Published By Guangdong Pharmaceutical University, Guangzhou

Journal of Holistic Integrative Pharmacy

2021, 2(4): 270-286

REVIEWS

Cancer-induced bone pain: spinal cord mechanisms and traditional Chinese medicine treatment

YANG Wei[1#], YANG Yachen[1#], WANG Yanqing[1,2*]

[1]*School of TCM, Department of Integrative Medicine and Neurobiology, School of Basic Medical Science, Institutes of Integrative Medicine, State Key Laboratory of Medical Neurobiology and MOE Frontiers Center for Brain Science, Institutes of Brain Science, Shanghai Medical College, Fudan University, Shanghai 200032, China;*

[2]*Shanghai Key Laboratory of Acupuncture Mechanism and Acupoint Function, Shanghai 200032, China*

[Abstract] Cancer-induced bone pain (CIBP) is a severe, intolerable, and complex pain condition caused by the primary bone tumor or bone metastasis. CIBP is a combination of complex pain states such as persistent dull pain, spontaneous pain, and mechanical allodynia. Its unique breakthrough pain makes patients suffer because of its unstable onset time and extremely strong pain. The mechanisms of CIBP involves inflammatory, neuropathic factors and specific peripheral local tumor destruction. Approximately 75% of patients with advanced cancer have experienced CIBP. With the survival time of patients with cancer being prolonged, only half of the CIBP can be well controlled. To develop more effective drugs and improve the quality of life of patients with CIBP, it is particularly urgent to extensively study the complex mechanisms of the occurrence and development of CIBP as well as to uncover new targets for developing new analgesics. The spinal cord is the primary center of nociceptive signal processing. During CIBP, unique neurobiochemical changes occur in the spinal cord level. Therefore, the study on the spinal cord level mechanisms of CIBP facilitates the development of efficient and accurate treatment of CIBP. During the development of CIBP, the central sensitization caused by the enhanced information transmission of "neuron glial cells" in the spinal cord is closely related to the central nervous inflammation (mainly activated by glial cells such as astrocytes and microglia). CIBP belongs to the category of "arthralgia" or other diseases in traditional Chinese medicine (TCM). The pathogenesis is mostly the empirical evidence of "impassability leads to pain" and the deficiency syndrome of "dishonor leads to pain", which is often mixed with deficiency and reality. Treatment should be based on the basic principles of "supporting righteousness and eliminating evil" and "treating both the symptoms and the root cause". TCM has a good analgesic effect in the treatment of CIBP, of based on syndrome differentiation and treatment tonic agents, rational blood agents, Qi-regulating agents, are mostly used in the selected of prescriptions, with effects as dispelling wind dampness, promoting blood circulation, and removing blood stasis, tonifying deficiency drugs and so on. With the development of integrated traditional Chinese and Western medicine research, the specific mechanisms of TCM to alleviate CIBP is gradually clear. This review summarizes the basic research on the spinal cord mechanism of CIBP and internal treatment of CIBP with TCM in recent 10 years.

[Key words] Cancer-induced bone pain; Spinal cord; Astrocytes; Microglia; Traditional Chinese medicine

[#]These authors contribute equally to this work;

[*Corresponding author] E-mail:wangyanqing@shmu.edu.cn.

1 Introduction

Cancer-induced bone pain (CIBP) is caused by the primary bone tumor or advanced bone metastasis, which is intensely excruciating and has a complicated mechanisms[1]. CIBP is a complex combination of persistent dull pain, spontaneous pain, and mechanical pain[2]. The characteristic breakthrough pain is much pain due to attack irregularity and significantly pain intensity[3-4]. CIBP occurs by mechanisms involving inflammatory pain, neuropathic pain, and specific peripheral local tumor destruction[5-6]. Approximately 75% of patients with advanced cancer experience CIBP[7], and their survival is prolonged with the development of medical technology; however, only half of them can temporarily relieve their pain with previous treatments and medications[6-8]. To develop more efficient and precise drugs to improve the quality of life of patients with cancer, it is necessary to study the complex mechanisms of CIBP and develop new therapeutic drugs. The spinal cord is the primary center of injury sensory signal processing, and unique neurobiochemical changes occur in the spinal cord level in CIBP[9]; therefore, studying the mechanisms of CIBP in the spinal cord provides greater possibility for the development of new drugs and efficient and precise treatment of this condition.

CIBP has been discussed in the ancient traditional Chinese medicine (TCM). "Magic Pivot, Needling Divisions, TRUE and Evil" said: "bone pain and flesh withering, internal injuries to the bone for bone erosion, for the former tumor, to hand press the firm, there is a knot, deep in the bone, gas due to the bone, bone and gas and, day to day to benefit from the larger, then the bone gangrene." CIBP belongs to the category of "arthralgia" in Chinese medicine, and its causes are mainly six evil poisons, seven internal injuries, dietary disorders, deficiency of vital energy, and disorders of internal organs. The pathogenesis of the disease is primarily the solid evidence of "pain if there is much block" and the deficiency evidence of "pain if there is less blood", often mixed with deficiency and reality; the treatment should be based on the basic principles of "helping the righteous and dispelling the evil" and "treating both the symptoms and the root cause". Clinical Chinese medicine has a good analgesic effect in treating CIBP. Based on evidence-based treatment, the selected formula primarily uses tonic agents combined with blood- and Qi-regulating agents to treat both the symptoms and the root cause, and the selected drugs are mainly efficacious drugs to dispel wind dampness, invigorate blood circulation, and remove blood stasis and tonic drugs for deficiency. With the development of research, the specific mechanisms of Chinese medicine to relieve CIBP has been gradually clarified. This study summarizes the research on the spinal cord mechanisms of CIBP and the basic research on the principles of internal treatment of CIBP by TCM in the past 10 years.

2 Summary of animal models for studying the spinal cord mechanism of CIBP

Current studies on the spinal cord mechanisms of CIBP are based on animal models that simulate the pathological state of clinical CIBP, in which the pathological mechanisms of CIBP development are analyzed to identify possible pain-causing and analgesic targets at the spinal cord level of CIBP. Therefore, establishing animal models of CIBP is of fundamental importance for developing drugs for specific types of CIBP. The current animal models of CIBP investigating mechanisms at the spinal cord level are organized as follows (Table 1).

3 Spinal cord mechanisms of CIBP

The spinal cord is the primary center for the transmission and processing sensory pain signals. Pain signals from injury receptors are transmitted from the primary afferent fibers to the dorsal horn of the spinal cord, and after initial integration, they act

Table 1 Animal models of cancer-induced bone pain for studying its spinal cord mechanisms

	Cell	Species	Location
Mice	NCTC 2472[10-11]	C3H/HeJ	Femur
	B16-F10 melanoma[12] cells	C57BL/6	Tibia
	RM-1 cells[13]	C57BL/6	Femur
	MC57G[14]	C57BL/6	Femur
	LLC	C57 BL/6	Femur
	4T1[11]	Bal/bc	Femur
Rat	MRMT-1[15]	Sprague Dawley	Tibia
	Walker 256[16]	Sprague Dawley	Tibia
	AT-3.1[17]	Copenhagen	Tibia
	PCCs[18]	Sprague Dawley	Tibia

on the motor cells in the ventral horn of the spinal cord to cause local defensive reflexes on the one hand and continue to be transmitted upward to the next level of centers on the other hand[19-20]. During the transmission of injurious stimulus signals, mechanisms such as excitation and inhibition of local neurons in the spinal cord, activation of glial cells, and downstream allodynia and inhibition in the brainstem directly determine the sensory signal output for processing at the spinal cord level[21-22]. Under conditions of nerve injury, inflammation, or bone tumors, the spinal cord undergoes central sensitization, and the excitatory and inhibitory mechanisms regulating spinal cord excitability are altered, resulting in enhanced responses of spinal cord dorsal horn neurons to both afferent and output signals to the brain[19, 23].

