiatae	Whole grass	[81]
53	Curcumin	458-37-7	$C_{21}H_{20}O_6$	Jianghuang	*Curcuma longa*	Zingiberaceae	Rhizomes	[81]
				Yujin	*Curcuma wenyujin*	Zingiberaceae	Root tubers	[81]
				Ezhu	*Curcuma aeruginosa*	Zingiberaceae	Rhizomes	[81]

54	Kempferol-3,4′-di-*O*-*α*-L-rhamnopyranoside		$C_{27}H_{30}O_{14}$	Suoluolinmaojue	*Dryopteris cycadina*	Dryopteridaceae	Rhizomes	[115]
55	Myricitrin	17912-87-7	$C_{21}H_{20}O_{12}$	Renxinguo	*Manilkara zapota*	Sapotaceae	Fruits	[116]
				Hongguozi	*Eugenia uniflora*	Myrtaceae	Leaves	[116]
Terpenes								
56	1,8-Cineole	470-82-6	$C_{10}H_{18}O$	Donglingcao	*Rabdosia rubescens*	Labiatae	Whole grass	[94]
				Ganjiang	*Zingiber officinale*	Zingiberaceae	Dryingrhizomes	[94]
				Huajiao	*Zanthoxylum bungeanum*	Rutaceae	Peels	[94]
				Qinghao	*Artemisia annua*	Compositae	Whole grass	[94]
				Shengjiang	*Zingiber officinale*	Zingiberaceae	FreshRhizomes	[94]
				Xixin	*Asarum sieboldii*	Aristolochiaceae	Whole grass	[94]
				Liaoxixin	*Asarum heterotropoides*	Aristolochiaceae	Whole grass	[94]
				Manjingzi	*Vitex trifolia*	Verbenaceae	Fruits	[94]
				Zhizhuxiang	*Valeriana jatamansii*	Valerianaceae	Rhizomes	[94]
				Baidoukou	*Amomun kravanh*	Zingiberaceae	Mature fruits	[94]
				Zhaowabaidoukou	*Amonum compactum*	Zingiberaceae	Mature fruits	[94]
				Yangshicao	*Achillea millefolium*	Compositae	Whole grass	[94]
				Dayezizhu	*Callicarpa macrophylla*	Verbenaceae	Root or leaves	[117]
				Xiaodoukou	*Elettaria cardamomum*	Zingiberaceae	Seeds	[118]
57	*p*-Cymene	99-87-6	$C_{10}H_{14}$	Donglingcao	*Rabdosia rubescens*	Labiatae	Whole grass	[81]
				Dusong	*Juniperus rigida*	Cupressaceae	Branch leavescone	[81]
				Ganjiang	*Zingiber officinale*	Zingiberaceae	Dryingrhizomes	[81]
				Gangsong	*Baeckea frutescens*	Myrtaceae	Branch leaves	[81]
				Duhuo	*Angelica pubescens*	Umbelliferae	Roots	[81]
				Houpu	*Magnolia officinalis*	Magnoliaceae	Barks and roots	[81]
				Xixin	*Asarum sieboldii*	Aristolochiaceae	Whole grass	[81]
				Liaoxixin	*Liaoxixin*	Aristolochiaceae	Whole grass	[81]

				Shengjiang	*Zingiber officinale*	Zingiberaceae	FreshRhizome	[81]
				Yinchenhao	*Artemisia capillaris*	Compositae	Aerial part	[81]
				Wusemei	*Lantana camara*	Verbenaceae	Flowers	[81]
				Kuanyeqianghuo	*Notopterygium forbesii*	Umbelliferae	Root and rhizomes	[81]
				Baishantai	*Ledum palustre*	Ericaceae	Leaves	[81]
				Baidoukou	*Amomun kravanh*	Zingiberaceae	Mature fruits	[81]
				Peilan	*Eupatorium fortune*	Compositae	Aerial part	[81]
				Zhizhuxiang	*Valeriana jatamansii*	Valerianaceae	Rhizomes	[81]
				Zhaowabaidoukou	*Amonum compactum*	Zingiberaceae	Mature fruits	[81]
				Yangshicao	*Achillea millefolium*	Compositae	Whole grass	[81]
58	Menthol	2216-51-5	$C_{10}H_{20}O$	Bohe	Mentha canadaensis	Labiatae	Whole grass or leaves	[81]
59	Paeoniflorin	23180-57-6	$C_{23}H_{28}O_{11}$	Baishao	*PaconialactifloraPall*	Paeoniaceae	Roots	[81]
				Caoshaoyao	*Paeonia obovata*	Paeoniaceae	Roots	[81]
				Meilishaoyao	*Paeonia mairei*	Paeoniaceae	Roots	[81]
				Zhaiyeshaoyao	*Paeonia anomala*	Paeoniaceae	Roots	[81]
				Kuaigenshaoyao	*Paeonia anomala*	Paeoniaceae	Roots	[81]
				Mudanpi	*Paeonia suffruticosa*	Paeoniaceae	Root barks	[81]
60	Borneol	507-70-0	$C_{10}H_8O$	Ainaxiang	*Blumea balsamifera*	Compositae	Whole grass	[81]
				Zhaowabaidoukou	*Amonum compactum*	Zingiberaceae	Mature fruits	[81]
				Gangsong	*Baeckea frutescens*	Myrtaceae	Branch leaves	[81]
				Juhua	*Dendranthema morifolium*	Compositae	Capitulum	[81]
				Midiexiang	*Rosmarinus officinalis*	Labiatae	Whole grass	[81]
				Yangchunsharen	*Amomum villosum*	Zingiberaceae	Seeds	[91]
				Lvkesharen	*Amomum villosum*	Zingiberaceae	Seeds	[91]
				Shabnai	*Kaempferia galangal*	Zingiberaceae	Rhizomes	[91]
				Shengjiang	*Zingiber officinale*	Zingiberaceae	Freshrhizomes	[91]
61	Swertiamarin	17388-39-5	$C_{16}H_{22}O_{10}$	Longdan	*Gentiana scabra*	Gentianaceae	Roots and Rhizomes	[81]
62	Geniposide	24512-63-8	$C_{17}H_{24}O_{10}$	Duzhong	*Eucommia ulmoides*	Eucommiaceae	Barks	[91]

