

Overview of the Mechanism of Action of Gentiana Scabra in the Treatment of Rheumatoid Arthritis

Hongli Miao¹, Yanchun Zhang^{2,*}

¹Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China

²Xi'an People's Hospital (Xi'an Fourth Hospital), Xi'an 710004, Shaanxi, China

*Correspondence Author

Abstract: ***Objective:** To provide a comprehensive review of the research on the analgesic, anti-inflammatory, anti-swelling and analgesic effects of Radix Gentiana Macrophylla. **Methods:** Gentiana macrocephala has an analgesic effect in modern research, commonly used in various rheumatism and paralysis, numbness, contracture and soreness of the muscles and bones and other diseases of the pain treatment, can be extracted from the sterol glycoside salts and other medicinal components, its anti-inflammatory and analgesic and treatment of acute arthritis episodes of the clinical effect of the performance of the particularly unique and significant. The results can make the joint swelling, pain and other symptoms can be reduced, and the risk of reoccurrence can also be reduced after the introduction of the drug. **Conclusion:** In the treatment of rheumatoid arthritis, Gentiana Macrophyllae alone and in combination can improve joint symptoms such as stiffness, swelling, pain, distension and deformity as well as other systemic symptoms of rheumatoid arthritis.*

Keywords: Gentiana macrocephala, Rheumatoid arthritis, Mechanism of action, Compounding, Review.

1. Introduction

Gentiana Macrophyllae is commonly used in traditional Chinese medicine for dispelling wind-dampness and cold-dampness, and because it is one of the top ten ancient Chinese medicinal herbs, it is mildly pungent and bitter in flavor, flat in nature, and belongs to the stomach, liver and gallbladder meridians of the human body. In the whole system of traditional Chinese medicine culture medical treasure trove has dispel wind-heat and chase wind-dampness, clearing cold and draining damp-heat, stopping paralysis and micro-pain, and eliminating the heat shower of the hands and feet of the deficiency and other main clinical effects. It is used for treating cold pain in limbs of wind-dampness, cold paralysis after stroke, hemiplegia, numbness of muscles and limbs, soreness and pain of bones and joints, damp-heat and wind-cold cold and jaundice, hot and dampness in limbs, afternoon fever in children's chamomile. In the field of modern zoological research, Gentiana Macrophylla (alias: Gentiana macrocephala) is a plant of the genus Gentiana in the family Gentianaceae of the order Gentiana. This kind of plant is produced in Mongolia, Russia, China, Inner Mongolia, Ningxia, Hebei, Shaanxi, Xinjiang, Northeast, Shanxi and other places.

2. Pharmacological Effects

2.1 Active Ingredients

Combined with the relevant clinical research data search, isolated to Gentiana scabra active ingredient samples 27, the 27 in the composition according to certain scientific methods of analysis and summarization, screening and purification only from which contains OB Qin \geq content of less than 30% and DL Qin \geq concentration of 0.18 Gentiana content of the content of the active ingredients of the effective plant content is relatively small. The main phytoconstituents of Mulberry twig extract were mainly sansin, ketone, other active

ingredients, and zhujun acid, bittersweet and gentianin extracted from Gentiana macrophylla, in addition to effective ingredients such as essential oil of vinpocetine tree were also detected [1]. Several of these substances can produce pharmacological effects after combining with some specific targets to achieve therapeutic effects.

2.2 Targets of Action

Modern research on the treatment has shown that Gentiana Macrophylla contains active ingredients which have their own target points of action. Its therapeutic effects are realized through these action points. In this study, the levels of two inflammatory factors increased significantly, which preliminarily verified that the active ingredients of Radix Gentiana Macrophyllae interfered with the NF-KB signaling pathway and regulated the downstream target proteins for the treatment of RA in the active phase [2]. The serological test results have indicated that the efficacy of Gentiana Macrophyllae Huanghuang Tongpi Tang is positively correlated with the changes in inflammatory factors downstream of the NF-KB signaling pathway, and that the NF-xB signaling pathway is most likely a candidate signaling pathway of Gentiana Macrophyllae Huanghuang Tongpi Tang for the treatment of RA, but further animal experiments are needed to verify this [3].

