Application of Huangqi Guizhi Wuwu Decoction in Orthopaedics and Traumatology

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Introduction

It is recorded in Essentials of the Golden Cabinet (Jin Gui Yao Lue) that, “In blood impediment disease, both yin and yang are weak, the pulse on the upper of cunkou region is faint, the pulse on the middle of chi area is small and tight, the body is numb in external syndrome like wind impediment. It should be treated by Huangqi Guizhi Wuwu Decoction (HQGZWWT).”¹ This prescription had been used for the treatment of blood impediment syndrome by physicians of the past dynasties which is of great efficacy and thus has been inherited nowadays. Numerous literature and data show that this prescription has outstanding curative effects on neck stiffness, shoulder and back pain, lower back pain, and joint pain with few adverse reactions and good safety. With the advancement of modern science and technology and the rapid development of traditional Chinese medicine (TCM) pharmacology, many TCM scholars have performed in-depth researches on the pharmacological effects of the main drugs in the prescription and achieved a series of important results which provides reliable modern pharmacological support for its application in clinical practice. This paper has overviewed the modern pharmacological effects of each herb in HQGZWWT and its wide application in cervical spondylosis, frozen shoulder, lumbar disc herniation, knee osteoarthritis, rheumatoid arthritis, and other orthopaedic diseases.

Keywords

- Huangqi Guizhi Wuwu Decoction
- cervical spondylosis
- scapulohumeral periarthritis
- lumbar disc herniation
- knee osteoarthritis
- rheumatoid arthritis
- orthopaedics and traumatology
- pharmacological research

Abstract

The Huangqi Guizhi Wuwu Decoction (HQGZWWT) is composed of Huangqi (Astragali Radix), Shaoyao (Paeoniae Radix Alba), Guizhi (Cinnamomi Ramulus), Shengjiang (Zingiberis Rhizoma Recens), and Dazao (Jujubae Fructus) which has various pharmacological anti-inflammatory, analgesic, antioxidant, antitumor, lipid-lowering, and immunity-regulating activities. It has certain advantages in the treatment of orthopaedic diseases, such as cervical spondylosis, scapulohumeral periarthritis, lumbar disc herniation, knee osteoarthritis, rheumatoid arthritis, myofascial pain syndrome, etc., with outstanding clinical efficacy, few adverse reactions, and high patient compliance. However, modern pharmacological researches on the whole prescription of HQGZWWT are insufficient and the therapeutic targets are not clear which needs further exploration. Besides, this prescription cannot treat all orthopaedic diseases, so we should adhere to the thinking of four diagnostics in traditional Chinese medicine (TCM), select prescriptions based on syndrome differentiation, closely follow the pathogenesis, innovate and expand its scope of application, reflect the application advantages of this prescription in orthopaedics and traumatology and improve the total clinical efficiency.

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Huangqi Guizhi Wuwu Decoction

Origin and Explanation of the Prescription
The original prescription of HQGZWWT is composed of 9 g of Huangqi (Astragali Radix), 9 g of Shaoyao (Paeoniae Radix Alba), 9 g of Guizhi (Cinnamomi Ramulus), 18 g of Shengjiang (Rhizoma Zingiberis Recens), and 4 Dazao (Jujubae Fructus). Its effects include supplementing qi and harmonizing blood, warming the meridians and relieving pain, which is commonly used for the treatment of blood impediment syndrome. Among them, Huangqi (Radix Astragali) tonifies qi and raises yang, nourishes blood, and relieves arthralgia which is the medicinal king; Guizhi (Ramulus Cinnamomi) promotes sweating and relieves exterior and helps yang to transform qi; and Shaoyao (Radix Paeoniae Alba) harmonizes nutrient blood. These herbs together are ministerial medicines; Shengjiang (Rhizoma Zingiberis Recens) warms the middle energizer to disperse cold and Dazao (Jujubae Fructus) nourishes qi and blood, both of which are assistant medicines. This prescription is well prepared, rigorous in composition, ingenious in compatibility, and takes both healthy qi and pathogenic factors into consideration. It has been highly appreciated by physicians of past dynasties and widely and flexibly applied to the treatment of orthopaedic diseases based on the understanding of the pathogenesis of blood impediment syndrome and treatment based on syndrome differentiation in TCM.

