MEDS Chinese Medicine (2022)
Clausius Scientific Press, Canada

DOI: 10.23977/medcm.2022.040406
ISSN 2616-1753 Vol. 4 Num. 4

Research Progress on the Pharmacological Mechanism of Chuanxiong Rhizome in the Treatment of Migraine

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Keywords: Chuanxiong, migraine, chuanxiongzine, ferulic acid, ligustilide, nervous system, pharmacological mechanism

Abstract: Migraine is a common clinical cause of primary neurovascular headache, which is closely related to psychosocial factors and has a great impact on people's daily life. The pathogenesis of migraine is diverse, and the more mature mechanisms include vascular theory, neuronal theory, inflammatory mediator theory, neurotransmitter theory, neurotrophic factor, central sensitization and activation of the limbic system of the thalamus, and dopaminergic system-related gene theory. Chinese medicine believes that headache can occur when the evil of the six leucorrhea attacks the top of the body, stagnating the evil qi and blocking the clear yang, or when internal injuries lead to the reversal of qi, and blood, stagnation of the meridians, and loss of nourishment for the brain. Chuanxiong, as a common clinical herb, has the function of promoting blood circulation, dispelling wind, and relieving pain. Based on the pattern of medication used in the treatment of migraine during the Song, Jin, and Yuan dynasties, it was found that Chuanxiong was used very frequently in the treatment of headaches, headwinds, first wind, and migraine. In addition, modern pharmacological studies have found that the main components of Chuanxiong Ligusticum include tetramethylpyrazine (Chuanxiongzin), ferulic acid, volatile oil, ligustilide, chuanxiong lactone and alkyl phenyl peptides such as butenolide and that Chuanxiong Ligusticum has analgesic, anti-inflammatory, antioxidant, anti-tumor, anti-coagulant, anti-depressant, anti-aging, anti-atherosclerosis, cytoprotective, and cardiac function improving effects. In conclusion, Chuanxiong has great research potential in the treatment of migraine. In this paper, we mainly classify and summarize the effects of Chuanxiong in the treatment of migraine and provide a scientific basis for the application of Chuanxiong in the treatment of migraine.

1. Introduction

Migraine is an episodic disorder characterized by unilateral or bilateral throbbing pain. It is a recurrent moderate-to-severe neurovascular headache, often accompanied by nausea, vomiting, photophobia, and phonophobia [1]. The attacks can affect the daily life of patients and even lead to a series of complications that can endanger the lives of patients [2]. Epidemiology shows that 15%-30% of migraine patients have an aura before a headache attack [3]. Compared with other

cerebrovascular diseases, migraine is more common in young adults and has a higher disability rate, which seriously reduces the quality of life of patients. The pain attacks can affect the sleep of the patient, resulting in mental discomfort and drowsiness, which can lead to psychological problems, irritability, irritability, in severe cases, social danger. The main recognized pathogenic mechanisms include vascular theory, neuronal theory, inflammatory mediator theory, neurotransmitter theory, neurotrophic factor, central sensitization and activation of the limbic system of the thalamus, and dopaminergic system-related gene theory [4]. Some studies have reported the presence of several potential biomarkers in migraine patients, including inflammatory markers, nociceptive transmission neurotransmitters, oxidative stress-related molecules, etc. When a migraine occurs, a series of biochemical reactions occur in the body[5]. In TCM, it is mostly divided into two categories: external sensation and internal injury. The external sensation refers to the headache caused by wind, cold, dampness, heat, and other six evil spirits that invade the head and block the clear yang, while the internal injury is mostly caused by qi deficiency, blood stasis, and phlegm turbidity, which alone or in combination cause the body's qi and blood to run poorly and the meridians to be blocked. In this paper, we summarize the pathological mechanism of migraine and the related pharmacological study of Chuanxiong Ligustici and comprehensively analyze the advantages of Chuanxiong in the treatment of migraine.

