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•Review•

Taohong Siwu Decoction: a classical Chinese prescription for treatment of orthopedic diseases

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[ABSTRACT] The pathogenesis of orthopedic diseases is intimately linked to blood stasis, frequently arising from damage to primary and secondary blood channels. This disruption can lead to "blood leaving the meridians" or Qi stagnation, resulting in blood stasis syndrome. Taohong Siwu Decoction (THSWD) is a renowned classical Chinese medicinal formula extensively used to promote blood circulation and mitigate blood stasis. Clinical studies have demonstrated its significant therapeutic effects on various orthopedic conditions, particularly its anti-inflammatory and analgesic properties, as well as its efficacy in preventing deep vein thrombosis post-surgery. Despite these findings, research on THSWD remains fragmented, and its interdisciplinary impact is limited. This review aims to provide a comprehensive evaluation of the efficacy and pharmacological mechanisms of THSWD in treating common orthopedic diseases. Additionally, we employ bibliometric analysis to explore research trends and hotspots related to THSWD. We hope this review will enhance the recognition and application of THSWD in orthopedic treatments and guide future research into its pharmacological mechanisms.

[KEY WORDS] Taohong Siwu Decoction; Classical prescriptions; Orthopedic diseases; Fracture; Femoral head necrosis; Joint replacement

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Introduction

Taohong Siwu Decoction (THSWD), one of China's 100 classic prescriptions [1], was originally known as Jiawei Siwu Decoction (or Modified Siwu Decoction). It is derived from the Siwu Decoction, which is renowned as "the best prescription for gynecology" and is primarily used to treat blood stasis and blood deficiency syndromes [2]. This prescription was first documented in the *Yi Lie Yuan Rong* and cited in *Yu Ji Wei Yi*, with the name "Taohong Siwu Decoction" appearing in the Qing Dynasty's *Yi Zong Jin Jian*. Clinically, THSWD has been applied across various disciplines, especially in gynecology, for conditions such as dysmenorrhea and abnormal uterine bleeding [3, 4]. Additionally, it has shown significant efficacy in the adjunctive treatment of cardiovascular diseases (e.g., heart and brain ischemia-reperfusion injury, coronary heart disease) and cancers (e.g., breast cancer) [5–7].

Orthopedics is a prominent field within traditional Chinese medicine and a key area for integrative medicine. While surgery can effectively restore physiological structures, it often leads to sharp pain, severe swelling, prolonged recovery times, and slow functional rehabilitation. Common postoperative complications include infection and thromboembolism, which, in severe cases, can cause nervous system injuries [8, 9]. In traditional Chinese medicine, the occurrence and treatment of orthopedic diseases are often associated with meridian damage, resulting in "blood leaving the meridians" or Qi and blood flow obstruction, which are common causes of blood stasis syndrome. Consequently, THSWD is frequently used as an adjunct therapy in orthopedics to activate and nourish blood circulation. This use is well-documented in orthopedic literature. The mechanisms of THSWD include inhibiting inflammatory reactions, reducing

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oxidative stress, preventing platelet aggregation, prolonging coagulation time, combating fibrosis, improving hemorheology and vascular pathology, and regulating related signal pathways [10].

Despite the notable therapeutic effects of THSWD, its influence remains largely confined to Asian countries, and reports on its efficacy in orthopedics are predominantly clinical studies with limited research on its pharmacological mechanisms. Therefore, this review examines the research trends and hotspots of THSWD through bibliometric analysis and evaluates its clinical efficacy and potential molecular mechanisms in orthopedics. Our objective is to provide a theoretical foundation and data support to broaden the application of THSWD in orthopedics and to guide future scholarly research.

Quantitative Study on the Literature of THSWD

Due to the limited availability of English-language articles on the use of THSWD in orthopedics, a quantitative analysis of Chinese-language publications was conducted to assess development trends and research hotspots over the past decade.

Data were sourced from the China National Knowledge Infrastructure (CNKI) on the treatment of orthopedic diseases with THSWD from 2013 to 2023. Keywords were extracted and analyzed using Citespace 6.2.4, and burst keywords for the past decade were identified.

The results revealed an upward trend in the number of papers on THSWD in orthopedic research since 2013 (Fig. 1A). The main research themes included clinical observations, femoral intertrochanteric fractures, femoral head necrosis, tibiofibular fractures, distal radius fractures, and limb swelling (Fig. 1B), with a primary focus on fractures. Keyword clustering analysis using Citespace 6.2.4 identified key clusters such as network pharmacology, knee joint fractures, blood coagulation function, distal radius fractures, and deep vein thrombosis (DVT) (Fig. 1C).