				Zhizi	*Gardenia jasminoides*	Rubiaceae	Fruits	[91]
63	Geraniol	106-24-1	$C_{10}H_{18}O$	Lushaxiangmao	*Cymbopogon martini*	Gramineae	Leaves	[119]
				Yaxiangmao	*Cymbopogon nardus*	Gramineae	Leaves	[119]
				Fengmao	*Cymbopogon winterianus*	Gramineae	Stems and leaves	[119]
				Xiangyetianzhukui	*Pelargonium graveolens*	Geraniaceae	Leaves	[119]
64	[6]-Gingerol	23513-14-6	$C_{17}H_{26}O_4$	Shengjiang	*Zingiber officinale*	Zingiberaceae	Freshrhizomes	[=120]
65	Myrtenol			Juhao	*Tanacetum vulgare*	Compositae	Aerial part	[-78]
Aromatic compounds								
66	Paeonol	552-41-0	$C_9H_{10}O_3$	Baishao	*PaconialactifloraPall*	Paeoniaceae	Roots	[81]
				Mudanpi	*Aeonia suffruticosa*	Paeoniaceae	Root barks	[81]
				Xuzchangqing	*Paniculate Swallowwort*	Asclepiadaceae	Roots	[81]
67	Divaricatol		$C_{17}H_{18}O_7$	Fangfeng	*Saposhnikouia diuaricata*	Umbelliferae	Roots	[81]
68	Cinnamaldehyde	104-55-2	C_9H_8O	Guipi	*Cinnamomum japonicum*	Lauraceae	Barks	[81]
				Guizhi	*Cinnamomum cassia Presl*	Lauraceae	Shoots	[81]
				Moyao	*Commiphora myrrha*	Burseraceae	Resin	[81]
				Rougui	*Cinnamomum cassia*	Lauraceae	Barks	[81]
69	Sinapyl alcohol	537-33-7	$C_{11}H_{14}O_4$	Tiannvmulan	*Magnolia sieboldii*	Magnoliaceae	Stem barks	[121]
70	Caffeic acid	501-16-6	$C_9H_8O_4$	Bianxu	*Polygonum aviculare*	Polygonaceae	Whole grass	[81]
				Bohe	*Mentha canadaensis*	Labiatae	Whole grass or leaves	[81]
				Chuanxiong	*Ligusticum chuanxiong*	Umbelliferae	Rhizomes	[81]
				Danshen	*Slauia miltiorrhiza*	Labiatae	Roots	[81]
				Huanghemaorendong	*Lonicera fuluotomentosa*	Caprifoliaceae	Flower bud	[81]
				Mutianliao	*Actinidia polygama*	Actinidiaceae	Branch leaves	[81]
				Ningmeng	*Citrus limonia*	Rutaceae	Fruits	[81]
				Pugongying	*Taraxacum mongolicum*	Compositae	Whole grass	[81]
				Yinchenhao	*Artemisia capillaris*	Compositae	Seedling	[81]
				Zhizhuxiang	*Valeriana jatamansii*	Valerianaceae	Rhizomes	[81]
				Xiakucao	*Prunella vulgaris*	Labiatae	Ear	[85]