Modern Pharmacological Researches of the Main Constituent Herbs
Huangqi (Radix Astragali)
Huangqi (Radix Astragali) is the dried root of leguminous plants, first recorded for medicinal use in Shennong’s Classic of Materia Medica (Shen Nong Ben Cao Jing). It is used unprocessed or fried with honey. The herb is sweet in taste and slightly warm in nature, with the effects of invigorating qi and raising yang, consolidating the exterior and checking dampness and swelling, nourishing blood and unblocking impedance. Modern pharmacological studies have shown that Huangqi (Radix Astragali) contains polysaccharides, flavonoids, saponins, amino acids, vitamin D, choline, protein, and trace elements. Researches have found that certain components in Huangqi (Radix Astragali) can promote the formation of osteoblasts, delay osteoporosis, and may be beneficial for senile osteoporosis. It has also confirmed that astragaloside IV in Huangqi (Radix Astragali) can promote the differentiation of bone marrow–derived mesenchymal stem cells which may provide new ideas for the treatment of osteoporosis. At present, studies have also verified that Huangqi (Radix Astragali) has the effects of antioxidant, anti-inflammatory, analgesic, anticancer, thrombosis preventing, hypoglycemic, lipid regulating, immune regulating, and antiaging.

Guizhi (Ramulus Cinnamomi)
Guizhi (Ramulus Cinnamomi) is the dry twigs of the Lauraceae plant cinnamon, mainly growing in the Guangdong, Guangxi and Yunnan provinces. Its medicinal use was first recorded in Shennong’s Classic of Materia Medica (Shen Nong Ben Cao Jing), followed by the books on herbal medicines of all dynasties. It is warm in nature, pungent, and sweet in taste, passes through the 12 meridians of the human body, enters the heart, lung, and bladder meridians, and has the functions of promoting sweating and relieving exterior, warming, and dredging the meridians, and helping yang to transform qi. In recent years, related pharmacological studies of Guizhi (Ramulus Cinnamomi) have found that its main medicinal components are volatile oils, followed by organic acids, flavonoids, calamus, terpenes, and glycosides. It has many pharmacological activities of blood coagulation function, tumor suppressor, vasodilation, and nerve nutrition. In addition, Wu et al found that through the phosphoinositide-3 kinase/protein kinase B (PI3K/AKT) signaling pathway, transcinnamaldehyde in Guizhi (Ramulus Cinnamomi) can inhibit the level of interleukin-1β (IL-1β) and the inflammatory response of chondrocytes and prevent joint damage, suggesting that some active ingredients in Guizhi (Ramulus Cinnamomi) are beneficial to the treatment of bone and joints and it needs further research.

Baishao (Radix Paeoniae Alba)
Baishao (Radix Paeoniae Alba) is the dry root of the Ranunculaceae plant, Paeonia lactiflora, first recorded for medicinal use in Fifty-Two Diseases Prescriptions (Wu Shi Er Bing Fang). It is mainly produced in Hangzhou, Bozhou, and others, used unprocessed or fried. It is slightly cold in nature and bitter and sour in taste, enters the liver and spleen meridians, and has the effects of nourishing blood and astringing yin, softening the liver and relieving pain, calming and suppressing liver yang. In recent years, with the continuous development and progress of TCM pharmacology, the understanding of Shaoyao (Radix Paeoniae Alba) has been further developed. Studies have found that the components of the most medicinal value are paeoniflorin and albiflorin represented by monoterpenes and glycosides. In addition, it also contains chemical components such as volatile oils, flavonoids, polysaccharides, and benzoic acid. Baishao (Radix Paeoniae Alba) has a variety of biological activities and a wide range of pharmacological effects which has anti-inflammatory, antispasmodic, analgesic, liver-protecting, antioxidant, anticancer, blood lipid-lowering, osteoarthritis-relieving, and immune-regulating effects. A recent study has discovered that the total glucosides of peony isolated from Baishao (Radix Paeoniae Alba) can effectively reduce the degree of joint swelling and pain, rate of erythrocyte sedimentation, and indicators such as C-reactive protein and rheumatoid factor. It has also confirmed that the target of the drug is closely related to tumor necrosis factor-α (TNF-α) which can significantly improve the clinical symptoms of rheumatoid arthritis patients by inhibiting the expression of TNF-α. With the in-depth study of this herb, its active molecules will be continuously discovered, and its pharmacological effects will be further revealed.
Shengjiang (Rhizoma Zingiberis Recens)