3.1 Biochemical mechanisms at the spinal cord level in CIBP

3.1.1 Multiple receptors in the spinal cord mediate CIBP

3.1.1.1 Cannabinoid receptors

Cannabinoid (CB) receptors are distributed throughout the body and together with their agonists and antagonists constitute the endocannabinoid system[24]. The CB receptor structures are G protein-coupled receptors containing seven transmembrane structural domains, a class of cell membrane receptors[25-26]. This study revealed the existence of two structural isoforms: CB1 and CB2[27]. In the study of the spinal cord mechanisms of CIBP, both subtypes were involved in the spinal cord mechanisms of CIBP. CB1 is mainly expressed at the end of the spinal cord axonal segments, and the exogenous administration of the CB1 agonist arachidonyl-2′-chloroethylamide to activate spinal cord CB1 receptors can relieve CIBP behaviors, such as spontaneous pain and motor touch-induced pain[28]. The CB2 agonist AM1241 relieved thermal and mechanical pain sensitivities in two CIBPs (NCTC 2472 osteosarcoma and B16-F10 melanoma cells), and the subcutaneous intrathecal injection of the CB2 antagonist SR144528 blocked the analgesic effect of the agonist AM1241, while the protein expression of CB2 in the spinal cord was not significantly altered[12].

3.1.1.2 Opioid receptors

Opioid receptors are a class of G protein-coupled receptors that use opioid-like peptides as ligands[29], and the four main subtypes are δ, κ, μ, and ζ[30]. The δ-opioid receptor-specific agonist deltorphin II dose-dependently reversed mechanical pain sensitivity at day 14 after CIBP in the MRMT-1 breast cancer cell model of femoral CIBP, and this effect is completely blocked by the δ-opioid receptor-specific antagonist naltrindole[31].

3.1.1.3 N-methyl-D-aspartate receptors

N-methyl-D-aspartate (NMDA) receptor is a glutamate receptor and ion channel protein present in nerve cells and is one of the ionotropic glutamate receptors[32]. NMDA receptors have an important role in inducing and maintaining central sensitization in the pain state[33]. NMDA receptors consist of NR1, NR2 (A, B, C, and D), and NR3 (A and B) subunits, of which those containing NR2B subunits feel particularly strong injurious stimuli and NR2B-selective antagonists can also relieve pain[33].

In a study of the spinal cord mechanisms of CIBP, the activation of EphB1 receptors by the administration of ephrinB2-Fc, an exogenous ligand for EphB1 receptors, upregulates the NR1 and NR2B receptor phosphorylation levels[34]. The activation of the spinal mTOR signaling pathway is also involved in the NMDA receptor-mediated central sensitization of the spinal cord[18]. The NMDA receptor/nNOS can be activated by upstream CCR2 to upregulate downstream Toll-1[35]. The NR2B receptor/nNOS can also be activated by upstream MrgC and mediate CIBP. The intrathecal injection of the Sigma-1 receptor antagonist BD1047 attenuates mechanical tenderness caused by bone tumors and alleviates NR1 activation and corresponding Ca^{2+} signaling in rats with CIBP[36]. The inhibition of the spinal astrocyte phosphorylation of the gap junction protein Cx43 and NR2B alleviates CIBP[37]. NR2D may be involved in the development of CIBP through peripheral mechanisms[38].

3.1.1.4 Chemokine receptors

Chemokine receptors are G protein-coupled receptors with seven transmembrane structural domains expressed on the surface of specific cells that bind to extracellular chemokine ligands, triggering an inward flow of Ca^{2+} to produce a cellular chemotactic response that induces cells to a specific site in the organism[39]. The upregulation of chemokines[39] is one of the mechanisms underlying the development and maintenance of chronic pain, while both CX and CC chemokine receptor families have involved in the spinal cord mechanisms of the development of CIBP[40].

Spinal MCP-1 and CCR2 are involved in mechanical pain sensitivity due to CIBP[41] and increased local protein expression in the spinal cord during CIBP[42]. Tumor cell inoculation upregulates CCR2 in the spinal dorsal horn neurons and microglia, and the intrathecal injection of neutralizing antibodies to MCP-1 partially reverses the mechanical ectopic pain caused by bone cancer[43]. CCR5 is significantly expressed in the spinal microglia of rats with CIBP, and the intrathecal injection of DAPTA, a specific antagonist of CCR5, relieves mechanical touch-induced pain and downregulates the expression levels of spinal CCR5 and *p*-PKCγ. The intrathecal injection of the CCR5-specific ligand RANTES reverses the analgesic effect of DAPTA[44]. The intrathecal injection of the protein kinase C (PKC) inhibitor GF109203X reduces mechanical touch-induced pain and decreases spinal *p*-PKCγ expression levels but does not affect CCR5 expression[44].

The spinal glial cell activation and upregulation of CXCR1 expression are observed in CIBP[45]. Spinal CX3CR1 expression is also upregulated, and it could be involved in CIBP through the activation of the downstream microglial *p*38 MAPK signaling pathway[46]. Moreover, it regulates CIBP via Akt and extracellular signal-regulated protein kinase (ERK) 1/2[47]. CXCR4 expression is upregulated in the spinal cord of rats with CIBP and mediates CIBP via RhoA/ROCK2[48].

3.1.1.5 Other receptors

The upregulation of the ST2 receptor and its ligand IL33 expression in the spinal cord of mice with femoral cancer pain[11]. The intrathecal injection of lipoxins A4 and B4 relieves mechanical touch-induced pain in mice on the seventh day of CIBP[49]. The lipoxin receptor ALX is mainly distributed in spinal astrocytes and relieves pain by decreasing the expression of spinal proinflammatory cytokines IL-1β and TNF-α mRNA in CIBP[49]. Vascular endothelial growth factor and its receptor VEGFR are upregulated in the spinal cord of rats with CIBP and can contribute to the release of cytokines through the activation of neuronal PKC/NMDAR and the downstream kinase pathway of the Src family of microglia leading to the development of CIBP[50].

3.1.2 Spinal protein kinase mediates CIBP

3.1.2.1 Cyclic AMP response element-binding protein

Cyclic AMP (cAMP) response element-binding protein (CREB) is involved in central sensitization, spinal CRTC1 and CreB expressions are upregulated in CIBP, and the inhibition of spinal CRTC1 expression can relieve CIBP[51]. The intramedullary inoculation of osteosarcoma cells leads to the upregulation of spinal *p*-CREB, CRTC1, and CREB target genes (NR2B and *miR*-132), and the intrathecal injection of its target gene miR-132 effectively relieves mechanical touch-induced pain and spontaneous pain induced by bone tumors[52]. The CaMKII/CREB pathway in the spinal cord of tumor-bearing rats mediates CXCR4-induced pain sensitivity[53].

3.1.2.2 ERK

The MAPK/ERK pathway is an intracellular protein chain that transmits signals from receptors on the cell surface to the DNA in the cell nucleus. Cellular switches for cancer therapeutic drugs[54]. The ERK intervention in different cell types such as spinal astrocytes, microglia, and neurons in rats with CIBP relieves CIBP sensitivity[55]. ERK is involved in CIBP by regulating the expression of MHC II in downstream STATI and spinal cord microglia[56]. The intrathecal administration of PDGF siRNA can effectively treat pain caused by bone cancer by blocking the AKT-ERK signaling pathway[57].

3.1.2.3 PKC and protein kinase A

PKC controls the functions of other proteins by phosphorylation of the hydroxyl groups of serine and threonine amino acid residues on the protein. PKC enzymes play an important role in several signal transduction cascade reactions[58]. Multiple subtypes of PKC, such as α, βI, βII, and γ, have been identified in the pain signal processing region of the superficial dorsal horn of the spinal cord[59]. In CIBP, PKC induces HMGB1 phosphorylation, drives HMGB1 translocation from the nucleus, and ultimately activates the release of spinal proinflammatory factors to induce CIBP sensitization[60].

Protein kinase A (PKA) is a class of enzymes whose activity depends on the level of cAMP in the cell[61]. PKA, also known as a cAMP-dependent protein kinase, has multiple functions in cells, including the regulation of glycogen, sugar, and lipid metabolism. The induction and maintenance of CIBP in the rat spinal cord are dependent on the activation of the cAMP-PKA signaling pathway[62]. PKA is a downstream signaling pathway of TDAG8-mediated CIBP formation[63].

3.1.3 Various chemokines in the spinal cord are involved in CIBP

Chemokines refer to a family of small cytokines or cell-secreted signaling proteins that are divided into four main subclasses: CXC, CC, CX3C, and XC. All of these proteins exert their biological effects by interacting with G protein-linked transmembrane receptors (chemokine receptors)[64-65].

