

Review of Pharmacological Effects and Clinical Applications of Gancao Fuzi Decoction

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ABSTRACT

Gancao Fuzi(GF)decoction is from the "Treatise on Typhoid Fever" by the famous physician Zhang Zhongjing, and the formula is well known in the field of traditional Chinese medicine for its unique composition and therapeutic efficacy. The purpose of this article is to provide a comprehensive summary of the modern clinical applications of GF decoction and to explore its utility in depth from multiple perspectives, including the treatment of rheumatoid arthritis, adjuvant arthritis, ankylosing spondylitis, osteoarthritis of the knee, and other diseases. By analyzing the therapeutic effects of GF decoction in these diseases, it is hoped that it can provide a strong reference basis for Chinese medicine treatment in the clinic, and help doctors to better utilize GF decoction to improve the therapeutic effects and alleviate the pain of patients. Meanwhile, the pharmacological mechanism of GF decoction in modern research will also be explored, as well as its specific application methods in the treatment of different diseases, so as to provide a scientific basis for further research and application of GF decoction.

KEYWORDS

Gancao Fuzi decoction; Pharmacodynamic material basis; Review; Clinical applications

"Gancao Fuzi (GF) decoction " is from 'The Treatise on Typhoid Fever' by Zhang Zhongjing, which consists of four medicines:Aconite,Licorice, Atractylodes Macrocephalae, and Cinnamon Branches. The dosage commonly used in modern clinics is 6 grams of Licorice, 12 grams of Aconite , 6 grams of Atractylodes Macrocephalae and 12 grams of Cinnamon Branches, with Aconite being a poisonous medicine that needs to be decocted first.

"Yi Kao Fang" further describes the principle of its combination, Atractylodes macrocephala dry spleen, then the wet has the control. Is the formula also, to cinnamon, with the pungent heat and cure wet, as if the scribbling of the ground, get the sun exposure, not the end of the day and wet to go, but also one of the ways to cure wet. The intention is to use appendicitis to invigorate yang qi, use gui zhi to disperse cold and open the veins, use atractylodes macrocephala to strengthen the spleen and dampness, and licorice to harmonize the stomach and strengthen the spleen. The study showed that the MRT, AUCo and AUCo of glycyrrhizic acid increased significantly after oral intake of GF decoction with Licorice and Licorice as the monarch drug, suggesting that Licorice, when combined with Licorice, Atractylodes macrocephala and Cinnamomum cinnamomum, facilitates the absorption of glycyrrhizic acid in the body, increasing its bioavailability and lengthening the duration of its action, and proving the reasonableness and science of GF decoction's formulae from the view of pharmacokinetics^[1].

The main treatment of this formula is described in the Treatise on Typhoid Fever, and in modern clinical practice, GF decoction is mainly used for the treatment of rheumatoid arthritis, rheumatoid arthritis, peri-arthritis, ankylosing spondylitis, sciatica, gout, and thrombo-occlusive vasculitis, and other diseases. Therefore, this paper intends to summarize from the now published articles about the modern treatment of GF decoction, analyze the application of modern clinical treatment of GF decoction ,and provide ideas for the subsequent clinical use.

1 The basis of GF to increase effect and reduce toxicity

Licorice is sweet in nature.,based on the law of Chinese medicine flavor, such as pungent and sweet, sour and sweet, the combination can play a role in enhancing the effect. With the flavor of acrid, with licorice, acrid and sweet transform yang, i.e., the pairing of acrid and sweet herbs can help to warm and transport yang qi, and increase the effect of the passage of Licorice^[2]. Moreover, relevant experiments showed that the combination of Licorice alkaloids and licorice active substances could effectively anti-inflammatory, alleviate the symptoms of rat adjuvant arthritis (AA), improve the immune function and tissue structure of AA rats, and the effect of the two pairings was superior to that of Licorice alkaloids alone^[3], reflecting that the GF medicinal pairs pairing did have better anti-inflammatory effects.