3. Mechanism of Action

3.1 Signaling Pathways

In the study of inflammatory signaling pathways in RA, the NF-KB signaling pathway has received extensive attention from researchers, mainly including p65 and p50 [4]. These proteins act as immune homodimers and antigenic heterodimers, respectively, and play extremely important roles in the bidirectional regulatory system of cellular inflammation and specific immune response. The classical NF- and xB-signaling pathways can be directly triggered by a

variety of specific pro-inflammatory growth factors, specific antigens, receptor proteins and specific ligands. When these initial triggers and activators are combined with the receptor proteins, they activate the expression of an additional receptor, IKK, which can be further activated to phosphorylate the receptor I κ B-coenzyme a protein and ubiquitinate the protein directly via the ubiquitin ligase body, allowing the receptor protein to be simultaneously activated by the 26S protein and the 26S ligand. The receptor protein is selectively recognized and degraded by the 26S proteasome [5].

3.2 Effects on Arthritis

Macrophyllum officinale, a kind of Macrophyllum officinale, can effectively inhibit the antibody activity level of anti-cyclic citrullinated peptidase inhibitor (CCP) in the serum liver of arthritic rats at an early stage and reduce the antibody level of free TNF-alpha protein in vivo, improve the swelling of the diseased joint capsule, and reduce the degree of severe inflammation, and it can also improve the symptoms of knee synovitis, thus improving the condition of the damaged joints, as found in X-ray examination [6]. It can also improve the symptoms of synovitis in knee joints, thus improving the condition of damaged joints [6]. Gentiana Macrophylla ethanol and its extracts can also selectively reduce the damage of articular cartilage in the sodium urate gout model in rats. Gentiana Macrophylla also has certain antipyretic, analgesic, and anti-inflammatory and analgesic effects, and the combination of Gentiana Macrophylla Flower Extracts and Macrophylla Flower Ginseng can also improve the symptoms of knee synovitis and improve the condition of damaged joints [6]. Gentiana macrophylla flower extract and Macrophyllum officinale flower glycoside can also reduce the number of generalized muscle and torsion joint movement episodes due to acetic acid stimulation-induced severe pain, strengthen the pain threshold of joints, alleviate the pain of patients, and prolong the latency period of spasm caused by the inflammatory period [7]. Thus, the hypnotic analgesic and tranquilizing analgesic efficacy of Gentiana macrophylla flowers can be seen from this experiment.

3.3 Traditional Chinese Medicine (TCM) Treatments

External wind-heat, or cold and dampness in the body, condensation of evil qi and not resolved, see the image of depression and heat, dampness and heat of the evil qi and steam, invasion in the whole body limbs, skin and flesh, tendons and veins, meridians and collaterals, joints within the positive qi is dampness and heat and bias for the heat and toxin abound in the joints, joints redness, swelling and stinging pain and accompanied by a mild feeling of muscle heaviness, activities and joints obstacles, thirst to drink or extremely happy to drink, urination is short more than yellow and turbid, like the tongue is red like a thick moss, yellow and slippery pulse, it should be considered to be Dampness and heat in the body lead to qi and blood clearing, clear the etiology of heat, in order to carry out clearing dampness to remove fire and heat medicine solution [8]. Indicates that in China's modern clinicians in the exploration of rheumatoid arthritis evidence for a series of traditional Chinese medicine and treatment of new program practice, deep evidence of mute wind-heat toxin mechanism in the promotion of the further development of the disease, or the evolution of the process of

the body's pathology plays an important role in another more important role in the location of the body, the choice of clinical doctors of the principle of identification of the drug can often be closely related to the treatment of this disease and coincide with the timing of the treatment. The timing is closely related and coincides with the treatment of this disease. If a part of the population suffers from rheumatoid arthritis at the same time with spleen and stomach yin and yang deficiency, it should be used with caution. The main consideration for the treatment of rheumatoid arthritis patients and the body yang deficiency and wetness; rheumatoid arthritis patients often, symptomatic dampness stagnation paralysis of the therapeutic use of drugs. Can also be used individually or in combination, for rheumatoid arthritis evidence of spleen Yang weakness and cold and damp blood stasis and stagnation of Qi, can be used for treatment. Single medicine and combination of medicine for rheumatoid arthritis stasis of blood and qi stagnation paralysis [9].