				Yinchimihoutao	*Actinidia callosa*	Actinidiaceae	Fruits	[122]
Coumarins								
71	Notopterol	88206-46-6	$C_{21}H_{22}O_5$	Qianghuo	*Notopterygium incisum*	Umbelliferae	Roots and rhizomes	[81]
				Kuanyeqianghuo	*Notopterygium forbesii*	Umbelliferae	Roots and rhizomes	[81]
72	Columbianadin	5058-13-9	$C_{19}H_{20}O_5$	Duhuo	*Angelica biserrata*	Umbelliferae	Roots	[123]
				Shechuangzi	*Cnidium monnieri*	Umbelliferae	Fruits	[123]
73	Daphnetin	486-35-1	$C_9H_6O_4$	Ruixianghua	*Daphne odora*	Thymelaeaceae	Flowers	[81]
				Ruixianggen	*Daphne odora*	Thymelaeaceae	Roots or root barks	[81]
				Jinbianruixiang	*Daphne odora*	Thymelaeaceae	Whole plant	[124]
74	Decursinol	23458-02-8	$C_{14}H_{14}O_4$	Chaoxiandanggui	*Angelica gigas* Nakai	Umbelliferae	Roots	[125]
75	7-Hydroxycoumarin	93-35-6	$C_9H_6O_3$	Jiulixiang	*Murraya exotica*	Rutaceae	Stems and leaves	[126]
76	Osthole	484-12-8	$C_{15}H_{16}O_3$	Shechuangzi	*Cnidium monnieri*	Umbelliferae	Fruits	[50]
				Duhuo	*Angelicae pubescentis*	Umbelliferae	Roots	[127]
				Changchunqi	*Libanotis buchtormensis*	Umbelliferae	Roots	[81]
77	Albiflorin	39011-90-0	$C_{23}H_{28}O_{11}$	Baishao	*PaconialactifloraPall*	Paeoniaceae	Roots	[77]
				Chishao	*Paeonia veitchii Lynch*	Paeoniaceae	Roots	[77]
78	Scopoletin	92-61-5	$C_{10}H_8O_4$	Yuanzhuihuayuanzhi	*Polygala paniculata*	Polygalaceae	Whole grass	[128]
Aliphaticnaturalproducts								
79	Fumaric acid	110-17-8	$C_4H_4O_4$	Yanhusuo	*Corydalis yanhusuo*	Papaveraceae	Tubers	[91]
80	Embelin	550-24-3	$C_{17}H_{26}O_4$	Maguihua	*Embelia oblongifolia*	Myrsinaceae	Fruits	[91]
				Zhushagen	*Ardisia crenata*	Myrsinaceae	Roots	[91]
				Baihuasuantengguo	*Embelia ribes*	Myrsinaceae	Fruits	[129]
Lignans								
81	Liriodendrin	573-44-4	$C_{34}H_{46}O_{18}$	Ciwujia	*Acanthopanax senticosus*	Araliaceae	Roots/rhizomes/stems/ leaves	[81]
				Duzhong	*Eucommia ulmoides*	Eucommiaceae	Bark	[81]
				Liuchuanyu	*Linaria vulgaris*	Scrophulariaceae	Whole grass	[81]

	Roucongrong	*Cistanche deserticola*	Orobanchaceae	Fleshy stems	[81]

Note:

1: The plants which the compound was isolated from;

2: The Latin name of the corresponding plant;

3: The medical part of the corresponding plant;

Table 2 Experimental studies with positive results carried out on analgesic compounds *in vivo*

No.	Name	Doses	Analgesic effect	Ref
Alkaloids				
1	Trilobine	5/10/20/40 mg/kg i.p	Hot-plate test in mice	[130]
		5/10/20/40 mg/kg i.p	Acetic acid writhing test in mice	[130]
		50/75/100 mg/kg i.p	Radiant heat tail flick test in rats	[130]
2	Palmatine	20/100/200 mg/kg p.o	*p*-Benzoquinone-induced abdominal constriction test in mice	[131]
		14/56 mg/kg i.p	Acetic acid-induced writhing in rats	[93]
3	Tetrandrine	45 mg/kg i.p	Induction of hyperalgesia by LPS in BALB/C mice	[132]
4	Berberine	200 mg/kg p.o	*p*-Benzoquinone-induced abdominal constriction test in mice	[131]
		50 mg/kg p.o	Visceral hypersensitivity in inducted colitis rats	[71]
5	Rhoifoline A	20–80 mg/kg i.p.	Acetic acid-induced writhing in mice	[41]
		10–80 mg/kg i.p.	Formalin test in mice	[41]
		20–80 mg/kg i.p.	Tail-flick test in mice	[41]
		10–80 mg/kg i.p.	Hot-plate test in mice	[41]
6	Dicentrine	0.15g/rat i.c.v	Electrical stimulation in rats	[95]
		100 mg/kg p.o	Mechanical hypersensitivity in CFA-induced inflammatory pain in mice	[59]
		100 mg/kg p.o	Thermal hypersensitivity in CFA-induced inflammatory pain in mice	[59]
		100 mg/kg p.o	Cold-Hot plate test in capsaicin-induced pain in mice	[59]
		100 mg/kg p.o	Cold-Hot plate test in cinnamaldehyde-induced pain in mice	[59]
7	Govaniadine	1.25–5.0 mg/kg i.p	Acetic acid induced writhing in mice	[19]
		2.5/5 mg/kg i.p.	Hot-plate test in mice	[19]
8	Sinomenine	10–40 mg/kg	Von Frey test in CCI rats	[133]
		10–80 mg/kg po/i.p	Von Frey test in postoperative pain model in rats	[133]
		80 mg/kg p.o	Von Frey test in carrageenan induced inflammation pain in mice	[37]
		80 mg/kg p.o	Heat hyperalgesia test in carrageenan induced inflammation pain in mice	[134]