2. Overview of research on chuanxiong

Rhizoma Chuanxiong is the dried rhizome of Chuan Reed, family Umbelliferae. It is mostly grayish brown or brown, with a rough and wrinkled epidermis and more raised nodules, with a firm texture that is not easily broken. It is pungent and warm in nature, bitter in taste, slightly numb to the tongue, and slightly sweet, and is classified as a member of the liver, gall bladder, and pericardium meridians. Chuanxiong is used to invigorate the blood and move Qi, dispel wind and relieve pain. The clinical experience of National Medical Master Zhang Xuewen in the use of Chuanxiong pairs was compiled and analyzed, and it was found that Chuanxiong was used in combination with several types of drugs to enhance its effect of invigorating the blood, promoting the flow of Qi and relieving pain. For example, Chuanxiong Ligusticum with Salviae, Chuanxiong Ligusticum with Radix Achyranthis Bidentatae, Chuanxiong Ligusticum with Radix Astragali, Chuanxiong Ligusticum with Panax notoginseng, Chuanxiong Ligusticum with Musk, and Chuanxiong Ligusticum with Radix Saxifraga, can invigorate blood and move Qi, dispel cold and relieve pain.

Modern pharmacological studies have found that chuanxiong contains a variety of active ingredients such as tetramethylpyrazine (Chuanxiongzin) and alkyl phenyl peptides such as ferulic acid, volatile oil, ligustilide, and butenolide, and have shown that chuanxiong mainly has analgesic, anti-inflammatory, antioxidant, anti-tumor, anti-coagulant, anti-depressant, anti-aging, anti-atherosclerosis, cytoprotective and cardiac function effects. However, there is a lack of studies based on the pharmacological effects of Chuanxiong in the treatment of migraine. This paper focuses on clarifying the pharmacological mechanisms related to the treatment of migraine by analyzing and organizing the common points between the pharmacological effects of Chuanxiong and the pathogenesis of migraine.

3. Therapeutic mechanism of chuanxiong in migraine

3.1. Regulation of neurotransmitters

It has been demonstrated that the trigeminal neurovascular doctrine is one of the most dominant doctrines affecting migraine attacks [6], the central aspect of which is neurogenic inflammation.

When migraine occurs, central pentraxin (5-HT) function is low, the homeostatic balance of excitatory and inhibitory neural pathways in the body is imbalanced, nociceptive neurons in the intracranial dura are activated, calcium channels are opened and activated, and calcium ions flow into the cells, initiating a series of cascade reactions followed by an inflammatory response [7]. CGRP dilates the meningeal vessels and increases blood flow, which in turn stimulates the secondary trigeminal nerve CGRP dilates the meningeal vasculature, increases blood flow, and stimulates increased excitability of trigeminal secondary neurons, contributing to migraine attacks. Therefore, inhibition of CGRP release is one of the entry points for the treatment of migraine attacks [8]. The most commonly used CGRP receptor antagonists in the clinical treatment of migraine are pharmacological agents that inhibit the release of CGRP and thus exert an anti-migraine effect [9]. Studies have shown that the specific anti-migraine drug sumatriptan reduces the occurrence of migraine by inhibiting TRPV1-mediated inward currents in the trigeminal ganglion and spontaneous excitatory postsynaptic potentials triggered by capsaicin in superficial layer II of the TNC region [10]. Chinese herbal medicine has remarkable efficacy in the treatment of migraine, and Chuanxiong plays a very important role in the treatment of all kinds of headaches and has been praised as "an important medicine for all kinds of pains up and down the body" since ancient times. Especially in the past 30 years, Chuanxiong has been used 86.9% of the time in Chinese herbal remedies for migraine [11]. The active ingredients of Chuanxiong Ligusticum, including chuanxiongzin, ferulic acid, and volatile oil, have all been shown to have a beneficial effect on migraine headaches by regulating the levels of neurotransmitters. Among them, chuanxiongzine, also known as tetramethylpyrazine, is one of the main components of chuanxiong, which has been shown to promote the excretion of calcium ions from cells and reduce calcium overload, as well as reduce the expression levels of various inflammatory factors and inhibit inflammation, thereby relieving headache symptoms [12]. In addition, ferulic acid has been shown to act as an antagonist to vascular endothelin, thereby inhibiting vasoconstriction and the resulting increase in blood pressure, and accelerating the synthesis of nitric oxide, which acts as a vasodilator [13]. It has been suggested that the volatile oil of Chuanxiong may act on nerve cells in the PAG region to increase 5-HTergic neuronal activity, thus achieving relief and treatment of migraine [14].