3.1.3.1 CC chemokine

In the spinal cord of rats with CIBP, the CCL5 mRNA and protein expression levels were significantly increased in a time-dependent manner, and the intrathecal injection of anti-CCL5-neutralizing antibody significantly reduced mechanical nociceptive hypersensitivity, suggesting that spinal CCL5 is involved in the development of CIBP[66]. Rat spinal cord MCP-1 may be involved in CIBP through the activation of PI3K/AKT pathway and, thus, spinal cord microglia[67].

3.1.3.2 CXC chemokine

Spinal CXCL12 protein is time-dependently upregulated in rats with CIBP and is mainly expressed in spinal astrocytes. The intrathecal injection of specific inhibitors of JNK can eliminate

CXCL12 expression induced by CIBP[68]. In contrast, the intrathecal injection of the selective Cx43 blocker Gap26 significantly alleviated mechanical pain sensitivity and reduced the expression of phosphorylated CX43 and CXCL12 in CIBP on day 18 after tumor inoculation. The intrathecal injection of CXCL12-neutralizing antibody did not affect the expression of *p*-Cx43[57].

CXCL1 expression is time-dependently upregulated in mouse CIBP spinal cord astrocytes. The intrathecal administration of a CXCL1-neutralizing antibody relieves mechanical and thermal pain sensitivities induced by bone tumor cells, the intrathecal administration of a CXCL1 inhibitor also relieves pain and downregulates spinal CXCL1 expression, and astrocytic CXCL1 can be involved in CIBP spinal cord mechanisms through NF-κB[13]. Meanwhile, CXCL1 can also be involved in mediating CIBP formation through JNK[69].

The upregulation of CXCL10 and its receptor CXCR3 expression in the spinal cord of rats with CIBP and blockade of the CXCL10/CXCR3 pathway by CXCL10-neutralizing antibodies or CXCR3 antagonists alleviate the rapid development of CIBP and microglia activation induced by bone tumor cell inoculation[70].

3.2 Cellular mechanisms at the spinal cord level in CIBP

3.2.1 Spinal cord glial cell activation in CIBP

The two main cell types studied in CIBP at the spinal cord level are neuronal and nonneuronal cells, such as astrocytes and microglia. Under pathological conditions, nonneuronal cells in the spinal cord, that is, i.e., astrocytes and microglia, can affect pain transmission via the dorsal horn[19]. In the pathological state of CIBP, multiple mechanisms at the spinal cord level can lead to glial cell activation, morphologically in the form of cell hypertrophy and proliferation and functionally in the form of glial cell or glial cell-neuron interactions that cause the release of proinflammatory cytokines, which act on the corresponding membrane receptors and cause neuronal sensitization or a state of sustained glial cell activation[6, 20].

3.2.2 Neuron sensitization in the dorsal horn of the spinal cord in CIBP

The central end of afferent sensory nerve fibers is distributed in the dorsal horn of the spinal cord, which is divided into different laminae from superficial to deep[19]. Most injurious sensory afferent nerve fibers, such as Aδ and C-terminal nerve fibers, terminate in superficial laminae I—II, with a small number distributed in deeper laminae, while Aβ nerve fiber terminals are mainly distributed in deeper laminae III—IV[71]. Different types of neuronal cells in the spinal cord form synaptic connections with the corresponding primary afferent nerve endings to respond to the corresponding afferent signals. When a painful stimulus is perceived in the periphery, nerve cells in the spinal cord send the signal to generate an action potential.

The activation of sensory neurons in the superficial layer of the dorsal horn of the spinal cord in mice with CIBP and expression of substance P and *c*-Fos, a marker of neuronal activation, were observed in the dorsal horn plate I layer[72]. Basal and stimulus-induced increases in CGRP release from sensory neuron terminals in the dorsal horn of the spinal cord and increased expression of CGRP receptor protein in the dorsal horn of the spinal cord and expressed in activated astrocytes[10]. Mice with CIBP exhibited severe CIBP sensitivity on day 14 after tumor inoculation, while the MrgC ubiquitination level and intracellular calcium concentration in spinal dorsal horn neurons significantly increased, and MrgC ubiquitination was involved in the formation of CIBP sensitivity by regulating the intracellular calcium concentration in the neurons of mice with CIBP[73]. The sensitization of wide range neurons was observed in the deep dorsal horn of the spinal cord of

rats with CIBP, the inhibition of KCNQ/M channels induced pain sensitization in normal rats, and the activation of KCNQ/M channels significantly alleviated the activation of wide range neurons and CIBP sensitization[74].

4 Research on the mechanisms of traditional Chinese medicine formula to relieve CIBP

In the basic research on the efficacy mechanisms of CIBP by the internal treatment method of traditional Chinese medicine, the administration mode is mostly based on gavage, and the selected adult formulas and corresponding mechanisms are as follows (Table 2).

4.1 Blood-regulating prescription

Generalized Pain Stasis-Expelling Decoction is from "Yi Lin Gai Cuo"; the function of the whole formula is to facilitate the blood circulation process and dispel stasis, dispel wind and eliminate dampness, relieve pain, which can free Bi, blood stasis and wind-damp, channels (and collaterals) impede. This formula alleviates spontaneous nociception and mechanical and thermal nociceptive hypersensitivities in rats with Walker 256 breast cancer cell-induced tibial cancer pain[75]. It also alleviated the mechanical pain sensitivity of rats with NCTC2472 fibrosarcoma cell-induced femoral cancer pain and reduced the mRNA and protein expression of GFAP, a marker of spinal astrocytes in CIBP mice, 14 days after modeling, indicating that it could alleviate CIBP by dose-dependently inhibiting the proliferation and activation of astrocytes at the spinal cord level in mice with CIBP[76].

4.2 Qi-rectifying prescription

The Xinzhi formula is made of Dahurian angelica, asarum, Rhizoma Ligustici, centipede, white peony, olibanum, monkshood, and Radix Glycyrrhizae, which was derived by Henan healer Zhang Haizen based on his family's experience in traditional Chinese medicine treatment and the theory of traditional Chinese medicine. This is commonly used in clinical practice for the treatment of neuropathic pain. The functions of the whole formula include warming Yang and moving Qi,

Table 2 traditional Chinese medicine prescriptions for relieving CIBP

Classify	Year	Name	Form	CIBP model	Mechanisms	References
Blood-regulating prescription	2011	Generalized Pain Stasis-Expelling Decoction	Radix Gentianae Macrophyllae, Rhizoma Ligustici, Semen Persicae, Flos Carthami, Radix Glycyrrhizae, notopterygium, myrrh, angelica, squirrel's droppings, Rhizoma Cyperi, Radix Cyathulae, lumbricus	Mouse NCTC2472 Femoral cancer pain model	Affects on the mRNA and protein expression of the spinal astrocyte marker GFAP	[76]
	2016	Generalized Pain Stasis-Expelling Variant Decoction	Olibanum, myrrh, Walnut seed, Flos Carthami, angelica, Rhizoma Ligustici, Radix Cyathulae, Rhizoma Cyperi, Fructus Meliae Toosendan, Radix Gentianae Macrophyllae, notopterygium, Radix Angelicae Pubescentis doubleteeth, Radix Glycyrrhizae	Walker 256 in rats Tibial cancer pain model	Affects the tibial bone density and pain behavior	[75]

Table 2 (Continued)