Shengjiang (Rhizoma Zingiberis Recens) is a perennial herb of the ginger family, with fresh rhizomes for medicinal use. The earliest records in the literature can be traced back to Shennong’s Classic of Materia Medica (Shen Nong Ben Cao Jing). Shengjiang (Rhizoma Zingiberis Recens) is both a herb and a commonly used condiment, representing the homology of herbs and food. It is mild in nature, pungent in taste, pertains to the lung, spleen and stomach meridians, and has the functions of relieving the exterior and dispelling cold, warming the middle energizer and relieving vomiting, resolving phlegm, and checking cough. In recent years, studies have suggested that Shengjiang (Rhizoma Zingiberis Recens) contains complex and diverse medicinal components, including volatile oils, gingerols, active polysaccharides, glycoproteins, and others. Many clinical data show that Shengjiang (Rhizoma Zingiberis Recens) has the effects of anti-inflammatory, analgesic, anti-tumor, oxygen-free radicals removing, anticoagulation, antieptic, immunity-enhancing, energy metabolism—increasing, healing-promoting, and nerves-protecting actions. In addition, some scholars have found that turmeric contained Shengjiang (Rhizoma Zingiberis Recens) has good antioxidant and anti-inflammatory effects, and has a certain effect on the prevention and treatment of arthritis-related diseases.

Dazao (Fructus Jujubae)

Dazao (Fructus Jujubae) is the jujube of Rhamnosus plant. The ripe dried fruit is used as medicine. As a medicinal use, it was first recorded in Shennong’s Classic of Materia Medica (Shen Nong Ben Cao Jing) and recorded by later books on Materia Medica. The ones produced in Qingzhou of Shandong province, Linfen and Xinjiang in Shanxi province are believed to be of the best quality. It is sweet in taste and warm in nature, pertains to the spleen, stomach, and heart meridians, with the effects of strengthening the spleen and tonifying qi, nourishing blood and calming the mind, moderating the nature of the herbs. In recent years, a large number of studies have confirmed that Dazao (Fructus Jujubae) contains polysaccharides, organic acids, alkaloids, flavonoids, saponins, steroids, amino acids, and other active ingredients which have the effects of immunity-enhancing, antioxidant, anti-inflammatory, tumor cells-regulating, allergy-reducing, liver-protecting, anemia-correcting, and aging-delaying functions, so it is widely used in the treatment of tumor diseases, cardiovascular diseases, liver diseases, and blood system diseases.

Clinical Application of Huangqi Guizhi Wuwu Decoction in Orthopaedic and Traumatic Diseases

Cervical Spondylosis

Cervical spondylosis is a disease caused by long-term chronic strain, cervical intervertebral disc degenerative changes, resulting in compression of spinal cord, nerves, blood vessels, and other important tissue structures, and thus showing a series of related symptoms. With the popularization of electronic technology products and the increased pace of the society, cervical spondylosis has occupied half of the cases in orthopaedic outpatient clinics. Surveys have showed that the incidence rate of cervical spondylosis in China is 17.5%; the incidence rate is increasing year by year, and the patient population tends to be younger. Among them, cervical spondylotic radiculopathy (CSR) accounts for more than half of all types of cervical spondylosis, and most patients present with discomfort such as dizziness, neck stiffness, and numbness of the upper arms. There is no name for “cervical spondylosis” in the ancient TCM books, but it can be classified into the categories of “cervical Bi” and “flaccidity syndrome.” The etiology and pathogenesis of the disease have two aspects: deficiency of healthy qi and excess of pathogenic factors. Most of the manifestations are due to deficiency of the root and excess of the superficial. It takes “deficiency of the liver and kidney, insufficiency of essence, and lack of nourishment of the muscles and bones” as the root causes and “invasion of the external pathogens and impediment of the phlegm and blood stasis” as the superficial causes. Based on the pathogenesis characteristics of “deficiency of healthy qi and excess of pathogenic factors,” this disease was treated based on the principle of “simultaneous consideration of the root and the superficial, and simultaneous implementation of reinforcing the healthy qi and eliminating pathogenic factors” by many physicians in the past dynasties. The physicians often used modified HOGZWWT in clinical practice and achieved satisfactory therapeutic effects. Hu et al treated 120 CSR patients. The treatment group was treated with oral administration of HOGZWWT combined with acupuncture and massage, and the control group was treated with cerebroside carnosine injection. Changes were found in the Cobb angle, score of the concise health survey scale, serum lipid peroxide, and indicator of IL-1β. The results showed that the levels of lipid peroxide and IL-1β in the oral administration of Chinese herbs treatment group decreased, suggesting that the prescription can reduce the inflammatory response in the patients with CSR, and the Cobb angle and score of the concise health survey scale in the treatment group were better than those in the control group, indicating that the prescription combined with acupuncture and massage therapy can improve the cervical vertebral joint function and improve the quality of life in patients with CSR. Zhang et al randomly divided 120 CSR patients into two groups and were given oral administration of HOGZWWT and Jingfukang Granules respectively. After three courses of treatment, the visual analogue scale (VAS), the evaluations of the neck disability index (NDI), and clinical efficacy were made, and the results showed that the VAS score and NDI score after oral administration of Chinese herbs were significantly reduced, suggesting that this prescription can effectively reduce the pain of CSR patients, improve cervical spine mobility and improve clinical efficacy. Chen et al conducted a meta-analysis on the treatment of CSR with HOGZWWT which showed that it could improve the total effective rate of the treatment of CSR, whether it was used alone or in combination with massage manipulations.