According to Chinese medicine, Chuanxiong is effective in the treatment of migraine through different combinations with various herbal medicines, among which, Chuanxiong-Adanggui, Chuanxiong-Glycyrrhiza, Chuanxiong-Bai Shao, Chuanxiong-Shu Dihuang, and Chuanxiong-Astragalus are the most frequently seen pairs [15]. Li Shengnan [16] After using acupuncture combined with Chuanxiong Chajiao San plus reduction in migraine patients, it was found that the patients' cerebral artery blood flow velocity, headache degree, and complication rate were reduced. Sun Zhuo-bi [17] et al. also used Chuanxiong Ligusticum Tea Tonic San Plus and Flunarizine to intervene in migraine patients and found a decrease in serum levels of norepinephrine, 5-HT, histamine, and other substances that can cause vasoconstriction, which in turn led to a decrease in cerebral blood flow velocity, thus relieving headache symptoms. In conclusion, Chuanxiong can improve migraine symptoms and improve the quality of life of migraine patients by regulating the release of neurotransmitters such as 5-HT and CGRP.

3.2. Inhibition of neuroinflammatory

There is evidence that neuroinflammation is strongly associated with the development of migraine, particularly aseptic inflammation. Inflammatory factors such as interleukin (IL), tumor necrosis factor-α (TNF-α), PGE2 (prostaglandin-E2) and COX-2 (cyclooxygenase-2) play a crucial role in the inflammatory response. Inflammatory factors, such as prostaglandin E2, prostaglandin E2 and COX-2 (cyclooxygenase-2, cyclooxygenase-2), play a crucial role in the inflammatory

response [18], which is significantly increased in the plasma during migraine attacks [19], inducing aseptic inflammation of the meningeal vessels and triggering a series of inflammatory cascades that exacerbate the occurrence of migraine [20,21]. There are several components in chuanxiong that can produce anti-inflammatory effects through different signaling pathways. Lin Hong et al [22] intervened with chuanxiong lactone A in rats with cerebral ischemia, and the levels of IL-1β and IL-6 in their brain tissues were significantly decreased, and cerebral ischemia-reperfusion injury was significantly reduced, indicating that chuanxiong lactone A can inhibit IL-1β and IL-6, alleviate the inflammatory response and migraine symptoms, reduce the incidence of migrainous cerebral infarction, and play a preventive role in migraine. In addition, a study showed that the cellular secretion of NO was significantly reduced in the ligustrolactone group compared with the model group, and the expression of the glial fibrillary acidic protein (GFAP) and TNF-α in the hippocampus of mice was significantly inhibited, indicating that ligustrolactone could inhibit neuroinflammation and relieve migraine symptoms. Another study showed that after the intervention of ligustrazide in Chuanxiong rhizome in migraine rats, the serum levels of IL-1β, IL-6, and TNF-α in the ligustrazide group were significantly lower than those in the positive control group compared with the rest of the groups, indicating that ligustrazide can reduce the inflammatory response and relieve migraine by down-regulating the serum levels of IL-1β, IL-6, and TNF-α [23].