Classify	Year	Name	Form	CIBP model	Mechanisms	References
Qi-rectifying prescription	2015	Xin-Zhi-Fang	Dahurian angelica, asarum, Rhizoma Ligustici, centipede, white peony, olibanum, monkshood, Radix Glycyrrhizae	Walker 256 in rats Tibial cancer pain model	Affects the expression of spinal GFAP and NF-κB, TLR-2/4 proteins	[77]
Supplementing formula	2020	Shenling Baizhu formula	Radix Codonopsis, Poria, Rhizoma Atractylodis Macrocephalae, Rhizoma Dioscoreae, Radix Glycyrrhizae, Semen Dalichoris Album, Radix Angelicae Sinensis, Rhizoma Ligustici, Radix Paeoniae Alba, rehmanniae praeparatum, Semen Nelumbinis, Semen Coicis, Fructus Amomi Villosi, Radix Platycodonis, Radix Astragali seu Hedysari, centipede, monkshood, cinnamon	Mouse human small cell lung cancer cells Tibial cancer pain model	Inhibits cell proliferation and promotes apoptosis through PI3K/AKT/mTOR signaling pathway	[79]
Wind controlling	2016	Dou Wu Xiao Sheng Tang	Radix Angelicae Pubescentis, southern mistletoe, Radix Achyranthis Bidentatae, Cortex Eucommiae, Radix Gentianae Macrophyllae, Herba Asari, cinnamon, Poria, Rhizoma Ligustici, parsnip, Radix Glycyrrhizae, Codonopsis pilosula, paeony, Chinese angelica, dried rehmannia	Mouse AT-31 Tibial cancer pain model	Affects the activation of spinal astrocytes	[81]
Others	2015	Yunnan Baiyao		Mouse NCTC2472 Femoral cancer pain model	Affects the expression of NR2B protein at the spinal cord level	[82]
	2015	Kajuan Qing Pills	Turtle worm, Yan Huo Suo, Xu Chang Qing	Walker 256 in rats Tibial cancer pain model	Alleviates pain sensitivity in bone cancer in rats	[84]
	2017	Gu Tong Ling formula	Herba Epimedii, Rhizoma Drynariae, centipede, Radix Aconiti Preparata, Radix Aconiti Kusnezoffii Preparata	Mouse Lewis cells Tibial cancer pain model	Reduces spinal MCP-1 protein expression and promotes NGF protein expression	[87]
	2020	Gu Tong Ling formula	Herba Epimedii, Rhizoma Drynariae, centipede, Radix Aconiti Preparata, Radix Aconiti Kusnezoffii Preparata	Mouse Lewis cells Tibial cancer pain model	Affects the expression of RANKL/OPG	[88]

Table 2 (Continued)

Classify	Year	Name	Form	CIBP model	Mechanisms	References
Others	2019	Yishen Gukang formula	Radix Rehmanniae Preparata, cornus, Herba Hedyotis, Poria, stir-fried dioscorea, Rhizoma Drynariae, Cortex Moutan Radicis, Rhizoma Alismatis, Herba Scutellariae Barbatae	Walker 256 in rats Tibial cancer pain model	Inhibits the expression of P38, MAPK, and downstream inflammatory factors and inhibits osteoclast activation through the OPG/RANK/RANKL signaling pathway	[83]
	2020	Long Ling formula	Venenum Bufonis	Walker 256 in rats Tibial cancer pain model	Inhibits the IKKb/NF-κB signaling pathway and reduces synthesis and release of TNF-α, IL-1b, and IL-6	[89]

activating blood circulation to dissipate blood stasis, relieving pain, and freeing Bi. This formula inhibits the proliferation and activation of NF-κB and Toll-like protein receptors 2 and 4 in the spinal astrocytes of rats with CIBP, thus exerting analgesic effects[77].

4.3 Supplementing formula

The Shenling Baizhu formula is made of lanceolate, cocos, Radix Codonopsis, Poria, Rhizoma Atractylodis Macrocephalae, Rhizoma Dioscoreae, Radix Glycyrrhizae, Semen Dalichoris Album, Radix Angelicae Sinensis, Rhizoma Ligustici, Radix Paeoniae Alba, rehmanniae praeparatum, Semen Nelumbinis, Semen Coicis, Fructus Amomi Villosi, Radix Platycodonis, Radix Astragali seu Hedysari, centipede, monkshood, and cinnamon. Twenty-eight kinds of natural medicinal plants, including compound preparation, show anticancer efficacy in previous studies[78]. Gaminarin and Atractylodes can inhibit cell proliferation and promote apoptosis through the PI3K/AKT/mTOR signaling pathway, exert analgesic effects, and prolong the survival time of mice with lung cancer bone metastases[79].

4.4 Wind controlling

Douwuxiaosheng Tang is made of Radix Angelicae Pubescentis, southern mistletoe, Radix Achyranthis Bidentatae, Cortex Eucommiae, Radix Gentianae Macrophyllae, Herba Asari, cinnamon, Poria, Rhizoma Ligustici, parsnip, Radix Glycyrrhizae, Codonopsis pilosula, paeony, Chinese angelica, and dried rehmannia and is from Sun Simiao's "A Thousand Gold Pieces Emergency Formulary". It is mainly used for the treatment of wind and cold paralysis but also has analgesic, antiinflammatory, and immune system effects[80]. Moreover, it can inhibit the activation of astrocytes in the spinal cord of mice with prostate cancer bone metastases to alleviate mechanical pain sensitivity in mice with CIBP[81].

4.5 Others

Yunnan Baiyao is a national secret formula for the treatment of bruises and bleeding wounds. A study found that gavage with Yunnan Baiyao can also alleviate thermal and mechanical pain sensitivities in mice with CIBP by inhibiting the upregulation of NR2B protein at the spinal cord level[82].

It is mainly made up of Liu Wei Di Huang Wan plus flavor, which is clinically applied to treat cancer pain in patients with middle- and late-stage cancer, especially bone metastasis pain, with

remarkable effect. The main mechanism is to inhibit the expression of P38MAPK and downstream inflammatory factors. It can also inhibit P38MAPK phosphorylation through regulating the OPG/RANK/RANKL signaling pathway and osteoclast activation, reduce bone destruction, and, thus, relieve CIBP[83].

Jia-Yuan-Qing pill is an analgesic formulated with the ratio of 9∶7∶7 of turtle worm, Yan Huo Suo, and Xu Chang Qing. A basic study was conducted to investigate the analgesic effect of Jia-Yuan-Qing pill on CIBP in a Walker 256 rat CIBP model and found that Jia-Yuan-Qing pill has a good analgesic effect without side effects, such as addiction and toxicity[84].

Three Bone Soup is composed of Bone Tonic, Bone Crushed Tonic, and Bone Rushes in the ratio of 5∶5∶3, which was found to relieve CIBP by reducing osteolytic destruction[85].

In addition, Osteogenic Pain Relief Pill can promote the proliferation of progenitor chondrocytes and significantly increase the proproliferative activity of chondrocytes while having a certain inhibitory effect on the differentiation of chondrocytes and the destruction of the extracellular matrix. Through the regulation of kidney genes, Osteogenic Pain Relief Pill can promote the proliferation of chondrocytes and differentiation of chondroprogenitor cells, inhibit the differentiation of chondrocytes, maintain the stability of cartilage scaffold, and then participate in cartilage formation, protect cartilage structure, and achieve the effect of tonifying kidney and strengthening bone[86].

5 Research on the mmechanisms of traditional Chinese medicine monomer to relieve CIBP

In the study of the efficacy mechanism of traditional Chinese medicine on CIBP, most of the experiments were conducted in the form of herbal monomers for drug delivery. Structurally, herbal monomers are mainly classified into various structural types: flavonoids, alkaloids, glycosides, phenols, phenylpropanoids, and other parts. The selected monomers and specific mechanisms are summarized as follows (Table 3).

5.1 Flavonoids

Tanshinone IIA (TSN-IIA), a bioactive component of the Chinese herb Salvia miltiorrhiza, has anticancer effects[90]. In pain studies, TSN-IIA alleviates late proinflammatory cytokine high-mobility group protein B1 (HMGB1) by downregulating neuropathic and inflammatory pain[91]. TSN-IIA also relieves CIBP by inhibiting the high expression of HMGB1 and other inflammatory factors (IL-1β, TNF-α, and IL-6) in the spinal cord and suppressing

Table 3 Herbal monomers for the relief of CIB

Classify	Name	Source	Animal models	Mechanisms	Reference
Flavonoids	Tanshinone IIA, TSN-IIA	Salvia	Walker 256 in rats Tibial cancer pain model	Inhibits the high expression of spinal HMGB1 and other inflammatory factors (IL-1β, TNF-α, and IL-6) and spinal neuronal excitability	[92]
	Baicalein	Scutellaria	Walker 256 in rats Tibial cancer pain model	Inhibits the high expression of spinal cord inflammatory cytokines IL-6 and TNF-α and activates the *p*-P38 and *p*-JNK and MAPK signaling pathways in the spinal cord	[96]
Phenol	Demethoxycurcumin, (DMC)	Curcumin	Nude rat MDA-MB-231 Tibial cancer pain model	Inhibits the early activation of the ERK, JNK, and MAPK pathways and tumor cells and osteoblasts	[120]

Table 3 (Continued)

Classify	Name	Source	Animal models	Mechanisms	Reference
Alkaloids	Corydalis saxicola Bunting total alkaloids, CSBTA	Thill bamboo	Walker 256 in rats Tibial cancer pain model	Downregulates the RANKL/OPG ratio and inhibits the RANKL-induced NF-κB and *c*-Fos/NFATc1 pathways and osteoclast formation	[102]
	Sinomenine	Ovientvine	Walker 256 in rats Tibial cancer pain model	Inhibits spinal microglia JAK2/STAT3 and neuronal CAMKII/CREB	[110]
	Levo-corydalmine	Corydalis	Walker 256 in rats Tibial cancer pain model	Inhibits NMDA and mGlu1/5 receptors and downstream PKC c, ERK1/2 signaling pathways in the spinal cord	[112]
Glycosides	Ginsenoside	Ginseng	Walker 256 in rats Tibial cancer pain model	Inhibits spinal microglial activation and expression of proinflammatory cytokines	[117]
Others	Tetrahydroxystilbene glucoside	Radix Polygoni multiflori	Walker 256 in rats Tibial cancer pain model	Alleviates pain sensitivity in bone cancer in rats	[118]
	Icariin Epimedium	Herba Epimedii	MRMT-1 in rats Tibial cancer pain model	Inhibits osteoclast overactivation	[119]

the excitability of spinal cord neurons[92].