4. Different Combinations

4.1 Gentiana Macrophyllae with Di Long, Sang Zhi, Lonicera Japonica

According to the results of domestic clinical trials in recent years, Gentiana Macrophyllae Injection was used as an adjunctive treatment for rheumatoid arthritis after a long-term combination of the extracts of the green snake Dillon, Mulberry twig, and Lonicera japonica for 8 weeks of follow-up, mainly observing the patients' low blood-urine sedimentation rate, blood sedimentation rate, distribution of anti-cyclic citrullinated peptide antibodies and their rate of change, CRP, the number of pain sites, pressure pain index, pain index, swelling, grip test of both hands, morning stiffness time and relief time, walking time per meter after a specified period of time, and other severe discomfort and clinical response. pain index, degree of swelling, grip strength test of both hands, time of morning stiffness and time of its relief, time of walking per meter after a specified period of time, and the degree of change in the distribution of such factors, as well as other clinical reactions to severe discomfort, and the rate of occurrence of this symptom [10]. Symptomatic manifestations of morning stiffness of joints, pain in the extremities, symmetrical onset of small joints, and deformities after developing the disease. Other symptoms, including pain in the hands, feet, wrists, ankles, temporomandibular joints and other types of acute and chronic arthritis pain episodes, as well as other related clinical symptoms of the disease, after treatment, has been able to basically completely recover by itself or disappeared, and after the rheumatology and immunology doctors long-term follow-up and examination, it can be observed that the patient and the deformity of the limbs left behind in the past has been able to stabilize the condition of the basically completely, or has been restored to normal; at present, patients with severe pain and morning stiffness, muscle aches and pains, joint symmetry, and malformations of the limbs. At present, the patient's limbs, bones and joints, severe muscle aches and stiffness in the morning, congenital joint deformity and pain, as well as other acute rheumatoid arthritis pain manifestations, including hands, feet, wrists, ankles, temporomandibular joints, and other corresponding clinical symptoms in recent years have also been some or slight or disappeared [11].

4.2 Contraindications for the Combination of Gentiana Macrophyllae with Lonicera Japonica, Lonicera Japonica, Lonicera Japonica, and Lonicera Japonica

Hai Feng Teng, Qing Feng Teng, Luo Shi Teng, Lonicera japonica, and other drugs have more obvious through the Shu muscle and muscle and the vitality of the great work of the sinews and bones of the qi and blood, to help the king's medicine can be through the elimination of evil wind and cold to remove dampness to eliminate swelling and swelling through the Chinese herbal medicine to eliminate dampness to eliminate swelling and swelling and pain, according to the study of China's modern Clinical Immunology Laboratory of Pharmacology, but also confirms that it contains a variety of saponins and saponin compounds and can be quickly restored to improve the plasma of normal rats or the normal effective content of red cell plasma containing various vitamins C and -carotenoids AMP, thus significantly enhancing the humoral immune function. Erythrocyte plasma contains a variety of vitamin C and - carotenoids AMP normal effective content, thus significantly enhancing the humoral immune function. It can effectively and rapidly improve the circulation of normal hematopoietic function in the periphery of the bone marrow of the patients, and can also strengthen the proliferation and regulation of lymphocytes in the body, as well as the enhancement of non-specific immune function of the bone marrow also has obvious help [12]. The grading of therapeutic effect, clinical basically can be cured: all the symptoms have been relieved or even disappeared, the activity signs are restored to normal, the main tissues of the bone and joint function of the physical and chemical test and other indicators of the examination are all correct; the basic indicators of the obvious effect: all the symptoms have been improved and basically eliminated, the symptoms are invalid or although there is a change in the main activity of the joints, the symptoms are almost completely eliminated.