2 GF decoction and Rheumatoid arthritis (RA)

In traditional Chinese medicine theory, it can be understood that the main cause of RA is exogenous six obscene evils,

and to the evil blockage of meridians and channels, poor qi and blood flow, and pain when there is no communication. The pathogenesis of RA is hypothesized to be related to the following aspects in modern medical research: (1) immune cells, (2) inflammatory factors, (3) MMPs, (4) oxidative stress abnormalities, (5) genetic and survival environmental factors, etc^[4].

Current clinical treatment for RA uses NSAIDs for symptomatic relief, such as ibuprofen, tylofen, and naproxen sodium. Corticosteroids are used to alleviate the disease process, such as prednisone, hydrocortisone, methylprednisolone, and so on. However, long-term use of NSAIDs is prone to gastrointestinal damage, as well as nephrotic syndrome, and other side effects. These drugs cannot cure rheumatic diseases and all of them have certain side effects, while traditional Chinese medicine is a natural, low-toxicity library of compounds in search of precursors, so the study of traditional Chinese medicine is very necessary^[5].

Liu Yuanyuan^[5] investigated the anti-inflammatory, analgesic and immunological effects of the single drug of Heishunpian and its pairs, the chemical components of alkaloids and their combinations in the GF decoction formula through four in vivo and one in vitro pharmacodynamic experiments. It was hypothesized that the drugs with analgesic effects in the GF decoction formula were mainly Black Cisplatin and Licorice, and the chemical components were mainly alkaloids and flavonoids; the drugs with anti-inflammatory effects in the GF decoction formula were mainly Licorice, and the chemical components were mainly alkaloids and flavonoids. In the formula of GF decoction, the drugs with anti-inflammatory effect are mainly Licorice, and the chemical components are mainly saponin and flavonoid; in the formula of GF decoction, Aconite, Licorice and Cinnamon Branches have immunosuppressive effect, Atractylodis Macrocephalae has immune-enhancing effect, and the alkaloid and flavonoid components have immunosuppressive effect, and the saponin component has immune-enhancing effect. The alkaloid component and flavonoid component have immunosuppressive effect, and the saponin component has immunoenhancing effect.

Cai Yue^[6] and other experimental research results show that GF decoction can reduce the overexpression of Cyclin D1 and PCNA, and increase the transcription and translation of p53 and p21 in synovial tissues of AA rat, and then have an effect on their proliferation and expression; GF decoction can also reduce the level of synovial inflammatory factors, and both aspects work together to prevent the RA condition from further deterioration. further deterioration of RA.

Wang Yongping^[7] and others proved that GF decoction could dissolve osteolysis and bone destruction in RA rats through successful modeling of RA rats. And the results of ELISA experiment showed that ASIC3 and HIF-1 α have important roles in the occurrence and formation of RA, and GF decoction affects the expression of ASIC3 and HIF-1 α , thus affecting the condition of RA.

3 GF decoction and Adjuvant Arthritis(AA)

Adjuvant arthritis model was created by Freund in the 1950s, also known as Freund's adjuvant arthritis, there are obvious cellular immune abnormalities in this model, a typical immune inflammatory model, the mechanism of which is that Mycobacterium tuberculosis causes arthritis with the antigen of 65kD heat shock protein (HSP).

Cai Yue [8-10] et al. have conducted three animal experiments on GF decoction, injecting Fuchs' complete adjuvant to establish the AA model, and group experiments, the results showed that (1) GF decoction AA rat have obvious therapeutic effects, and its mechanism may be related to the reduction of production of inflammatory factors and the reduction of the synovial tissue of the expression of MMP-1 and MMP-3. (2) GF decoction has a significant ameliorative effect on joint and synovial injuries in AA rat, which may be related to the reduction of local chronic inflammation, regulation of abnormal protein expression of Cyclin D1, PCNA, p53 and p21 in synovial membranes of AA rat and inhibition of FLS proliferation. (3) GF decoction can reduce the formation of vascular opacities in synovial tissue and inhibit neovascularization by down-regulating the expression of VEGF, NF- κ B, and GATA4 proteins in synovial tissues, thus preventing and controlling bone destruction and protecting the joints of the AA model rat.