The clustering analysis highlighted the primary disease areas addressed by THSWD and underscored its potential to prevent postoperative complications in orthopedic surgery. The therapeutic efficacy of THSWD is widely acknowledged. Conditions such as intertrochanteric fractures and bone necrosis often require surgical intervention, whereas fractures can be managed surgically or non-surgically based on individual cases. For conditions requiring surgery, THSWD may alleviate preoperative symptoms, enhance postoperative recovery, and crucially, prevent high-risk complications like DVT. For conditions treatable conservatively, THSWD may

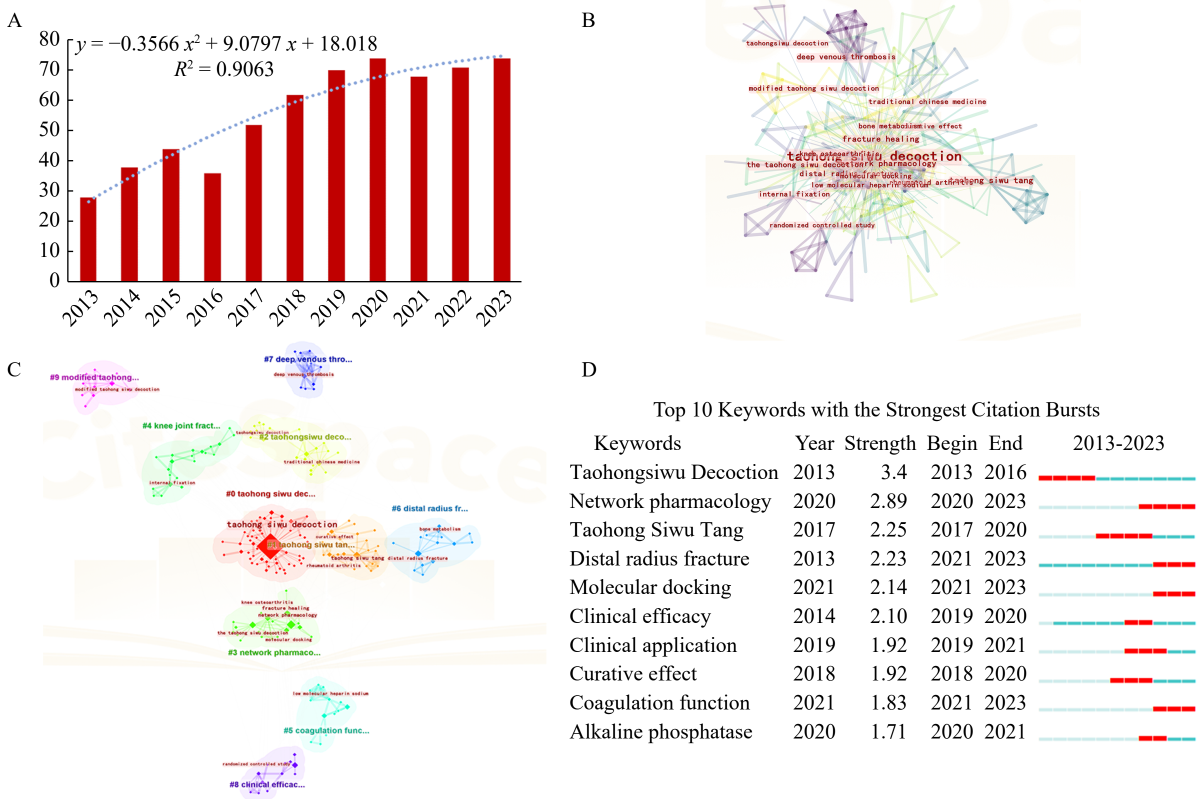

Fig. 1 Bibliometric analysis results of the application of THSWD in orthopedics. (A) Counting of literature from 2013 to 2023. The trend line equations and R^2 values are marked in the figure, and the results increased in a positive proportion, and the budget results were reliable ($R^2 > 0.9$). (B) Distribution of main themes in the literature. (C) Cluster analysis results of literature. (D) Burst keywords results.

have even broader applications. Keyword clustering analysis indicated that limb swelling is a common symptom in the occurrence and treatment of orthopedic diseases. This suggests that THSWD's application in orthopedics might be particularly effective in relieving limb swelling, preventing DVT, and addressing other related symptoms. Therefore, the potential roles of THSWD in managing orthopedic diseases include symptom relief, prevention of postoperative complications, and overall recovery enhancement.