4.3 Gentiana Macrophyllae and Fenugreek

The data of the study report show that: the swollen and serious parts of the foot-plantar area of rats in the medicated group began to have slightly obvious pain symptoms, the disappearance of fighting sounds and the number of hissing sounds obviously had a slight reduction in the symptoms; rats were clinically observed for seven consecutive cycles, the swelling appeared to have an obvious degree of improvement and no obvious symptoms gradually reduced, the ulcers could be almost completely healed, the phenomenon of fever gradually appeared to be reduced, and the color of the swollen parts began to be the most The color of the swollen area changed from deep red or bright red to dark red to light; the redness and swelling of the skin in the area subsided almost completely when the affected area was observed after about three weeks of medication [13]. Touching the affected part, it can be clearly felt that the touch becomes softer, the subsidence of fever is less obvious, and the refusal to press does not necessarily occur; observation of the model group, the disease model group, found that the above symptoms of the two did not see obvious improvement. Compared with the model group and the disease model group, the duration of pain threshold was significantly prolonged by the combination of Radix Gentiana Macrophyllae and Radix et Rhizoma Pinelliae

($P < 0.01$). The mean plasma TNF- α , IL-1 β , and PGE2 content values were significantly reduced in different degrees in each administration group compared with the control group of the disease model group, among which the mean peak serum TNF- α content was significantly reduced in the Qinfeng group ($P < 0.01$) [14].

4.4 Gentiana Macrophyllae and Qiangwu Compatibility

Qiangwu Tang has the efficacy of dispelling wind and activating blood circulation, removing blood stasis and dispelling wind-cold, transforming phlegm and dampness, relieving pain and dispersing cold paralysis, while Gentiana Macrophyllae Drink has the efficacy of clearing away heat, promoting qi and activating blood circulation and dispelling all kinds of rheumatism and wind-dampness, clearing away internal dampness and heat, clearing away wind and dispelling wind and relieving swelling and relieving pain and relieving pain and relieving pain and relieving swelling, and so on. The two main drugs can effectively promote the efficacy of dispelling wind, activating blood and dispelling wind and dampness, dispersing cold and paralysis and pain, activating blood and reducing swelling, relieving pain and relieving pain. Patients after treatment of fracture two weeks later did not appear obvious swelling and pain around the joint capsule. The effective rate of total patient treatment in the observation group was much higher than that in the control group, which shows that the single use of Qiangwu gentiana treatment can also significantly improve the total patient efficacy of RA treatment in the observation group; and the amount of adverse reactions in the same observation group was much less than that in the control group, which shows that the joint application of Qiangwu gentiana can also greatly reduce the total patient efficacy in the same observation group. This shows that the combined application of Qiangwu and gentiana can also greatly reduce the clinical adverse reactions of RA patients in the control group. This experiment verifies the value of the classic combination of Qiangwu and gentiana in rheumatoid arthritis, and proves that the combination of gentiana and Qiangwu can be used to alleviate the symptoms of patients with rheumatoid arthritis [16].

4.5 Gentiana and Licorice

Licorice, first recorded in the Compendium of Materia Medica "Shen Nong Ben Cao Jing", classified as licorice, nature of pungent, salty, sweet, flat, to the heart, lungs, small intestine through the spleen into the middle, stomach meridian. Functions include: benefiting the qi, tonifying the spleen, clearing heat and removing toxins, expelling phlegm, moistening the lungs, removing phlegm and relieving coughs, relieving anxiety and detoxifying the lungs, promoting circulation of qi and relieving pain, and harmonizing the medicinal properties of various foodstuffs." Yang is not enough to make up for the sweet", this product is sweet and flat, hot with warm and tonic, with ginseng, atractylodes, poria, can be beneficial to the spleen, such as "Taiping Huimin and the Bureau of Dosage Square" said that the Sen-Poria Four Gentlemen's Soup. Licorice, when used raw is bitter and cool, both can activate blood and clear heat, but also diuretic detoxification, can be used for cold and damp evil phlegm and toxicity of dampness and heat and the formation of such rheumatoid arthritis, in addition, there is the "Jingyu