4 GF decoction and ankylosing spondylitis(AS)

Rheumatoid arthritis and ankylosing spondylitis are autoimmune diseases and belong to the same category of paralytic disease in traditional Chinese medicine^[11]. Ankylosing spondylitis is an unexplained, chronic inflammatory disease of the middle-axis joints, mainly involving the sacroiliac joints, spine, paraspinal soft tissues, and peripheral joints of the limbs such as hips, knees, ankles and shoulders. The overall prevalence of AS in China is 0.3%^[12], which occurs at the age of 10-40 years, and is more common in young adult males. The disease has a family genetic predisposition and a strong correlation with HLA-B27. Modern AS treatment also often uses non-steroidal anti-inflammatory drugs and corticosteroids.

The results of Gao Caixia^[13] and other studies suggest that compared with conventional western anti-inflammatory

and analgesic therapy alone, supplementing GF decoction with flavored formula is more effective in treating patients with active AS, helping to improve inflammatory indexes and pain symptoms, and has a higher therapeutic safety. Wei Genhong^[14] and others showed that the combination of salicylazosulfapyridine and GF decoction in the treatment of AS can significantly reduce the levels of ESR, CRP, TNF- α and DKK-1, and increase the levels of SPARC and TGF- β 1, which is more effective than the single application of salicylazosulfapyridine.

In the clinical treatment application of Chinese medicine, acupuncture treatment is often used in combination with prescription medicine, and relevant experiments have verified the rationality of this treatment program. Liu Jiang^[15] and others designed the conventional acupuncture treatment, and the control group of acupuncture and moxibustion with GF decoction treatment, and the comparative analysis of inflammation indicators and other data, the results show that the effectiveness of acupuncture and moxibustion with GF decoction is higher than that of conventional acupuncture treatment, which is able to improve the clinical symptoms and enhance the effectiveness of the treatment. Huang Mingxiong^[16] showed that the efficacy of GF decoction combined with acupuncture therapy was better than that of the control group, and the total effective rate of GF decoction combined with acupuncture therapy in the treatment of renal-yang deficiency type ankylosing spondylitis could reach 93.3%, while the total effective rate of acupuncture therapy alone was only 80%.

5 GF decoction and Knee osteoarthritis(KOA)

KOA usually occurs due to degenerative knee joint disease, trauma, and overexertion. It is most common in the clinic and is mainly characterized by knee pain and limited movement. The key to modern treatment is to prevent further wear and tear of cartilage, such as glucosamine sulfate, a chondroprotective agent that promotes cartilage synthesis and inhibits the decomposition of articular cartilage.

Modern TCM clinics mostly use GF decoction combined with sodium vitrate combination therapy. Yang Min^[17], Hu Dongming^[18], Yang Daiqing^[19] in the clinical study, the patients will be divided into GF decoction combined with sodium vitrate treatment group, sodium vitrate treatment group, the results show that GF decoction combined with sodium vitrate treatment group of patients at the end of the treatment of the proportion of significant effect is significantly higher than that of the sodium vitrate treatment group, to improve the functional efficacy of the treatment is better.

As well as Deng Wei^[20] in the clinical treatment experiments, the treatment group was given GF decoction internal, the control group was given Futalin extended-release tablets orally, the results showed that the treatment group's C-reactive protein and blood sedimentation improved significantly better than that of the control group, which verified the therapeutic effect.

6 Clinical therapeutic observations of GF decoction

The purpose of this kind of experiment is to observe the clinical efficacy of GF decoction in treating diseases.