The burst keyword analysis revealed that "network pharmacology" "distal radius fractures" and "macromolecular docking" had the highest burst strength over the past three years (Fig. 1D). Notably, while the burst strength of "clinical effect" and "clinical application" was not as high as that of network pharmacology, their duration has been significantly longer, peaking in 2019 and 2020. This indicates a sustained interest among researchers in the clinical efficacy of THSWD. Fractures represent the most frequently studied and longest-applied condition for THSWD, with a notable increase in attention since 2020. The keyword "coagulation function" suggests that THSWD's mechanism in treating fractures may involve its effects on blood coagulation. Current trends indicate that researchers are focusing on the mechanisms of THSWD through network pharmacology and molecular docking, highlighting a potential gap in extensive laboratory research. Moreover, clinical studies tend to prioritize efficacy over the exploration of underlying mechanisms. Overall, keyword clustering and burst analysis reflect a general consensus on THSWD's role in affecting coagulation function, reducing swelling, and preventing deep vein thrombosis, particularly in the context of fractures. The primary focus remains on the regulation of coagulation by THSWD.

Based on these findings, the following recommendations are proposed: a) While clinical research has validated the effectiveness of THSWD, further investigation into its pharmacology, molecular biology, and histology is necessary. b) Network pharmacology is a valuable omics research method, but its heavy reliance on algorithms may affect the reliability of its results. Therefore, more in-depth mechanistic studies are recommended. c) Fractures are the most extensively studied clinical application of THSWD, and its anticoagulant effect is a key pharmacological mechanism, meriting further research.

Pharmacological Study on THSWD in Orthopedic Diseases

THSWD is composed of six herbs: Semen Persicae (Taoren), Flos Carthami (Honghua), Radix Rehmanniae (Dihuang), Radix Angelicae Sinensis (Danggui), Rhizoma Chuanxiong (Chuanxiong), and Radix Paeoniae Alba (Baishao). The primary function of this decoction is to relieve blood stasis and alleviate pain, with the additional benefits of nourishing the blood and promoting Qi circulation. THSWD is mainly comprised of potent stasis-breaking herbs, which are crucial to its therapeutic effectiveness.

Pharmacological analysis of herb pairs

Semen Persicae and Flos Carthami

Semen Persicae is derived from the seeds of *Prunus persica* or *Prunus davidiana*, while Flos Carthami comes from the flowers of *Carthamus tinctorius*. These herbs are known for their ability to regulate angiogenesis and influence hemorheology [11, 12], making them effective in relieving blood stasis caused by orthopedic trauma or surgery and restoring blood flow to affected areas. The active component in Semen Persicae, amygdalin, is involved in anti-inflammatory processes through multiple pathways [13]. Additionally, the high vitamin B content nourishes the nervous system. Flos Carthami contains safflower polysaccharides, which interact with the immune system by activating and proliferating immune cells. These polysaccharides also protect against steroid-induced avascular necrosis of the femoral head by preventing fat accumulation [14, 15] and contributing to anti-inflammatory and antioxidant regulation [16].

Rhizoma Chuanxiong and Radix Angelicae Sinensis

Rhizoma Chuanxiong, the rhizome of *Ligusticum chuanxiong*, is highly regarded as "the best blood-tonifying medicine among Qi-promoting medicines". It enhances the effects of Semen Persicae and Flos Carthami by activating blood flow, removing blood stasis, and promoting Qi circulation. The active ingredients of Rhizoma Chuanxiong, including essential oils, alkaloids, phenolic acids, and phthalic acid lactones, act as biological regulators in combination with other herbs [17, 18]. Ligustrazine, a component of Rhizoma Chuanxiong, also provides analgesic and anti-inflammatory benefits [19]. Radix Angelicae Sinensis, from *Angelica sinensis*, is known as "the best Qi-promoting medicine among blood tonics". It excels in tonifying blood, promoting blood circulation, and enhancing Qi flow. The combination of Rhizoma Chuanxiong and Radix Angelicae Sinensis is frequently used and documented in the Dictionary of *Traditional Chinese Medicine Prescriptions*, with a synergistic effect peaking at a 2 ∶ 1 ratio. This combination regulates blood coagulation, relieves pain, and offers additional therapeutic benefits [20]. Chinese angelica, a highly esteemed herbal medicine, contains organic acids, volatile oils, and polysaccharides that promote hematopoiesis and anticoagulation, prevent inflammation and pain, and regulate immunity [21–23].