3.3. Protective neurotrophic factors

A growing number of studies have confirmed that the treatment of migraine through neuronal protection has become a research hotspot. BDNF can be produced by a variety of cells, such as sensory neurons, motor neurons, immune cells, microglia, and astrocytes, and BDNF is mainly distributed in the hippocampus, amygdala, hypothalamus, trigeminal ganglion, etc. These regions play a key role in the regulation of pain, and emotion These areas play a key role in the regulation of pain, emotion, and behavioral expression. [24]. BDNF can protect neurons in these areas to a certain extent and relieve the onset of pain, on the other hand, it can also interact with 5-HTergic, dopaminergic neurons, and CGRP and other neurotransmitters [25], which are involved in the physiopathology of migraine. By exploring the active components of the neuroprotective effect of chuanxiong [26] et al established a model of oxyglucose deprivation-reoxyglucose SH-SY5Y cells and found that five components, namely, chuanxiong lactone I (SEI), chuanxiong lactone H (SEH), chuanxiong lactone A (SEA), ferulic acid (FA), and ligustrolactone (LIG), could reduce intracellular ROS. Another study showed that ferulic acid sodium can exert neurocytoprotective effects by inhibiting miRNA-9 and reducing the expression of AChE and BDNF [27]. In addition, ferulic acid can inhibit thrombospondin-like substances (TXA2) and adenosine diphosphate (ADP) for antithrombotic, and inhibit platelet aggregation by reducing phosphodiesterase activity, thus ameliorating thrombotic and platelet aggregation-induced neuronal cell damage [28]. By studying the protective effect of Astragalus membranaceus in combination with Chuanxiong on hypoxia and glucose deficiency injury in hippocampal neuronal cells of mammary rats, Wan Hao Yu [29] et al found that Chuanxiong was able to increase SOD and GSH-PX activities, reduce NO levels and LDH activity, and thus inhibit early apoptosis.

3.4. Regulation of the dopaminergic system

It has been suggested that dopaminergic disturbances are closely related to the development of migraine prodromal symptoms, and studies have shown that dopamine (DA) levels, dopamine receptor levels, and dopamine anabolic-related gene expression are abnormal in migraine patients [30]. During migraine attacks, dopamine D2 receptors in the trigeminal midbrain nucleus (Vme) of the periaqueductal gray matter (PAG) are hypersensitive and activate the hypothalamic

paraventricular nucleus to produce oxytocin and regulate neuronal firing in the trigeminocervical complex (TCC), resulting in nausea, vomiting, yawning, cervical Dopaminergic symptoms such as nausea, vomiting, yawning, and neck tonicity, which are positively correlated with dopamine receptors [31,33]. Cheng Jing [34] et al demonstrated an increased expression of D2 receptors in Vme of migraine rats and a decreasing trend of dopamine D2 receptors in the group of rats with Chuanxiong-Tianma intervention, further demonstrating that Chuanxiong could inhibit dopamine D2 production and reduce the appearance of migraine prodromal symptoms.

3.5. Inhibition of central sensitization

When a migraine occurs, neuronal-glial cells, especially microglia, are closely related to central sensitization. Pain stimulation causes activation of the P2X7 receptor (P2X7R), and purinergic receptor activation induces microglia activation through the RhoA/ROCK pathway. TNF-α and brain-derived neurotrophic factor, etc., promote NF-κB phosphorylation, induce NF-κB transcription, and release adenosine triphosphate (ATP), glutamate, and chemokines, etc., further promoting central sensitization [35,37]. Studies have shown that chuanxiongzin significantly reduces the mechanical pain threshold in rats [38], and chuanxiong can achieve central analgesia by modulating the brain/spinal Panx1-Src-NMDAR-2B pathway [39]. Ligustrolactone inhibits the activation of NF-κB and PNF-κB in microglia, thereby reducing the release of IL-1b, TNF-α, and IL-6 and relieving the onset of headache [40]. Chuanju Pain Relief Capsules intervened in migraine rats and proved that Chuanju Pain Relief Capsules could inhibit the activation of the NF-κB signaling pathway, reduce the expression of inflammatory factors and inhibit the expression of c-fos and c-jun in brain tissues, inhibit the transmission of pain information and reduce the central sensitization effect to alleviate the occurrence of migraine.