		40/80 mg/kg i.p	Von Frey test in photochemically induced SNI in mice and rats	[135]
		40/80 mg/kg i.p	Von Frey test in photochemically-induced spinal cord injury in rats	[43]
		40 mg/kg i.p	Hot plate test in rats	[43]
		40 mg/kg i.p	Tail flick test in rats	[43]
		50 mg/kg i.p	Formalin test	[43]
9	Tetrahydropalmatine	40/60 mg/kg i.g	Thermal hyperalgesia test in bone cancer pain model in rats	[65]
		40/60 mg/kg i.g	Mechanical allodynia test in bone cancer pain model in rats	[65]
		20/200 nmol i.p	Formalin test in mice	[136]
		20 nmol i.p	Mechanical allodynia test in CCI mice	[136]
		2 nmol i.t	Mechanical allodynia test in CCI mice	[136]
		20 nmol i.p	Mechanical allodynia test in CCI mice	[136]
		2 nmol i.t	Mechanical allodynia test in CCI mice	[136]
		1–4 mg/kg i.p.	Mechanical hyperalgesia test in inflammatory pain model	[32]
		1–4 mg/kg i.p.	Mechanical hyperalgesia test in neuropathic pain model	[32]
		60mg/kg i.g	Acetic acid-induced writhing in rats	[137]
10	Gelsemine	ED_{50}=21.1 μg	Formalin test in rats	[138]
		ED_{50}=0.5 μg	Mechanical allodynia in bone cancer rats	[52]
		ED_{50}=0.5 μg	Mechanical allodynia in PSNL rats	[52]
		ED_{50}=5.85 mg/kg s.c	Acetic acid induced writhing in mice	[139]
		2.0 mg/kg s.c	Formalin test in rats	[139]
		0.8 mg/kg p.o	Thermal threshold test in CFA-induced inflammation pain model	[139]
		0.28 mg/kg, twice/day for 7 days s.c	Thermal/Mechanical test in CCI rats	[139]
		0.28 mg/kg, twice/day for 7 days s.c	Thermal/Mechanical test in L5 SNL ratsThermal/Mechanical test in rat model of	[139]
		8/200 μg i.t	postoperative painMechanical allodynia in diabetic neuropathic pain in rat	[76]
		0.056–7 mg/kg s.c		[140]
11	Coronaridine	10 mg/kg i.p	Acetic acid-induced writhing in mice	[141]
12	Rutaecarpine	100 mg/kg	Acetic acid-induced writhing in mice	[142]
13	Mitragynine	35 mg/kg i.p	Hot-plate test in mice	[98]

14	Harmine	10/15 mg/kg i.p	Hot-plate test in mice	[99]
		2.5/5/10 i.p	Formalin test in rats	[99]
15	(3*S*,4*S*,15*S*,20*R*)- antirhine N_4-oxide	20 mg/kg i.p	Hot-plate test in mice	[100]
16	21-*O*-syringoylantirhine	20 mg/kg i.p	Hot-plate test in mice	[100]
17	Alangine	20 mg/kg i.p	Hot-plate test in mice	[100]
18	Antirhine	20 mg/kg i.p	Hot-plate test in mice	[100]
19	Harmane	5–20 mg/kg i.p	Hot-plate test in mice	[99]
		2.5/5/10 i.p	Formalin test in rats	[99]
20	Norharmane	5–15 mg/kg i.p	Hot-plate test in mice	[99]
		2.5/5/10 mg/kg i.p	Formalin test in rats	[99]
21	Mesaconitine	2 mg/kg p.o	Acetic acid-induced writhing in mice	[143]
		5μg/rat injected into the NRPG/ NRM/PAG	Paw pressure test in rats	[144]
		0.5 mg/kg p.o	Randall-Selitto method in adjuvant arthritis rats	[145]
		0.5 mg/kg p.o	The repeated cold stress in rats	[145]
		60 μg/kg p.o	Tail-flick test in mice	[145]
		0.025 mg/kg i.p	Acetylcholine cramp model	[146]
		0.025 mg/kg i.p	Inflammatory hyperalgesia in outbred rats	[146]
22	Yunaconitine	100 μg/kg s.c	Hot-plate test in mice	[147]
		30 μg/kg s.c	Formalin test in rats	[147]
		0.4 mg/kg p.o	Acetic acid-induced writhing in mice	[102]
23	Lappaconitine	2.5/2.6/3.0mg/kg iv	Formalin test in NMRI mice	[148]
		1,127 μg/mouse i.t.	Tail pinch test in mice	[149]
		2,333 μg/mouse icv	Tail pinch test in mice	[149]
		2,413 μg/mouse i.cist	Tail pinch test in mice	[149]
		644 μg/mouse i.t.	Hot plate test in mice	[149]
		607 μg/mouse icv	Hot plate test in mice	[149]