Scapulohumeral Periarthritis

Scapulohumeral periarthritis refers to a specific, sterile disease caused by the degeneration of the soft tissues around...
the shoulder joint and the acute and chronic injury of its adjacent structures (tendons, ligaments, synovium, etc.). The incidence of this disease is 2 to 5%, and it is common in women around the age of 50 years, so it is also called “shoulder in 50 years old.” TCM classifies this disease in the category of “Bi syndrome” and “shoulder Bi.” The etiology and pathogenesis of the disease include invasion of the external pathogens, internal obstruction of cold dampness, qi stagnation and blood stasis, blockage of the meridians, liver and kidney deficiency, weakness of the tendons, and bones. Hu divided 66 patients with scapulohumeral periarthritis into two groups, 33 cases in each group. The treatment group was given oral administration of HQGZWWT plus electroacupuncture, while the control group was given electroacupuncture alone. The improvement rates of VAS score and Japanese Orthopaedic Association (JOA) scores in the treatment group were significantly higher than those in the control group. Zhang and Yang found that modified HQGZWWT combined with Huixi Lijing manipulations had certain advantages in the treatment of scapulohumeral periarthritis which could effectively relieve local pain in the shoulder joint, improve the range of motion of the joint, and the overall therapeutic effect. An animal study by Dong and Zan found that after administration of HQGZWWT to the rabbit model with scapulohumeral periarthritis, the contents of hydroxyproline and protein in the injured local muscles both decreased, suggesting that this prescription can reduce scar adhesion caused by scapulohumeral periarthritis and improve joint function.

**Lumbar Intervertebral Disc Herniation**

Lumbar intervertebral disc herniation is a common disease in orthopaedics, most of which are ipsilateral radiculopathy caused by ipsilateral intervertebral disc herniation, and some patients may also have symptoms of contralateral radiculopathy. In TCM, it belongs to the categories of “Bi syndrome,” “lower back pain,” and “tendon injury.” According to the discussion in Bi Syndrome of Plain Conversation, “The interaction of wind, cold, and dampness causes Bi (stagnation or obstruction).” In the discussion in Treatment of Lumbago with Acupuncture of Plain Conversation, it says “Lumbago due to disorder of the channel in the muscles makes the patient unable to cough and causes spasm when the patient coughs.” The disease is deficient in root and excess in superficial, and it takes “deficiency of the liver and kidney, insufficiency of qi and blood, and weakness of defensive Yang” as the root causes and “invasion of wind, cold, and dampness, obstruction of qi movement, retention of blood stasis” as the superficial causes. In recent years, the number of patients with lumbar disc herniation has increased year by year, and they tend to be younger. The treatment methods include conservative treatment and surgical treatment. The short-term efficacy after surgery is relatively significant, but the long-term efficacy is not yet clear, and complications, such as lower back pain and weakness, often occur. More and more clinical studies have confirmed that TCM has unique advantages in the treatment of this disease. The treatment methods include oral administration of Chinese herbs, external plaster application, acupuncture, massage, cupping, and small-needle knife. The pain-killing effect was obvious and definite. Li and Xu treated 100 patients with lumbar intervertebral disc herniation. The control group was treated with acupuncture, and the treatment group was treated with HQGZWWT on the basis of the control group. The effective rate was higher than that of acupuncture alone (86% > 70%) which further proved that this prescription could improve the clinical efficacy of lumbar disc herniation. Mao and Zhou treated 64 patients with lumbar intervertebral disc herniation, and all of them underwent endoscopic-assisted lumbar intervertebral disc excision. 50% of the patients were given oral administration of supplemented HQGZWWT after surgery, and the improvement rate of JOA score in the postoperative oral administration of Chinese herb group was 81.25%. All of the above showed that this prescription could be used to treat lumbar disc herniation and achieved good clinical results, whether it was in conservative treatment or postoperative rehabilitation.