Radix Paeoniae Alba and Radix Rehmanniae

According to *The Chinese Pharmacopoeia* (2015 Edition) and the *Chinese Herbal Medicine Encyclopedia*, Radix Rehmanniae is derived from the root tuber of *Rehmannia glutinosa*, while Radix Paeoniae Alba originates from *Paeonia lactiflora*. Radix Paeoniae Alba is primarily used to relieve spasms and pain and has significant anti-inflammatory effects [24]. It likely achieves this by inhibiting the activation of pain pathways mediated by pro-inflammatory cytokines. When paired with Radix Angelicae Sinensis, Radix Paeoniae Alba not only harnesses its individual benefits but also offers unique protective effects on the nervous system [25], facilitating postoperative nerve repair. The primary active ingredient, paeoniflorin, exhibits anti-inflammatory, immune-regulatory, and neuroprotective properties [26, 27], aiding in restoring limb function and alleviating emotional disorders caused by illness. Radix Rehmanniae, known for nourishing blood and Yin, complements Radix Angelicae Sinensis by promoting blood cell regeneration and regulating immune function. This combination enhances the therapeutic effects of THSWD, particularly in addressing blood stasis and supporting postoperative recovery [28].

Therefore, THSWD can exert analgesic and anti-inflammatory effects, promote angiogenesis, and regulate hemorheology through the independent and combined effects of a variety of drugs (Fig. 2).

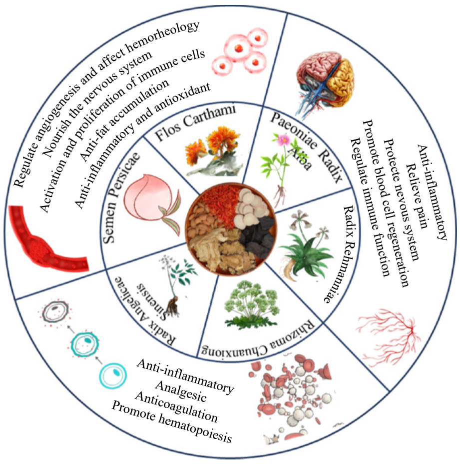

Fig. 2 Schematic diagram of the pharmacological mechanism of THSWD.

Pharmacological analysis of prescription

The Chinese Pharmacopoeia (2020 Edition) identifies seven key quantitative detection indexes for THSWD: hydroxysafflor yellow A, kaempferol, amygdalin, ferulic acid, paeoniflorin, catalpol, and rehmannioside [29]. These compounds, sourced from the six herbs in THSWD, form the main active ingredients and the core material basis for its therapeutic effects. Researchers have explained the blood-circulating and stasis-removing effects of THSWD from a modern scientific perspective. The decoction influences platelet adhesion, generation, and aggregation, regulating the coagulation mechanism. This regulation helps achieve the therapeutic effect of "removing blood stasis" by modulating platelet distribution, production, and function, enhancing thrombin activity, and reducing fibrinogen levels [30-32]. Metabonomic studies reveal that THSWD affects at least ten metabolic pathways in rats with acute blood stasis syndrome [33]. These pathways primarily involve amino acid metabolism and lipid metabolism [32]. For instance, the L-glutamate metabolic pathway is integral to energy metabolism and neurotransmitter synthesis. Arachidonic acid metabolism plays roles in inflammatory responses, immune regulation, platelet aggregation, and vascular tension regulation. *N*-acyl sphingosine metabolism is linked to cell composition, lipid metabolism, and immune regulation.

The mechanisms of THSWD extend beyond blood stasis relief, exhibiting anti-tumor and tissue repair properties. These effects suggest potential applications in treating cardiovascular, gynecological, and neurological conditions. The pharmacological benefits of THSWD are achieved through various mechanisms, including the inhibition of tumor cell proliferation, the suppression of tumor tissue angiogenesis, the repair of tissue injury, the prevention of the spread of tissue injury caused by inflammation, and the modulation of neurotransmitter release.

Clinical Application and Experimental Study of THSWD in Orthopedics

Numerous clinical reports highlight the use of THSWD in orthopedics. Through network pharmacology, it has been predicted that THSWD may be effective in treating sixty-nine diseases and conditions, including osteoarthritis, osteoporosis, various orthopedic diseases, multiple cancers, cardiovascular diseases, and rheumatic immune diseases [34]. In orthopedics, THSWD is commonly prescribed as an adjunct treatment post-surgery. Current literature indicates that THSWD is frequently used to improve the prognosis of fractures, joint replacements, femoral head necrosis, osteoporosis, athletic injuries, and acute soft tissue contusions. Its significant effects include anti-inflammatory action, prevention of DVT, and pain relief.