Baicalein is the main component of Scutellaria baicalensis, which clears heat and dampness, relieves fire and toxicity, stops bleeding, calms the fetus[93-95], and shows antiinflammatory and neuroprotective effects. Baicalein inhibits the high expression of inflammatory cytokines IL-6 and TNF-α in the spinal cord of rats with CIBP and activates the *p*-P38 and *p*-JNK and MAPK signaling pathways in the spinal cord to relieve CIBP[96].

5.2 Phenol

Demethoxycurcumin (DMC) is a derivative of curcumin and is one of the most abundant curcumin compounds in turmeric powder[97]. Turmeric is commonly used as a therapeutic medicine in traditional Chinese medicine or as a culinary spice. Dimethyl curcumin has a variety of biological activities and exerts antioxidant and antiinflammatory effects[98-99]. In a nude mouse MDA-MB-231 tibial cancer pain model, it was clarified by *in vitro* and *in vivo* experiments that DMC could alleviate CIBP by inhibiting early activation of the ERK, JNK, and MAPK pathways to suppress tumor cells and osteoclasts.

5.3 Alkaloids

Corydalis saxicola Bunting total alkaloids (CSBTAs) are alkaloids extracted from the roots of Corydalis saxicola with anticancer and analgesic effects[100-101]. The oral administration of CSBTA in rats with CIBP can alleviate CIBP sensitivity, and *in vitro* experiments showed that CSBTA can reduce RANKL expression and downregulate the RANKL/OPG ratio in breast cancer cells; in addition, CSBTA can inhibit osteoclast formation by inhibiting the RANKL-induced NF-κB and *c*-Fos/NFATc1 pathways[102].

Sinomenine is the main active ingredient of Gymnema sylvestre, which has been shown to have antiinflammatory, cough-suppressant, and anticardiac ischemic effects in systemic inflammation, arthritis, asthma, cardiovascular diseases, etc[103-107]. Several pain studies have shown that aminophylline can

also relieve pain caused by inflammation and diabetes[108-109]. It also relieves CIBP by inhibiting the JAK2/STAT3 and neuronal CAMKII/CREB pathways in spinal microglia[110].

Levo-corydalmine is the main active ingredient of Yan Hu Suo, which is commonly used in traditional Chinese medicine for clinical pain relief[111]. It has been shown that levoransoprine alleviates CIBP in rats with TCI by inhibiting the NMDA and mGlu1/5 receptors in the spinal cord and downstream PKC c and ERK1/2 signaling pathways[112].

5.4 Glycosides

Ginsenoside is the main constituent of ginseng, a valuable herb used for nearly a thousand years, and has been reported in many studies to have antiinflammatory, antioxidant, and neuroprotective effects[113-114] and relieve pain[115-116]. In a study of CIBP in rats, the intraperitoneal injection of ginsenosides partially alleviated mechanical and thermal nociceptive hypersensitivity in rats with CIBP, and ginsenosides also inhibited the expression of the microglial marker IBA-1 protein and upregulation of IL-1β, IL-6, and TNF-α in the spinal cord of rats with CIBP. It showed that ginsenosides could alleviate CIBP by inhibiting the microglia activation and expression of proinflammatory cytokines[117].

5.5 Others

The effects of *P. officinale* include laxative, malaria treatment, liver and kidney tonic, and helping essence and blood. Tetrahydroxystilbene glucoside (TSG) is the active ingredient of *P. officinale*, and it relieves CIBP in rats[118].

The effects of Epimedium include tonifying kidney yang, strengthening tendons and bones, and dispelling wind and dampness. In a study on CIBP in rats, Epimedium can reduce bone resorption and protect the bone quality, inhibit osteoclast overactivation, and, thus, relieve CIBP in rats[119].

6 Summary

At present, there are stable animal models for CIBP research, and most of the studies on the spinal cord mechanisms of CIBP focus on local neuroinflammation and sensitization of nerve cells at the site of injurious sensory information transmission in the dorsal horn of the spinal cord. Moreover, the efficacy and mechanisms of different drugs on CIBP have been explored including the study on the spinal cord mechanisms of CIBP. However, the mechanism of CIBP is complex which is not the result of either single peripheral or spinal cord action. The spinal cord mechanisms has not yet been extensively studied and efficient and safe drugs for cancer pain treatment are yet to be developed. Therefore, a more in-depth and multifaceted study of the spinal cord mechanisms of CIBP, as well as the connection between the spinal cord and peripheral or superior centers, is important for finding therapeutic targets and developing new drugs for cancer pain treatment. This review on TCM treatment of CIBP is mainly based on administering formulas and Chinese herbal monomers, and primarily focuses on the mechanisms affecting the activation of local tumor microenvironment osteoclasts, central sensitization of the spinal cord, and inflammatory factor storm. The mechanisms of the systemic immune system regulation and the influence of the higher centers in the spinal cord are yet to be further clarified. Traditional Chinese medicine is a great treasure of the Chinese nation, and traditional Chinese medicine analgesia has the characteristics of long-lasting efficacy and low side effects. A detailed investigation of the mechanism of traditional Chinese medicine for CIBP can provide a solid theoretical basis for the clinical treatment of CIBP in traditional Chinese medicine.

7 Conflict of Interest

These authors have no conflict of interest to declare.

8 Acknowledgments

This work was supported by the National Key Research and Development Program of China (2017YFB0403803), National Natural Science Foundation of China (81771202, 81873101, and 81971056), Innovative Research Team of High-level Local Universities in Shanghai, Shanghai Municipal Science and Technology Major Project (2018SHZDZX01), ZJ Lab, Shanghai Center for Brain Science and Brain-Inspired Technology, and the National Natural Science Foundation of Shanghai (15ZR1402800).

References

[1] Thompson AL, Grenald SA, Ciccone HA, et al. The endocannabinoid system alleviates pain in a murine model of cancer-induced bone pain[J]. *J Pharmacol Exp Ther*, 2020, 373(2):230-238.

[2] Portenoy RK, Ahmed E. Cancer pain syndromes[J]. *Hematol Oncol Clin North Am*, 2018, 32(3):371-386.

[3] Mercadante S. Treating breakthrough pain in oncology[J]. *Expert Rev Anticancer Ther*, 2018, 18(5):445-449.

[4] Clohisy DR, Mantyh PW. Bone cancer pain[J]. *Cancer*, 2003, 97(3)(Supp):866-873.

[5] Yin JJ, Pollock CB, Kelly K. Mechanisms of cancer metastasis to the bone[J]. *Cell Res*, 2005, 15(1):57-62.

[6] Zajączkowska R, Kocot-Kępska M, Leppert W, et al. Bone pain in cancer patients: Mechanisms and current treatment[J]. *Int J Mol Sci*, 2019, 20(23):6047.

[7] Foley KM. Treatment of cancer-related pain[J]. *J Natl Cancer Inst Monogr*, 2004, 32(32):103-104.

[8] Siegel R, Desantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012[J]. *CA Cancer J Clin*, 2012, 62(4):220-241.

[9] Honore P, Mantyh PW. Bone cancer pain: From mechanism to model to therapy[J]. *Pain Med*, 2000, 1(4):303-309.

[10] Hansen RR, Vacca V, Pitcher T, et al. Role of extracellular calcitonin gene-related peptide in spinal cord mechanisms of cancer-induced bone pain[J]. *Pain*, 2016, 157(3):666-676.