**Knee Osteoarthritis**

Knee osteoarthritis is a chronic, degenerative joint disease characterized by pathological changes of articular cartilage degeneration, injury, and bone hyperplasia, with clinical manifestations of joint stiffness, pain, and limited mobility. According to statistics, the incidence of knee osteoarthritis among people aged 45 to 69 years in China is 8.5 to 9.4% which is positively correlated with the patient’s age. This disease belongs to the categories of “knee arthralgia,” “bone arthralgia,” and “Bi syndrome” in TCM. For the etiology and pathogenesis, it takes “liver and kidney deficiency, insufficiency of qi and blood, poor nourishment of the tendons and bones” as the root causes and “invasion of the external pathogens, qi stagnation and blood stasis, weakness of the tendons and bones” as the superficial causes. At present, it mainly adopts oral administration of nonsteroidal anti-inflammatory drugs and chondroprotective agents, intra-articular injection of sodium hyaluronate or platelet-rich plasma, surgery, and others. In the Western medicine treatment, the therapeutic effect is not satisfactory. TCM treatment can be used as an effective supplement to improve the curative rate of patients with knee osteoarthritis. Ye et al. studied the effect of HQGZWWT on cartilage damage and signaling pathways in rats with knee osteoarthritis, and the results suggested that the decoction could reduce the levels of IL-1β, IL-6, and TNF-α, and it could effectively reduce the degree of cartilage damage in knee osteoarthritis. Wang and Zhu treated 66 patients with knee osteoarthritis with qi deficiency and blood stasis syndrome. The control group were given intra-articular injection of sodium hyaluronate, and the treatment group were given oral administration of the modified HQGZWWT on the basis of the control group. The total effective rate of Chinese herb group was 87.9%. Research by Tang et al. showed that in the treatment of patients with knee osteoarthritis, the comprehensive treatment of conventional Western medicine + HQGZWWT + warm acupuncture could alleviate the symptoms of knee
osteoarthritis, reduce pain, and the destruction of articular cartilage. Compared with the use of conventional Western medicine, its curative effect was more prominent.

Rheumatoid Arthritis
Rheumatoid arthritis is a kind of common chronic, inflammatory, and autoimmune disease which is more common in women. Its pathological characteristics are mainly synovitis which mainly affects the joints (common in the hand and foot joints). In severe cases, it can lead to joint deformity and even disability.66,67 Based on the characteristic clinical manifestations of rheumatoid arthritis, it pertains to the category of “Bi syndrome,” “joint-running wind,” and “crane knee wind.” The main causes of the disease are the invasion of external pathogens, phlegm and blood stasis blockage, liver and kidney deficiency, deficiency of both qi and blood, and others.68 The modern pathogenesis of rheumatoid arthritis is still unclear, so the simple use of the Western medicine has poor efficacy, obvious adverse reactions, and poor patient compliance.69 A large number of clinical evidences have confirmed that the application of Chinese herbs combined with the conventional Western medicine in the treatment of this disease can reduce the incidence of deformity, improve joint function, and reduce gastrointestinal reactions. Zhang70 randomly divided 176 patients with rheumatoid arthritis into group A and group B. Group A was treated with oral administration of methotrexate tablets and HQGZWWT, and group B was treated with oral administration of methotrexate tablets. After 6 weeks of treatment, evaluations of the changes of TCM syndrome scores before and after treatment and clinical efficacy of patients in both groups A and B were performed, suggesting that the decrease in TCM syndrome scores in group A was greater than that in group B, and the therapeutic effective rates were 92.0 and 80.7%, respectively. Tao71 clinically used the conventional Western medicine combined with HQGZWWT for oral administration to treat 50 patients with rheumatoid arthritis, and the total effective rate was 92.0%. Lin et al72 found that HQGZWWT could inhibit the activation of nuclear factor kappa-B (NF-κB) signaling pathway, thereby exerting anti-inflammatory effect which may be the important target of rheumatoid arthritis. It provides a valuable reference for the treatment of rheumatoid arthritis. Liu et al73 confirmed that HQGZWWT could treat rheumatoid arthritis by regulating B-cell lymphoma/leukemia (Bcl-2) and promoting the expression of Bcl-2-related X-protein antibody, providing experimental basis for the clinical application.