quanquanben caozheng" mentioned in the "Licorice taste to sweet, and get in the neutral, have the tonic function, so poisonous drugs to get to the relief of its toxicity, and just medicine and the nature of the medicine". There is the function of harmonizing all medicines, each for the urgent need of medicine, so the ancients have its name "national old". Modern clinical experiments and pharmacological observations have also been able to confirm that licorice soup tracking extracts contained in and trace amounts of isoglycyrrhizin can indeed have some relatively obvious and mild and long-lasting local anti-inflammatory or antispasmodic and sedative effects. Glycyrrhiza glabra fruit and seeds contain and are rich in the active phytoconstituent glycyrrhizin, which can inhibit the selective oxidative and metabolic activity of eosinophilic neutrophilic leukocyte enzymes in vivo to achieve selective reduction of bacterial toxins in vivo to reduce the enzymatic activity of the ROS (Reactive Oxygen Species) enzyme to form and rapidly produce its significant anti-inflammatory and antiseptic and anti-inflammatory effects. One of the main detoxification and metabolism mechanisms of glycyrrhizinase is the selective adsorption of glycyrrhizin. Another component, glycyrrhizinic acid, promotes the synthesis of adrenocorticotrophic hormone, and its mechanism of action is similar to the receptor-selective binding of sodium glucuronides, as well as its influence on neurological function through the regulation of hypothalamic pituitary function [17].

5. Discussion

Preliminary studies of multi-tissue pathohistological and immunophysiological changes in many patients with chronic rheumatoid arthritis have amply demonstrated that the factors that cause periosteal destruction and formation of necrotic tissues in these acute rheumatoid arthritic joints can be collectively referred to as a variety of immune cytokines capable of stimulating the production of interferon antigens in the synovial membranes of rheumatoid arthritis, e.g., antibodies to IL-1, an anti-tumor immunopituitary necrosis factor (TNF α), and their antigenic complexes, which are named interferons. Inhibitory factor antibody (TNF α) and its antigenic complex, etc., named interferon, interferon can be associated with through the regulation of enzymes, such as collagenase, gene proteolytic enzymes, etc., in acute infections in the bacterial body of many special inflammatory factors, so it can play an important and even the primary role in bacterial organisms in the mechanism of systemic infection manifestation of the regulatory role. It can obviously and efficiently inhibit the localized swelling of the posterior tibial and toe nerves of the injected patients on the healthy side and the skin of the anterior and posterior limbs due to acute delayed hypersensitivity, inhibit the erythema and exudate of the ear and nodular swelling of the caudal tibial region of the injected patients and other cutaneous neurological reflexes damage [18]. The extract of *Gentiana scabra* was also able to rapidly and partially reduce the degree of congestion, swelling and pain in the affected feet within a short period of time, and at the same time, it was able to make the degree of congestion, swelling and pain in the skin of the lower limbs significant or more pronounced and reduced, and the damage of erythema and caudal nodules of the ear was significantly reduced.