4. Rhizoma Chuanxiong-related pairs of drugs

Chuanxiong is used very frequently in the treatment of migraine and has remarkable clinical efficacy. It is also often used in combination with other herbal medicines such as angelica, aromatic herbs, and asparagus to form pairs of medicines. Pairs are widely used in traditional Chinese medicine as the smallest unit in the composition of a prescription and are highly specific in the treatment of disease. This kind of combination can also strengthen the mutual restraint of flavors between drugs, to maximize the efficacy of the medicine and reduce the adverse effects on the body. Migraines can be caused by liver stagnation and qi stagnation, which leads to pain when the qi and blood are not in harmony. Chuanxiong and Chaihu can work together to relieve liver stagnation and move qi and blood, thus relieving headaches. Chuanxiong and Radix Paeoniae belong to the Heart and Liver meridians, and together they can regulate Qi and Blood, Cold and Heat, and they can protect nerve cells and slow down apoptosis of nerve cells through ErbB, VEGF, and other related signaling pathways. The combination of Chuanxiong and Paeonia lactiflora can disperse acid and reduce pain in the liver. Hu Kun [41] et al found that Chuanxiong-Paeonia lactiflora pairs can increase the pain threshold of migraine rats, improve the central nociceptive sensitization system, and reduce pain production. The decoction rate of ferulic acid was significantly increased when the two drugs were combined, which could achieve better treatment of migraine [42]. The combination of Chuanxiong and Tianma is one of the classical pairs in the treatment of migraine in traditional Chinese medicine, which has a significant modulating effect on substances involved in the development of migraines, such as pentazocine and nitric oxide [43]. Wu Sha [44] et al demonstrated that the alcoholic extract of Chuanxiong-Xiong can increase cerebral blood flow and promote cerebral blood flow in rats for a certain period, and found that this alcoholic extract can regulate the content of migraine-active substances such as dopamine and norepinephrine to achieve

the therapeutic effect of migraine. The combination of Rhizoma Chuanxiong and Radix Angelicae Sinensis not only tonifies but also restrains each other, preventing Rhizoma Chuanxiong from being too pungent and depleting the vital energy, and a study [45] showed that the two are used most frequently in the treatment of migraine. Some studies have even found that combining Qiangxiong with Chuanxiong can help to eliminate the wind and relieve pain. It is often used clinically for treating headaches caused by the invasion of wind, cold and dampness, and stagnation.

5. Summary and Outlook

In summary, it can be seen that Chuanxiong has significant efficacy in the treatment of migraine. By summarizing the pharmacological mechanisms of Chuanxiong in the treatment of migraine, this study can conclude that the main mechanisms of Chuanxiong in the treatment of migraine include regulation of neurotransmitters, inhibition of neuroinflammation, protection of neurotrophic factors, regulation of the dopaminergic system, and inhibition of central sensitization. In addition, the treatment of migraine with Chuanxiong is mostly highlighted by animal experiments, and little research has been done in clinical trials. Although Chuanxiong and its counterparts have a wide range of clinical applications and clear effects, there is a lack of animal studies on the mechanisms and pathways of action, and the effects of concoctions and their dosage on the active ingredients of Chuanxiong are still unclear. Therefore, in future studies, the effects of different concoctions of Rhizoma Ligusticum Chuanxiong on its active ingredients should be further explored, as well as the differences in the effects of different dosages of Rhizoma Ligusticum Chuanxiong, and the mechanisms of action of the active ingredients contained in Rhizoma Ligusticum Chuanxiong, such as alkyl phthalides, should also be studied in depth. At the same time, more clinical studies are needed to further confirm the differences in the therapeutic effects of chuanxiong and its concoctions with different herbal composition pairs, to find the optimal dosage and selection of concoctions and pairs, to provide more accurate clinical solutions and make chuanxiong more widely used in clinical practice.

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