		532 μg/mouse i.cist	Hot plate test in mice	[149]
		62.5 μg/mouse i.t.	Acetic acid-induced writhing test	[149]
		308 μg/mouse icv	Acetic acid-induced writhing test	[149]
		233 μg/mouse i.cist	Acetic acid-induced writhing test	[149]
24	Bullatine A	3 mg/kg s.c	Mechanical allodynia test in neuropathic model in rats	[24]
		3 mg/kg s.c	Heat hyperalgesia test in neuropathic model in rats	[24]
		3 mg/kg s.c	Mechanical allodynia test in diabetic neuropathic pain in rats	[24]
		3 mg/kg s.c	Heat hyperalgesia test in diabetic neuropathic pain in rats	[24]
		3 mg/kg s.c	Mechanical allodynia test in inflammatory pain model in rats	[24]
		3 mg/kg s.c	Heat hyperalgesia test in inflammatory pain model in rats	[24]
		3 mg/kg s.c	Mechanical allodynia test in bone cancer pain model in rats	[24]
		3 mg/kg s.c	Heat hyperalgesia test in bone cancer pain model in rats	[24]
		ED_{50}: 0.9 mg/kg s.c	Formalin test in mice	[150]
25	Aconitine	0.1 mg/kg p.o	Acetic acid-induced writhing in wild-type and Mdr1a$^{-/-}$ FVB mice	[151]
26	Guiwuline	ED_{50}=15 mg/kg i.g	Hot-plate test	[103]
27	Incarvillateine	10/20 mg/kg i.p	Acetic acid writhing test	[64]
		10/20 mg/kg i.p	Mechanical/thermal sensitivity measurement in SNI mice	[64]
		10/20 mg/kg i.p	Von Frey test in CFA-induced inflammation pain in mice	[64]
		10/20 mg/kg i.p	Mechanical sensitivity test in paclitaxel-induced neuropathic pain model	[64]
		10/20 mg/kg i.p	Thermal sensitivity test in paclitaxel-induced neuropathic pain model	[64]
28	8-O-ethylaconosine	50/100/200 mg p.o	Acetic acid induced writhing in mice	[104]
29	Aconicarmisulfonine A	1.0/0.3/0.1 mg/kg i.p	Acetic acid induced writhing in mice	[105]
30	Oxymatrine	80 mg/kg i.p	Von Frey test in CCI mice	[56]
		80 mg/kg i.p	Thermal hyperalgesia in CCI mice	[56]
		8.75–75 mg/kg i.p	Hot-plate test in mice	[56]
		150 mg/kg ip	Tail immersion test in mice	[56]
		18.75–150 mg/kg ip	Acetic acid-induced writhing in mice	[56]
		75–150 mg/kg	Formalin test in mice	[56]

		1.875–7.5 mg/kg icv	Tail immersion test in mice	[39]
31	(-)-Spectaline	300 μmol/kg p.o	Acetic acid-induced writhing in mice	[106]
		1-100 μmol/kg p.o	Capsaicin-induced pain in mice	[106]
		100 μmol/kg p.o	Acetylcholine-induced abdominal constriction in mice	[107]
32	Huperzine A	110 μg/kg i.p	Hot-plate test in mice	[27]
		ED_{50}=0.57 μg i.t	Formalin test in rats	[27]
		50-500 μg/kg i.t/i.p	Von Frey assay in static compression model in rats	[27]
		0.02/0.075mg/kg i.p	Mechanical allodynia test in rat's common peroneal nerve model	[27]
3	Matrine	30 mg/kg i.p	Von Frey test in CCI mice	[152]
		15/30 mg/kg i.p	Cold-plate test CCI mice	[152]
		15/30 mg/kg i.p	Plantar test in CCI mice	[152]
		15/30/60 mg/kg i.p	Von Frey test in vincristine induced neuropathic pain model in mice	[153]
		15/30 mg/kg i.p	Thermal hyperalgesia test in vincristine induced neuropathic pain in mice	[153]
		15/30 mg/kg i.p	Cold-plate test in vincristine induced neuropathic pain model in mice	[153]
		10/30 mg/kg s.c	Tail-flick tests	[154]
		10/20 mg/kg s.c	Acetic acid-induced writhing tests in mice	[154]
		10/20 mg/kg s.c	Tail-pressure test in mice	[154]
		10/20 mg/kg s.c	Hot-plate test in mice	[154]
		20 mg/kg i.c.v	Hot-plate test in mice	[154]
34	Capsaicin	10 μg i.p	Hot plate test	[155]
		25/50/100 μg Intraplantar injection	Formalin test in mice	[155]
		50/100 μg Intraplantar injection	von Frey test in chronic inflammatory pain model	[156]
		100 μg Intraplantar injection	von Frey test in chronic neuropathic pain model	[156]
35	Scotanamine B	40 mg/kg i.p	Tail-flick test in mice	[20]
36	Skimmianine	98mg/kg p.o	Acetic acid writhing test in mice	[157]
		20mg/kg p.o	Hot-plate test in mice	[157]
37	Veratraline A	0.5 mg/kg i.p	Acetic acid induced writhing in mice	[108]
38	Veratraline B	1.0 mg/kg i.p	Acetic acid induced writhing in mice	[108]