References

- [1] MA Tengmao, LIU Fei, WANG Rong, WU Guotai, GAO Huiqin. Effects of different combinations of Radix *Gentiana scabra* on analgesic effect and serum TNF - α , IL - 1 β , PGE2 in rats with rheumatic fever paralysis rheumatoid arthritis model[J]. Liaoning Journal of Chinese Medicine, 2017, 39(1):11-15.
- [2] Pang Xuefeng, Meng Yuhua. Treatment of 86 cases of rheumatoid arthritis by expelling wind and removing paralysis capsule[J]. Shaanxi Traditional Chinese Medicine, 2002, 23(12):1073-1075.
- [3] ZHAO Weigang. Treatment of rheumatoid arthritis with methotrexate and diclofenac sodium in 36 cases[J]. Rheumatism and Arthritis, 2013, 2(6):15-16, 30.
- [4] Xiao Wei, Mao Huihui, Zhang Xianjian, et al. Observation on clinical efficacy of external application of Xinzhuang tablet combined with western medicine in the treatment of gouty arthritis. Shizhen Guomao, 2017, 28(5): 137-138.
- [5] LANG Yu-Ying, WANG Bin. Study on the effect of *Gentiana scabra* extract on adjuvant arthritis in rats. Chinese Traditional Medicine Science and Technology, 2012, 19(5): 409-409.
- [6] Wei R P, Sun F L, Ai H X, et al. Progress in the study of anti-inflammatory effects and mechanisms of gentianoside [J]. Chinese Journal of Pharmacology and Toxicology, 2014, 28(4): 678-679.
- [7] Zhang Xinxin, Jia Na, Sun Chen, Zhao Wenna, Sun Wenji. Study on the anti-inflammatory paroxysmal effects of *Macrophyllum macrocarpon* flower and *Sesbania macrophyllum* flower[J]. Northwest Journal of Pharmacy, 2006, 12(9): 63- 64.
- [8] Li Jing. Clinical observation of 80 cases of frozen shoulder treated with small needle knife combined with macrophyte soup[J]. New Chinese Medicine, 2015, 47(4):247- 248.
- [9] Tian Delu. Internal medicine of traditional Chinese medicine [M]. Beijing: People's Health Publishing House, 2008: 370.
- [10] Wu Fenghai. Clinical observation on the treatment of rheumatoid arthritis by *Gentiana Macrophylla* Wuteng Drink[J]. Beijing: China Medical Science and Technology Press, 2018: 117- 119.
- [11] Jiang Shushu, Gao Zisan, Gan Junxue, et al. Progress of Th17- STAT3 positive feedback pathway in pro-inflammatory mechanism of rheumatoid arthritis[J]. Liaoning Journal of Chinese Medicine, 2015, 42(4):897-901.
- [12] Huang Youhan, Zhu Jian, Lin Tianxu. Observation on the efficacy of *Macrophyllum Gentianum* Soup plus reduction in the treatment of acute gouty arthritis[J]. Journal of Traditional Chinese Medicine, 2013, 41(3): 115.
- [13] Niu Sailong, Sun Fuzeng, Zhang Xingnai. Anti-inflammatory effects of total cyclic enol ether terpene glycosides of *Gentiana scabra* and its mechanism [J]. Journal of Pharmacy Practice, 2013, 31(3): 198-200.
- [14] Liu Weiwei, Zhang Fuqiang, Wu Xi, et al. Expression and clinical significance of miR-34a and miR-125b in peripheral blood mononuclear cells of rheumatoid

- arthritis patients. *World Scientific Research and Development* 2015, 37(3): 286-289.
- [15] Wang Guangming, Guo Xiaozhuang, Bai Rao. *Combination of Chinese and Western medicine in the treatment of rheumatic diseases*. Tianjin: Tianjin Science and Technology Press 1989:553.
- [16] TAN Yanjin, YANG Xiaofeng. Clinical efficacy and effect on serum inflammatory factor in rheumatoid arthritis treated with Tongpai Tang plus reduction combined with moxibustion[J]. *World Journal of Integrative Medicine*, 2020, 15(5):884-887+968.
- [17] ZHANG Yan, XU Qiong, CHEN Menglu. Efficacy and effect on joint function and inflammatory factors of DuoYu parasitic soup combined with leflunomide in the treatment of elderly rheumatoid arthritis[J]. *Chinese Journal of Gerontology*, 2019, 39(22):5569-5571.
- [18] ZHANG Shuhua, YANG Huiyong, ZHENG Chenna, et al. Correlation of IL-1, IL-10 and TNF- β single nucleotide polymorphisms with rheumatoid arthritis in the Han Chinese population in Quanzhou, Fujian[J]. *Chinese Journal of Pathophysiology*, 2020, 36(2): 354-359.