Others
Based on the TCM concept of “same disease treated by different therapies and different diseases treated by the same therapy,” the organic combination of disease differentiation and dialectical thinking, flexible application of this prescription to treat orthopaedic-related diseases are conducted, so as to expand the applicable population of this prescription, relieve the pain of patients, and improve the life quality of the patients. Wang et al74 used HQGZWWT combined with wrist brace fixation for the treatment of carpal tunnel syndrome. The results showed that the scores of the Boston carpal tunnel syndrome questionnaire and VAS were significantly reduced, and the neurological function gradually recovered after treatment. Zhang75 randomly divided 60 patients with primary osteoporosis of qi deficiency and blood stasis syndrome into two groups. One group was given oral administration of calcium carbonate D3 tablets + HQGZWWT, and the other group was only given oral administration of calcium carbonate D3 tablets alone. The results showed that the type-I collagen carboxyl terminal peptide in the oral administration of Chinese herb group decreased, and the bone mineral density (BMD) T-value increased ($p < 0.05$), further indicating that the prescription has the effects of inhibiting bone destruction and promoting bone formation and has a significant effect on the osteoporosis. A controlled study on HQGZWWT in the treatment of early ankylosing spondylitis was conducted by Shi et al76 and showed that this prescription relieved pain in patients with ankylosing spondylitis and reduced related inflammatory indicators. Clinically, it was often combined with prescriptions for activating blood circulation and resolving blood stasis and acupuncture to enhance therapeutic effect. By analyzing the application status of this prescription in orthopaedics in recent years, it has found that this prescription was mostly applied in the modified form in combination with other treatment methods. Besides the above commonly seen diseases, it can also be applied to other orthopaedic diseases such as myofascial pain syndrome, femoral head necrosis, limb numbness, and radial nerve injury.

Conclusion
To sum up, modern pharmacological studies have confirmed that Huangqi (Radix Astragali), Guizhi (Ramulus Cinnamomi), Shaoyao (Radix Paeoniae Alba), Shengjiang (Rhizoma Zingiberis Recens), and Dazao (Fructus Jujubae) as the constituent herbs of HQGZWWT have anti-inflammatory, analgesic, antioxidative, antitumor, lipid-lowering, and immune-regulating properties. However, it lacks modern pharmacological researches on the whole formula and the therapeutic target is still unclear which requires in-depth exploration. By studying the clinical application and development status of HQGZWWT in recent years, it confirmed that this prescription has certain advantages in the treatment of orthopaedic diseases with outstanding clinical efficacy, few drug adverse reactions, and high patient compliance. However, this prescription cannot treat all orthopaedic diseases, and it is necessary to perform differentiation in clinical diagnosis, closely follow the pathogenesis, and avoid applying mechanically. The rapid development of modern medicine is both an opportunity and a challenge for TCM. In the clinical diagnosis, we must always adhere to the thinking of the four TCM diagnostics, select prescriptions based on syndrome differentiation, innovate and expand their scope of application, and reflect the application advantages of this prescription in orthopaedics, so as to better serve the majority of patients, make up for the deficiency of the pure Western medicine treatment and improve the total clinical efficiency.
Credit Authorship Contribution Statement

Peng Xu: Searching, sorting out and summarizing the literature, formal analysis, writing—original draft. Yan Cheng: Conceptualization, methodology, supervision, and writing—review & editing. Miao Tan and Mingming Wang: Searching, sorting out and summarizing the literature, and writing—review & editing.

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Conflict of Interest
The authors declare no conflict of interest.

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