39	Veratraline C	0.5 mg/kg i.p	Acetic acid induced writhing in mice	[108]
40	Isomurrayafoline B	10/20 mg/kg p.o	Hot-plate test in mice	[109]
		10/20 mg/kg p.o	Acetic acid induced writhing in mice	[109]
Flavonoids				
41	Gossypin	12.5–100 mg/kg i.p	Acetic acid-induced writhing in mice	[158]
42	Hyperin	25–150 mg/kg i.p	Tail flick test in mice	[42]
43	Chrysin	2.5/10/20 mg/kg ip	Acetic acid-induced writhing in mice	[110]
		2.5/10/20 mg/kg ip	Formalin test in mice	[110]
		25/50/75/100 mg/kg i.p	Tail immersion test in mice	[38]
		31/100/316 mg/kg	Hot-plate test in mice	[159]
44	Lycopene	1/2/ 4 mg/kg p.o.	Tail immersion test in diabetic neuropathic pain in mice	[74]
		1/2/ 4 mg/kg p.o.	Hot-plate test in in diabetic neuropathic pain in mice	[74]
		10 nmol/5µl i.t	Mechanical hypersensitivity threshold test in PSNL mice	[86]
45	Eupatilin	100 mg/kg p.o	Von Frey test in osteoporotic rats	[111]
46	Acacetin	10/100 mg/kg i.p	Acetic acid-induced writhing in mice	[34]
		10/100 mg/kg i.p	Formalin test in mice	[34]
		56.2 mg/kg i.p	Thermal plantar test in carrageenan-induced pain in mice	[34]
		100/200/1,000 µg i.a	PIFIR test in rats	[34]
47	Ellagic acid	1,000 µmol/kg p.o	Tail-flick test in rats	[88]
		33/100/330/660 µmol/kg i.p	Tail-flick test in rats	[88]
		0.33/1/2µmol/ rat i.c.v.	Tail-flick test in rats	[88]
		1–33 µmol/kg i.p.	Acetic acid-induced writhing test	[89]
		10/30 mg/kg i.p	Formalin test in rats	[160]
		10 mg/kg p.o	Hot plate test in mice	[160]
48	Quercetin	25/50/100 mg/kg i.p	Tail flick test in mice	[161]
		25/50/100 mg/kg i.p	Hot plate test in mice	[161]
		10/30/100 mg/kg i.p	Mechanical hyperalgesia in Ehrlich tumor-induced cancer pain in mice	[162]
		10/30/100 mg/kg i.p	Thermal hyperalgesia in Ehrlich tumor-induced cancer pain in mice	[162]

		30/100 mg/kg i.p	Pain-induced functional impairment model in rats	[35]
		100 mg/kg i.p	Formalin test in rats	[35]
		50/100 mg/kg p.o	Tail-immersion test in diabetic neuropathic pain in mice	[163]
		10/30/60 mg/kg i.p	Acetic acid-induced abdominal writhing test	[164]
		10/30/60 mg/kg i.p	Capsaicin-induced pain in mice	[164]
		10/30/60 mg/kg i.p	Glutamate-induced pain in mice	[164]
		10/30/100 mg/kg s.c	Mechanical hypersensitivity test in zymosan-induced arthritis in mice	[165]
		10/30/100 mg/kg s.c	Mechanical hypersensitivity threshold test in gout arthritis in mice	[166]
		30/100 mg/kg i.p	Mechanical hypersensitivity titanium dioxide-induced arthritis in mice	[83]
		25/50 /100 mg/kg i.p	Mechanical hypersensitivity threshold test in mouse model of oxaliplatin-induced chronic painful peripheral neuropathy	[72]
		25/50/100 mg/kg i.p	Cold nociceptive threshold test in mouse model of oxaliplatin-induced chronic painful peripheral neuropathy	
49	Rutin	30-1000 mg/kg i.p	Formalin test in rats	[167]
		25/50 /100 mg/kg i.p	Mechanical hypersensitivity threshold test in mouse model of oxaliplatin-induced chronic painful peripheral neuropathy	[72]
		25/50/100 mg/kg i.p	Cold nociceptive threshold test in mouse model of oxaliplatin-induced chronic painful peripheral neuropathy	[72]
		10-100 mg/kg p.o.	Acetic acid-induced writhing test in mice	[168]
50	Kaempferol	16/32/64 mg/kg i.p	Von Frey test in alloxan-induced diabetic neuropathic pain in mice	[113]
		16/32/64 mg/kg i.p	Hot plate test in alloxan-induced diabetic neuropathic pain in mice	[113]
		16/32/64 mg/kg i.p	Tail flick test in alloxan-induced diabetic neuropathic pain in mice	[113]
		50/100 mg/kg p.o	Acetic acid-induced writhing test	[169]
51	Hesperidin methyl chalcone	3/10/30/100 mg/kg i.p	Acetic acid-induced writhing test in mice	[62]
		30 mg/kg i.p	Formalin/Carrageenan/CFA-induced pain in mice	[62]
		3/10/30/100 mg/kg i.p	Mechanical/Thermal hypersensitivity in carrageenan-induced inflammatory pain model in mice	[62]
		30 mg/kg i.p	Mechanical/Thermal hypersensitivity in CFA-induced inflammatory pain in mice	[62]