[11] Zhao J, Zhang H, Liu SB, et al. Spinal interleukin-33, and its receptor ST2 contribute to bone cancer-induced pain in mice[J]. *Neuroscience*, 2013, 253(23): 172-182.

[12] Curto-Reyes V, Llames S, Hidalgo A, et al. Spinal and peripheral analgesic effects of the CB2 cannabinoid receptor agonist AM1241 in two models of bone cancer-induced pain[J]. *Br J Pharmacol*, 2010, 160(3):561-573.

[13] Xu J, Zhu MD, Zhang X, et al. NFkappaB-mediated CXCL1 production in spinal cord astrocytes contributes to the maintenance of bone cancer pain in mice[J]. *J Neuroinflammation*, 2014, 11(1):38.

[14] Tian J, Song T, Wang H, et al. Thalidomide alleviates bone cancer pain by down-regulating expressions of NF-kappaB and GFAP in spinal astrocytes in a mouse model[J]. *Int J Neurosci*, 2019, 129(9):896-903.

[15] Meng W, Hao MM, Yu N, et al. 2-Bromopalmitate attenuates bone cancer pain via reversing mitochondrial fusion and fission imbalance in spinal astrocytes[J]. *Mol Pain*, 2019, 15(23): 744806919871813.

[16] Mao-Ying QL, Zhao J, Dong ZQ, et al. A rat model of bone cancer pain induced by intra-tibia inoculation of Walker 256 mammary gland carcinoma cells[J]. *Biochem Biophys Res Commun*, 2006, 345(4):1292-1298.

[17] Miao XR, Fan LC, Wu S, et al. DNMT3a contributes to the development and maintenance of bone cancer pain by silencing Kv1.2 expression in spinal cord dorsal horn[J]. *Mol Pain*, 2017, 13(12):1744806917740681.

[18] Shih MH, Kao SC, Wang W, et al. Spinal cord NMDA receptor-mediated activation of mammalian target of rapamycin is required for the development and maintenance of bone cancer-induced pain hypersensitivities in rats[J]. *J Pain*, 2012, 13(4):338-349.

[19] D'Mello R, Dickenson AH. Spinal cord mechanisms of pain[J]. *Br J Anaesth*, 2008, 101(1):8-16.

[20] Middlemiss T, Laird BJ, Fallon MT. Mechanisms of cancer-induced bone pain[J]. *Clin Oncol (R Coll Radiol)*, 2011, 23(6):387-392.

[21] Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain[J]. *Curr Opin Support Palliat Care*, 2014, 8(2):143-151.

[22] Tao ZY, Wang PX, Wei SQ, et al. The role of descending pain modulation in chronic primary pain: Potential application of drugs targeting serotonergic system[J]. *Neural Plast*, 2019, 4:1-16.

[23] Tsuda M. Modulation of pain and itch by spinal glia[J]. *Neurosci Bull*, 2018, 34(1):178-185.

[24] Mechoulam R, Parker LA. The endocannabinoid system and the brain[J]. *Annu Rev Psychol*, 2013, 64(1):21-47.

[25] Hua T, Vemuri K, Pu M, et al. Crystal structure of the human cannabinoid receptor CB1[J]. *Cell*, 2016,

167(3):750-762.

[26] Li X, Hua T, Vemuri K, et al. Crystal structure of the human cannabinoid receptor CB2[J]. *Cell*, 2019, 176(3): 459-467.

[27] Matsuda LA, Lolait SJ, Brownstein MJ, et al. Structure of a cannabinoid receptor and functional expression of the cloned cDNA[J]. *Nature*, 1990, 346(6284):561-564.

28] Furuse S, Kawamata T, Yamamoto J, et al. Reduction of bone cancer pain by activation of spinal cannabinoid receptor 1 and its expression in the superficial dorsal horn of the spinal cord in a murine model of bone cancer pain[J]. *Anesthesiology*, 2009, 111(1):173-186.

[29] Janecka A, Fichna J, Janecki T. Opioid receptors and their ligands[J]. *Curr Top Med Chem*, 2004, 4(1):1-17.

[30] Corbett AD, Henderson G, Mcknight AT, et al. 75 years of opioid research: The exciting but vain quest for the Holy Grail[J]. *Br J Pharmacol*, 2006, 147(1)(Supp 1):S153-S162.

[31] Otis V, Sarret P, Gendron L. Spinal activation of delta opioid receptors alleviates cancer-related bone pain[J]. *Neuroscience*, 2011, 183(3):221-229.

[32] Watkins JC, Jane DE. The glutamate story[J]. *Br J Pharmacol*, 2006, 147(Supp 1):S100-S108.

[33] Petrenko AB, Yamakura T, Baba H, et al. The role of *N*-methyl-D-aspartate (NMDA) receptors in pain: A review[J]. *Anesth Analg*, 2003, 97(4):1108-1116.

[34] Liu S, Liu WT, Liu YP, et al. Blocking EphB1 receptor forward signaling in spinal cord relieves bone cancer pain and rescues analgesic effect of morphine treatment in rodents[J]. *Cancer Res*, 2011, 71(13):4392-4402.

[35] Ren F, Jiao H, Cai H. Analgesic effect of intrathecal administration of chemokine receptor CCR2 antagonist is related to change in spinal NR2B, nNOS, and SIGIRR expression in rat with bone cancer pain[J]. *Cell Biochem Biophys*, 2015, 72(2):611-616.

[36] Zhu S, Wang C, Han Y, et al. Sigma-1 receptor antagonist BD1047 reduces mechanical allodynia in a rat model of bone cancer pain through the inhibition of spinal NR1 phosphorylation and microglia activation[J]. *Mediators Inflamm*, 2015, 2:650-656.

[37] Yang H, Yan H, Li X, et al. Inhibition of connexin 43 and phosphorylated NR2B in spinal astrocytes attenuates bone cancer pain in mice[J]. *Front Cell Neurosci*, 2018, 12(8):129.

[38] Xie X, Li X, Zhao H, et al. Expression of synaptic protein S in the DRGs and spinal cord in rats with bone cancer pain[J]. *Neurophysiology*, 2019, 51(1):9-17.

[39] Zlotnik A, Yoshie O, Nomiyama H. The chemokine and chemokine receptor superfamilies and their molecular evolution[J]. *Genome Biol*, 2006, 7(12): 243.

[40] Abbadie C. Chemokines, chemokine receptors and pain[J]. *Trends Immunol*, 2005, 26(10):529-534.

[41] Hu JH, Zheng XY, Yang JP, et al. Involvement of spinal monocyte chemoattractant protein-1 (MCP-1) in cancer-induced bone pain in rats[J]. *Neurosci Lett*, 2012, 517(1):60-63.

[42] Hu JH, Wu MY, Tao M, et al. Changes in protein expression and distribution of spinal CCR2 in a rat model of bone cancer pain[J]. *Brain Res*, 2013, 1509(9):1-7.

[43] Chen QY, Chen T, Zhou LJ, et al. Heterosynaptic long-term potentiation from the anterior cingulate cortex to spinal cord in adult rats[J]. *Mol Pain*, 2018, 14(1):1744806918798406.

[44] Hang LH, Li SN, Dan X, et al. Involvement of spinal CCR5/PKCgamma signaling pathway in the maintenance of cancer-induced bone pain[J]. *Neurochem Res*, 2017, 42(2):563-571.

[45] Cheng W, Zhao Y, Liu H, et al. Resveratrol attenuates bone cancer pain through the inhibition of spinal glial activation and CX3CR1 upregulation[J]. *Fundam Clin Pharmacol*, 2014, 28(6):661-670.

[46] Hu JH, Yang JP, Liu L, et al. Involvement of CX3CR1 in bone cancer pain through the activation of microglia p38 MAPK pathway in the spinal cord[J]. *Brain Res*, 2012, 1465:1-9.

[47] Guan XH, Fu QC, Shi D, et al. Activation of spinal chemokine receptor CXCR3 mediates bone cancer pain through an Akt-ERK crosstalk pathway in rats[J]. *Exp Neurol*, 2015, 263(12):39-49.

[48] Xu H, Peng C, Chen XT, et al. Chemokine receptor CXCR4 activates the RhoA/ROCK2 pathway in spinal neurons that induces bone cancer pain[J]. *Mol Pain*, 2020, 16(1):1744806920919568.