Luo Xiaoguang^[21] et al. designed a treatment group of 23 cases, oral GF decoction; control group of 20 cases, oral Tongxiao Sulunjiang capsule; the results of the treatment group compared with the control group, in terms of improvement of joint pain, C-reactive protein and clinical efficacy of the treatment group, there are statistically significant differences, and concluded that the GF decoction can rapidly improve the Chinese medicine symptoms of cold-damp paralytic obstruction type acute gouty arthritis, and it has a good It was concluded that GF decoction could rapidly improve the TCM symptoms of cold-damp paralytic arthritis with good analgesic effect.

Cao Jiangshan^[22] designed the treatment group with GF decoction, and the control group with MTX. After one course of treatment, the ESR, serum RF, IL-1, INF- α levels of the treatment group were lower than those of the control group, and the number of arthralgia, arthralgias, and grip strength of the treatment group were lower than those of the control group. It is concluded that GF decoction can reduce the levels of IL-1 and TNF- α in patients with rheumatoid arthritis and has better pain relief effect.

7 Discussion

To summarize, GF decoction has been widely used in clinical application for its therapeutic effect, which has been elucidated through clinical observation as well as relevant literature to have good therapeutic effect for the treatment of RA, AA, AS, KOA and other diseases. And the wonderful use of Gancao-Fuzi to increase the effectiveness and reduce the toxicity has demonstrated the wisdom of the ancient medical doctors who are familiar with the medicinal properties and good at summarizing in the treatment of diseases.

It is now known that the pathogenesis of RA is complex, mainly related to immune cells and inflammatory factors.

According to the summary of the existing literature, it is known that the treatment of RA is mainly through the effective compound components in GF decoction, such as the chemical components of epiphyllum alkaloids to play an anti-inflammatory and analgesic effect, licorice flavonoid components and so on to play an immunosuppressive effect, *Atractylodes Macrocephalae* has an immune-enhancing effect so that the level of synovial inflammatory factor is reduced, to control the overexpression of Cyclin D1 and PCNA, and targeted therapy, to inhibit the expression of inflammatory factors, ASIC3, HIF-1 α , from these aspects to achieve relief of rheumatoid arthritis symptoms, as well as control the condition.

AA is an artificially designed animal model, and then the study of drug efficacy experiments, the significance of the key, and now it has been concluded that the therapeutic mechanism of GF decoction may be related to reducing the production of inflammatory factors and reduce the synovial tissue of MMP-1 and MMP-3 expression, as well as reduce the local chronic inflammation, regulate the AA mouse synovial Cyclin D1, PCNA, p53, p21 and GF decoction can reduce chronic inflammation, regulate abnormal expression of Cyclin D1, PCNA, p53 and p21 in the synovial membrane of AA mice, inhibit proliferation of FLS, and GF decoction can reduce formation of vascular opacities and inhibit neovascularization by down-regulating the expression of VEGF, NF- κ B, and GATA4 in synovial membrane tissues, thus preventing and controlling bone destruction and protecting joints in AA model mice.

AS is an autoimmune disease that is often treated with anti-inflammatory drugs. GF decoction can help to improve the inflammatory index and pain symptoms, and it is more effective and safer than single application of salazosulfapyridine. In Chinese medicine, a combination of acupuncture and herbal medicine is often used, and the efficacy of the combined treatment has been proven to be better.

In the treatment of knee osteoarthritis, GF decoction combined with sodium vitrate is commonly used in the clinic, and the percentage of patients with significant effect at the end of the treatment is significantly higher than that of patients with sodium vitrate, which has better efficacy in improving function. Compared with other oral medications, and compared with the oral administration of Fitalin extended-release tablets, the results showed that the improvement of C-reactive protein and blood sedimentation of GF decoction was significantly better than that of Fitalin extended-release tablets, which verified the therapeutic effect.

The relevant modern studies of GF decoction soup are now organized, and the specific role of modern studies is described, hoping to provide new ideas for the future clinical application of GF decoction.

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