		30 mg/kg i.p	Mechanical/thermal hypersensitivity in capsaicin-induced inflammatory pain model in mice	[62]
52	Hesperidin	100–1,778.3 mg/kg i.p.	Pain-induced functional impairment model in rats	[170]
		10/30/100 mg/kg i.p.	Capsaicin-induced pain in mice	[170]
		10/100/, 1000 mg/kg i.p.	Mechanical/thermal hypersensitivity in CCI rats	[171]
		0.1/0.3/0.6/1 mg/kg i.p.	Acetic acid-induced writhing test in mice	[23]
		1/10/30 mg/kg i.p.	Hot plate test in mice	[23]
53	Curcumin	50 mg/kg i.p.	Thermal hypersensitivity in diabetic neuropathic pain in rats	[172]
		50 mg/kg i.p.	Mechanical allodynia in diabetic neuropathic pain in rats	[172]
		400 mg/kg p.o.	Formalin test in rats	[173]
		400 mg/kg p.o.	Hot plate test in rats	[173]
		50 mg/kg i.p.	Von Frey test in post-incisional nociceptive sensitization	[174]
		50 mg/kg i.p.	Hargreaves test in post-incisional nociceptive sensitization	[174]
		50 mg/kg i.p.	Mechanical allodynia test in spontaneous pain	[174]
		25–600 mg/kg i.p.	Nocifensive behavioral scoring in formalin-induced orofacial pain	[18]
54	Kempferol-3,4′-di-*O*-*α*-L-rhamnopyranoside	2.5/5/10 mg/kg i.p.	Acetic acid-induced writhing test in mice	[115]
		2.5/5/10 mg/kg i.p.	Formalin test in mice	[115]
55	Myricitrin	30–100mg/kg i.p	Cold and mechanical allodynia test in menthol induced pain in mice	[175]
		30-100mg/kg i.p	Cinnamaldehyde-induced pain in mice	[175]
		30–100mg/kg i.p	Acidified saline-induced pain in mice	[175]
		30–100mg/kg i.p	Menthol-induced pain in mice	[175]
		0.01–10 mg/kg i.p	Acetic acid-induced writhing in mice	[116]
		1–100 mg/kg p.o	Acetic acid-induced writhing in mice	[116]
		1–100 mg/kg i.p	Capsaicin-induced pain in mice	[116]
		1–100 mg/kg i.p	Glutamate-induced pain in mice	[116]
		0.01–10 mg/kg i.p	Phorbol myristate acetate-induced pain in mice	[116]
		30 mg/kg i.p	Mechanical hyperalgesia induced by bradykinin	[116]

		30 mg/kg i.p	Mechanical allodynia induced by PSNL in mice	[176]
		30 mg/kg i.p	Mechanical allodynia test in CFA-induced inflammation pain in mice	[176]
Terpenes				
56	1,8-Cineole	200/400 mg/kg p.o	Formalin test in mice	[177]
		200/400 mg/kg p.o	Acetic acid-induced writhing in mice	[177]
57	*p*-Cymene	50/100 mg/kg i.p	Acetic acid-induced writhing in mice	[12]
		25/50/100 mg/kg i.p	Formalin-induced pain in mice	[12]
		50/100 mg/kg i.p	Hot-plate test in mice	[12]
		25–100 mg/kg i.p	Tail flick test in mice	[13]
58	Menthol	3–10 mg/kg p.o	Hot-plate test in mice	[14]
		3–10 mg/kg p.o	Acetic acid-induced writhing in mice	[14]
		10 μg i.c.v	Tail flick test in mice	[14]
		10/20 mg/kg i.p	Chemically induced nocifensive behavior	[48]
		50/100 mg/kg i.p/i.t	Formalin-induced pain in mice	[48]
		50/100 mg/kg i.p/i.t	Von Frey test of CFA-induced pain in mice	[48]
59	Paeoniflorin	50 mg/kg i.p	Mechanical withdrawal threshold test in CCI ats	[77]
		50 mg/kg i.p	Thermal withdrawal latency test in CCI rats	[77]
		10/100/200 μg i.v	Spontaneous pain-related behaviors in rats	[21]
		10/100/200 μg i.v	Thermal pain sensitivity in rats	[21]
		10/100/200 μg i.v	Mechanical pain sensitivity in rats	[21]
		30 mg/kg p.o	Tail-pressure test in diabetic neuropathic pain in mice	[31]
		180 mg/kg i.p	Abdominal withdraw reflexin test in rats with neonatal maternal separation-induced visceral hyperalgesia	[57]
60	Borneol	5/25/50 mg/kg ip	Acetic acid-induced writhing in mice	[178]
		5/25/50 mg/kg ip	Formalin-induced pain in mice	[178]
61	Swertiamarin	100/200 mg/kg po	Tail immersion test in mice	[179]
		100/200 mg/kg po	Acetic acid-induced writhing in mice	[179]
		100/200 mg/kg po	Hot-plate test in mice	[179]