[49] Hu S, Mao-Ying QL, Wang J, et al. Lipoxins and aspirin-triggered lipoxin alleviate bone cancer pain in association with suppressing expression of spinal proinflammatory cytokines[J]. *J Neuroinflammation*, 2012, 9(1):278.

[50] Hu XM, Yang W, Du LX, et al. Vascular endothelial growth factor A signaling promotes spinal central sensitization and pain-related behaviors in female rats with bone cancer[J]. *Anesthesiology*, 2019, 131(5): 1125-1147.

[51] Liang Y, Liu Y, Hou B, et al. CREB-regulated

transcription coactivator 1 enhances CREB-dependent gene expression in spinal cord to maintain the bone cancer pain in mice[J]. *Mol Pain*, 2016, 12(2): 1744806916641679.

[52] Hou B, Cui X, Liu Y, et al. Positive feedback regulation between microRNA-132 and CREB in spinal cord contributes to bone cancer pain in mice[J]. *Eur J Pain*, 2016, 20(8):1299-1308.

[53] Hu XM, Zhang H, Xu H, et al. Chemokine receptor CXCR4 regulates CaMKII/CREB pathway in spinal neurons that underlies cancer-induced bone pain[J]. *Sci Rep*, 2017, 7(1):4005.

[54] Orton RJ, Sturm OE, Vyshemirsky V, et al. Computational modelling of the receptor-tyrosine-kinase-activated MAPK pathway[J]. *Biochem J*, 2005, 392(2):249-261.

[55] Wang LN, Yao M, Yang JP, et al. Cancer-induced bone pain sequentially activates the ERK/MAPK pathway in different cell types in the rat spinal cord[J]. *Mol Pain*, 2011, 7(1):48.

[56] Song Z, Xiong B, Zheng H, et al. STAT1 as a downstream mediator of ERK signaling contributes to bone cancer pain by regulating MHC II expression in spinal microglia[J]. *Brain Behav Immun*, 2017, 60(32):161-173.

[57] Xu Y, Liu J, He M, et al. Mechanisms of PDGF siRNA-mediated inhibition of bone cancer pain in the spinal cord[J]. *Sci Rep*, 2016, 6(1):27512.

[58] Ali ES, Hua J, Wilson CH, et al. The glucagon-like peptide-1 analogue exendin-4 reverses impaired intracellular Ca^{2+} signalling in steatotic hepatocytes[J]. *Biochim biophys acta*, 2016, 1863(9): 2135-2146.

[59] Igwe OJ, Chronwall BM. Hyperalgesia induced by peripheral inflammation is mediated by protein kinase C betaII isozyme in the rat spinal cord[J]. *Neuroscience*, 2001, 104(3):875-890.

[60] Yang H, Yan H, Li X, et al. Inhibition of connexin 43 and phosphorylated NR2B in spinal astrocytes attenuates bone cancer pain in mice[J]. *Front Cell Neurosci*, 2018, 12(8):129.

[61] Sassone-Corsi P. The cyclic AMP pathway[J]. *Cold Spring Harb Perspect Biol*, 2012, 4(12):653-660.

[62] Zhu GQ, Liu S, He DD, et al. Activation of the cAMP-PKA signaling pathway in rat dorsal root ganglion and spinal cord contributes toward induction and maintenance of bone cancer pain[J]. *Behav Pharmacol*, 2014, 25(4):267-276.

[63] Hou XR, Weng YQ, Wang TX, et al. Suppression of HDAC2 in spinal cord alleviates mechanical hyperalgesia and restores KCC2 expression in a rat model of bone cancer pain[J]. *Neuroscience*, 2018, 377(23):138-149.

[64] Tang P, Wang JM. WANG JM. Chemokines: The past, the present and the future[J]. *Cell Mol Immunol*, 2018, 15(4):295-298.

[65] Hughes CE, Nibbs RJB. A guide to chemokines and their receptors[J]. *FEBS Journal*, 2018, 285(16): 2944-2971.

[66] Hang LH, Shao DH, Chen Z, et al. Involvement of spinal CC chemokine ligand 5 in the development of bone cancer pain in rats[J]. *Basic Clin Pharmacol Toxicol*, 2013, 113(5):325-328.

[67] Jin D, Yang JP, Hu JH, et al. MCP-1 stimulates spinal microglia via PI3K/Akt pathway in bone cancer pain[J]. *Brain Res*, 2015, 1599:158-167.

[68] Shen W, Hu XM, Liu YN, et al. CXCL12 in astrocytes contributes to bone cancer pain through CXCR4-mediated neuronal sensitization and glial activation in rat spinal cord[J]. *J Neuroinflammation*, 2014, 11(2):75.

[69] Wang ZL, Du TT, Zhang RG. JNK in spinal cord facilitates bone cancer pain in rats through modulation of CXCL1[J]. *J Huazhong Univ Sci Technolog Med Sci*, 2016, 36(1):88-94.

[70] Zhou YQ, Gao HY, Guan XH, et al. Chemokines and their receptors: Potential therapeutic targets for bone cancer pain[J]. *Curr Pharm Des*, 2015, 21(34):5029-5033.

[71] Pinto V, Szucs P, Lima D, et al. Multisegmental A{delta}- and C-fiber input to neurons in lamina I and the lateral spinal nucleus[J]. *J Neurosci*, 2010, 30(6): 2384-2395.

[72] Schwei MJ, Honore P, Rogers SD, et al. Neurochemical and cellular reorganization of the spinal cord in a murine model of bone cancer pain[J]. *J Neurosci*, 1999, 19(24):10886-10897.

[73] Sun YE, Xu HY, Hao J, et al. The ubiquitination of spinal MrgC alleviates bone cancer pain and reduces intracellular calcium concentration in spinal neurons in mice[J]. *Neurochem Res*, 2019, 44(11):2527-2535.

[74] Cai J, Fang D, Liu XD, et al. Suppression of KCNQ/M (Kv7) potassium channels in the spinal cord contributes to the sensitization of dorsal horn WDR neurons and pain hypersensitivity in a rat model of bone cancer pain[J]. *Oncol Rep*, 2015, 33(3):1540-1550.

[75] Dong CS, Jiao LJ, Wang JY, et al. Effects of Shentong Zhuyu Decoction on the behavior in bone cancer pain rat[J]. *World J Integr Trad West Med*, 2016, 10(1): 24-28.

[76] Ren BT, Ma ZL, Qi YQ, et al. Effect of Shentong Zhuyu decoction on pain behavior and spinal cord astrocytes activation in a mouse model of osteocarcinoma pain[J]. *Chin J Integr Trad West Med*, 2011, 31(3):94-98.

[77] Zhang B.The mechanisms of Zhixin Formula and the pathway of TLR-NF-Kappa B in the rat model of bone cancer pain[D]. Nanjing University of Chinese Medicine, 2014.

[78] Zhen JW, Wen HH. Clinical research on Shenling Baizhu San in treating diarrhea irritable bowel syndrome[J]. *Clin J Chin Med*, 2015, 7(19):27-29.

[79] Feng Z, Feng Z, Han J, et al. Antinociceptive effects of Shenling Baizhu through PI3K-Akt-mTOR signaling pathway in a mouse model of bone metastasis with small-cell lung cancer[J]. *Evid Based Complement Alternat Med*, 2020, 2020:4121483.

[80] Chen Z, Ling XY. Advances in the study on Duhuojisheng decoction[J]. *Guide Chin Med*, 2012, 10(32):74-75.

[81] Sun PP, Yu ZM, Yu P. Duhuojisheng decoction intervention on pain behavior and spinal GFAP expression of astrocytes in mice with bone cancer pain[J]. *Chin Arch Trad Chin Med*, 2016, 34(2):4.

[82] Zhu W, Yang XL, Wu Y, et al. Effects of Yunnan Baiyao on pain behavior in mice model with bone cancer pain[J]. *Jiangsu Med J*, 2015, 41(21):3.

[83] Song HL.Study on the mechanism of Yishengukang decoction in inhibiting cancer induced bone pain and druggability research[D]. China Academy of Chinese Medical Sciences, 2019.

[84] Tian YE, Teng LR, Wang ZZ, et al. Study of the analgesic activities, chronic toxicity and addictive potential of Jia-Yuan-Qing pill in rats[J]. *Exp Ther Med*, 2015, 9(6):2349-2355.

[85] Bo D, Jia LQ, Gao FY, et al. Effect of Sangu Decoction, on metastatic bone destruction in rats with mammary cancer[J]. *Chin J Integr Med*, 2012,18(4): 304-307.

[86] Lu BC. Study on biological mechanism of Guzhi Zengsheng Zhitong wan based on "kidney governing bone" theory[D]. Changchun: Changchun University of Chinese Medicine, 2019.

[87] Luo QQ, Wang LF, Xu ZY, et al. Effects of Gutongling Prescription on the pain behavior in mice model of lung cancer with bone metastasis and MCP-1 and NGF in the spinal cord[J]. *Shanghai J Trad Chin Med*, 2017, 51(2):4.

[88] Luo QQ, Xu ZH, D HB. The effect of Gu Tong Ling prescription on the expressings of inflammatory factors and RANKL/OPG in lung cancer bone metastasis mouse mode[J]. *World J Integr Trad West Med*, 2020, 15(6):6.

[89] Yang B, Zhang Z, Yang Z, et al. Chanling gao attenuates bone cancer pain in rats by the IKKβ/NF-κB signaling pathway[J]. *Front Pharmacol*, 2020, 11:525.

[90] Fang ZY, Zhang M, Liu JN, et al. Tanshinone IIA: A review of its anticancer effects[J]. *Front Pharmacol*, 2020, 11:611087.

[91] Cao FL, Xu M, Wang Y, et al. Tanshinone IIA attenuates neuropathic pain via inhibiting glial activation and immune response[J]. *Pharmacol Biochem Behav*, 2015, 128:1-7.

[92] Hao W, Chen L, Wu LF, et al. Tanshinone IIA exerts an antinociceptive effect in rats with cancer-induced bone pain[J]. *Pain Phys*, 2016, 19(7):465-476.

[93] Lee E, Park HR, Ji ST, et al. Baicalein attenuates astroglial activation in the 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine-induced Parkinson's disease model by downregulating the activations of nuclear factor-κB, ERK, and JNK[J]. *J Neurosci Res*, 2014, 92(1): 130-139.

[94] Ke M, Zhang Z, Xu B, et al. Baicalein and baicalin promote antitumor immunity by suppressing PD-L1 expression in hepatocellular carcinoma cells[J]. *Int Immunopharmacol*, 2019, 75:105824.

[95] Gaire BP, Moon SK, Kim H. Scutellaria baicalensis in stroke management: Nature's blessing in traditional Eastern medicine[J]. *Chin J Integr Med*, 2014, 20(9): 712-720.

[96] Wang ZF, Jiang JW, Qiliang MY, et al. The analgesic and antineuroinflammatory effect of baicalein in cancer-induced bone pain[J]. *Evid-Based Complementray Altern Me*d, 2015, 2015(Print):1-8.

[97] Hatamipour M, Ramezani M, Tabassi SAS, et al. Demethoxycurcumin: A naturally occurring curcumin analogue for treating non-cancerous diseases[J]. *J Cell Physiol*, 2019, 234(11):19320-19330.

[98] Santos PDDF, Francisco C, Coqueiro A, et al. The nanoencapsulation of curcuminoids extracted from *Curcuma longa* L. and an evaluation of their cytotoxic, enzymatic, antioxidant and anti-inflammatory activities[J]. *Food Funct*, 2019, 10(2):73-82.

[99] Srirod S, Tewtrakul S. Anti-inflammatory and wound

healing effects of cream containing Curcuma mangga extract. *J Ethnopharmacol*, 2019, 238:111828.

[100] Zhang B, Huang R, Hua J, et al. Antitumor lignanamides from the aerial parts of Corydalis saxicola[J]. *Phytomedicine*, 2016, 23(13):1599-1609.

[101] Yu J, Liu Q, Lu X, et al. Inhibitory and inductive effects of Corydalis saxicola Bunting total alkaloids (CSBTA) on cytochrome P450s in rats[J]. *Phytother Res*, 2018, 32(9):1818-1827.

[102] Ju L, Hu P, Chen P, et al. Corydalis saxicola Bunting total alkaloids attenuate Walker 256-induced bone pain and osteoclastogenesis by suppressing RANKL-induced NF-κB and *c*-Fos/NFATc1 pathways in rats[J]. *Front Pharmacol*, 2020, 11: 609119.

[103] Yang H, Jiang C, Chen X, et al. Protective effects of sinomenine against LPS-induced inflammation in piglets[J]. *Microb Pathog*, 2017, 110:573-577.

[104] Xu M, Liu L, Qi C, et al. Sinomenine versus NSAIDs for the treatment of rheumatoid arthritis: A systematic review and meta-analysis[J]. *Planta Med*, 2008, 74(12):1423-1429.

[105] Kok TW, Yue PY, Mak NK, et al. The anti-angiogenic effect of sinomenine[J]. *Angiogenesis*, 2005, 8(1):3-12.

[106] Işık S, Karaman M, Micili SÇ, et al. Sinomenine ameliorates the airway remodelling, apoptosis of airway epithelial cells, and Th2 immune response in a murine model of chronic asthma[J]. *Allergol Immunopathol (Madr)*, 2018, 46(1):67-75.

[107] Feng S, Zhu L, Huang Z, et al. Controlled release of optimized electroporation enhances the transdermal efficiency of sinomenine hydrochloride for treating arthritis *in vitro* and in clinic[J]. *Drug Des Dev Ther*, 2017, 11:1737-1752.

[108] Rao S, Liu S, Zou L, et al. Erratum to: The effect of sinomenine in diabetic neuropathic pain mediated by the P2X3 receptor in dorsal root ganglia[J]. *Purinergic Signal*, 2017, 13(2):237.

[109] Li S, Han J, Wang DS, et al. Sinomenine attenuates chronic inflammatory pain in mice[J]. *Metab Brain Dis*, 2017, 32(1):211-219.

[110] Chen SP, Sun J, Zhou YQ, et al. Sinomenine attenuates cancer-induced bone pain via suppressing microglial JAK2/STAT3 and neuronal CAMKII/CREB cascades in rat models[J]. *Mol Pain*, 2018, 14:1744806918793232.

[111] Wang L, Zhang Y, Wang Z, et al. The antinociceptive properties of the corydalis yanhusuo extract[J]. *PLOS ONE*, 2016, 11(9):e0162875.

[112] Dai WL, Yan B, Jiang N, et al. Simultaneous inhibition of NMDA and mGlu1/5 receptors by levo-corydalmine in rat spinal cord attenuates bone cancer pain[J]. *Int J Cancer*, 2017, 141(4):805-815.

[113] Ahn EJ, Choi GJ, Kang H, et al. Antinociceptive effects of ginsenoside Rg3 in a rat model of incisional pain[J]. *Eur Surg Res*, 2016, 57(3-4):211-223.

[114] Jang M, Lee MJ, Choi JH, et al. Ginsenoside Rb1 attenuates acute inflammatory nociception by inhibition of neuronal ERK phosphorylation by regulation of the Nrf2 and NF-kappaB pathways[J]. *J Pain*, 2016, 17(3):282-297.

[115] Kim IJ, Park CH, Lee SH,et al. The role of spinal adrenergic receptors on the antinociception of ginsenosides in a rat postoperative pain model[J]. *Korean J Anesthesiol*, 2013, 65(1):55-60.

[116] Yoon MH, Huang LJ, Choi JI, et al. Antinociceptive effect of intrathecal ginsenosides through alpha-2 adrenoceptors in the formalin test of rats[J]. *Br J Anaesth*, 2011, 106(3):371-379.

[117] Yao FD, Yang JQ, Huang YC, et al. Antinociceptive effects of ginsenoside Rb1 in a rat model of cancer-induced bone pain[J]. *Exp Ther Med*, 2019, 17(5): 3859-3866.

[118] Zhang Y. Analgesic effect of active ingredients of Polygonum multiflorum on bone cancer pain in rats[D]. Guangxi Medical University, 2019.

[119] Yao X, Jia LQ, Tan HY, et al. Effects of Epimedium brevicornum on cancer pain and osteoclast in rat model of bonecancer pain[J]. *China J Trad Chin Med Pharm*, 2012, 27(5):1266-1269.

[120] Shen X, Sun X, Chen H, et al. Demethoxycucumin protects MDA-MB-231 cells induced bone destruction through JNK and ERK pathways inhibition[J]. *Cancer Chemother Pharmacol*, 2021, 87(4):487-499.