62	Geniposide	ED_{50}=17.3 μg ith	Formalin-induced pain in rats	[84]
63	Geraniol	12.5/25/50 mg/kg i.p/p.o	Acetic acid-induced writhing in mice	[119]
		25 mg/kg i.p.	Acetic acid-induced writhing test in mice	[119]
		12.5/25/50 mg/kg i.p	Formalin-induced pain in mice	[119]
		12.5/25/50 mg/kg i.p	Glutamate test in mice	[119]
64	[6]-Gingerol	12.5/25/50 mg/kg i.p	Acetic acid-induced writhing in mice	[120]
		25/50 mg/kg i.p	Formalin test in mice	[120]
65	Myrtenol	75 mg/kg i.p.	Acetic acid-induced writhing in mice	[78]
		75 mg/kg i.p.	Formalin test in mice	[78]
		75 mg/kg i.p.	Hot-plate test in mice	[78]
		75 mg/kg i.p.	Glutamate test in mice	[78]
		75 mg/kg i.p.	Capsaicin test in mice	[78]
Aromatic compounds				
66	Paeonol	10/50/100mg/kg p.o	Acetic acid-induced writhing in mice	[180]
		100 mg/kg p.o	Formalin-induced pain in mice	[180]
		30/50/100 mg/kg ip	Thermal threshold test in carrageenan induced inflammatory pain in mice	[181]
		80 mg/kg ip	Mechanical hypersensitivity threshold test in CFA-induced pain in mice	[55]
		80 mg/kg ip	Thermal threshold test in in CFA-induced pain	[55]
67	Divaricatol	1/5mg/kg	Acetic acid-induced writhing in mice	[182]
68	Cinnamaldehyde	100–400mg/kg p.o	Acetic acid-induced writhing in mice	[183]
		100–400mg/kg p.o	Hot-plate test in mice	[183]
69	Sinapyl alcohol	20/30 mg/kg p.o	Acetic acid-induced writhing in mice	[121]
		20/30 mg/kg p.o	Hot-plate test in mice	[121]
70	Caffeic acid	2.5–100 mg/kg p.o	Acetic acid-induced writhing in mice	[80]
		2.5–100 mg/kg p.o	Formalin test in mice	[80]
		200 mg/kg p.o	Randall–Selitto test in LPS/carrageenan-induced pain in rats	[80]
		2.5–10 mg/kg i.p	Hot plate latency test in alloxan-induced diabetic neuropathic pain in mice	[85]
		2.5–10 mg/kg i.p	Tail flick latency test in alloxan-induced diabetic neuropathic pain in mice	[85]

		2.5–10 mg/kg i.p	Von Frey filaments test in alloxan-induced diabetic neuropathic pain in mice	[85]
Coumarins				
71	Notopterol	100 mg/kg p.o	Acetic acid-induced writhing in mice	[184]
72	Columbianadin	50/100 mg/kg i.p	Formalin test in mice	[123]
73	Daphnetin	12.5/25/50 mg/kg p.o	Acetic acid-induced writhing in mice	[124]
		12.5/25/50 mg/kg p.o	Hot-plate test in mice	[124]
		12.5/25/50 mg/kg p.o	Electric stimulation induced pain in mice	[124]
74	Decursinol	10–60 mg/kg p.o	Tail-flick and	[125]
		10–60 mg/kg p.o	Hot-plate tests in mice	[125]
		10–100 mg/kg p.o	Acetic acid-induced writhing in mice	[125]
		10–100 mg/kg p.o	Formalin tests in mice	[125]
75	7-Hydroxycoumarin	30/60/120 mg/kg p.o	Von Frey filaments test in CFA induced pain in mice	[82]
		1–60 mg/kg p.o	Acetic acid-induced writhing in mice	[185]
		3/15/30/60 mg/kg p.o	Formalin tests in rats	[185]
		2.5/5/10 mg/kg p.o	Hot-plate tests in mice	[126]
76	Osthole	1%/2%/5% i.p	Von Frey test in nucleus pulposus-evoked pain in rats	[49]
		100 mg/kg i.p	*p*-Benzoquinone-induced writhing in mice	[79]
		50 µL 2% Epidural treatment	ED_{50} Von Frey test in nucleus pulposus-induced radicular inflammatory pain in rats	[50][1
		=5.43 mg/kg	Acetic acid-induced writhing in mice	86]
		ED_{50} =5.43 mg/kg	Formalin tests in mice	[186]
		2.5/5/10 mg/kg p.o	Hot-plate tests in mice	[126]
77	Albiflorin	1/3/10 mg/kg p.o	Tail-pressure test in diabetic neuropathic pain in mice	[31]
		50 mg/kg i.p	Mechanical withdrawal threshold testing	[77]
		50 mg/kg i.p	Thermal withdrawal latency testing.	[77]
78	Scopoletin	1/5/10 mg/kg i.p	Acetic acid-induced writhing in mice	[128]
		1/5/10 mg/kg i.p	Formalin tests in mice	[128]
Aliphaticnatural products				

79	Fumaric acid	2.5/5.0 mg/kg p.o	Acetic acid-induced writhing in mice	[187]
		1.25/2.5/5.0 mg/kg p.o	Hot-plate test in mice	[187]
		1.25/2.5/5.0 mg/kg p.o	Tail flick test in rats	[187]
80	Embelin	10/20 mg/kg i.p	Acetic acid-induced writhing in mice	[129]
		10/20 mg/kg i.p	Hot-plate test in mice	[129]
		10/20 mg/kg i.p	Tail immersion test in mice	[129]
Lignans				
81	Liriodendrin	5/10 mg/kg p.o	Acetic acid-induced writhing in mice	[188]
		5/10 mg/kg p.o	Hot-plate test in mice	[188]