There are significant differences in the reported dosages of drugs used in the treatment of different diseases. Among them, the dosages of Radix Rehmanniae and Radix Angelicae Sinensis are relatively consistent, usually 15 g. However, in a few studies, the dosage of Radix Rehmanniae can reach more than 20 g. The dosage of Radix Paeoniae Alba is 10−15 g, while the dosage of Rhizoma Chuanxiong is 5−15 g. The dosages of Semen Persicae and Flos Carthami range from 5 to 20 g and 5 to 15 g, respectively. The reported frequency of administration ranges from 1 to 3 times daily, and the administered dose ranges from 150 to 300 mL, with the most used single dose being 200 mL. The duration of administration ranges from 7 to 28 days, which is closely related to the course of the disease.

The most common combination of administered doses is Radix Rehmanniae and Radix Angelicae Sinensis, each at 15 g, Radix Paeoniae Alba, Flos Carthami, Semen Persicae, and Rhizoma Chuanxiong, each at 10 g. According to *The Chinese Pharmacopoeia*, there is a tendency for excessive use of Semen Persicae and Flos Carthami. The bitter almond glycoside in peach kernels (Semen Persicae) is dose-dependent in terms of toxicity, and it is recommended that the daily dosage should not exceed 10 g to avoid adverse effects.

Bone fractures

Bone fractures are the most common orthopedic injuries, involving the disruption of bone integrity or trabecular bone structure. The prognosis of a fracture is crucial in determining the appropriate treatment strategy [35]. Approximately 10% of fractures fail to heal properly, leading to chronic pain, disability, and often necessitating repeated surgical interventions [36]. A significant challenge in fracture healing is the reduced or interrupted blood supply to the fracture site, which is essential for the recovery of limb function post-surgery. Vascular injury at the fracture site can lead to hypoxia [37], resulting in local tissue necrosis in severe cases. This compromised blood supply is a major factor impeding the healing process. Fractures can be particularly detrimental to individuals with immunodeficiencies. Research conducted on rats with congenital immunodeficiency demonstrated significantly delayed fracture healing. For immunocompromised patients, fractures can lead to severe complications and, in some cases, can be fatal. Fractures significantly impact mortality rates among the elderly [38]. Studies have shown that over 30% of women and 20% of men experience a hip fracture by the age of 90. The mortality rate within one month post-fracture ranges from 5% to 10%. Furthermore, the mortality rate within one to two years post-fracture ranges from 14% to 36% for women and is approximately 19.7% for men [39].

Fractures can be classified into traumatic fractures, strain fractures, and pathological fractures. Despite the different types, the fracture healing process generally follows a consistent sequence consisting of four stages: hematoma organization, original callus formation, callus reconstruction, and bone remodeling. Each stage is characterized by specific histological changes: inflammation and mesenchymal stem cell recruitment, soft callus formation and revascularization, hard callus formation, and bone remodeling [40]. These stages often overlap, varying from patient to patient. The cellular and molecular mechanisms underlying fracture healing are intricate and well-coordinated. Transcellular signaling is a critical regulatory mechanism present in most healed fractures. Bone healing involves a variety of cellular components, starting with inflammatory cells such as T cells, B cells, mast cells, macrophages, eosinophils, and neutrophils, which are the initial responders in the fracture environment. An acute pro-inflammatory response is crucial for initiating fracture healing, followed by the involvement of mesenchymal stem cells, endothelial cells, chondrocytes, osteoblasts, and osteoclasts [41]. Effective fracture treatment, whether conservative or surgical, must address the acute inflammation and vascular injury that cause pain and swelling in the affected area. Additionally, managing fracture-related infections remains a significant challenge in fracture rehabilitation [42].

The auxiliary treatment effects of THSWD on fractures are extensive and versatile. THSWD can be used flexibly in fracture management, either preoperatively or postoperatively, to reduce swelling and pain and to accelerate healing. It can also be administered alone for patients without surgical indications. The duration of THSWD usage ranges from 1 to 8 weeks, covering critical phases of hematoma organization and callus formation. Clinical reports indicate that the overall efficacy of THSWD in treating postoperative femoral shaft fractures is 97.02%, with significant reductions in pain and swelling. Postoperative surveys revealed that 77% of patients rated their outcomes as excellent or good, significantly higher than the 66% in the control group, and demonstrated accelerated healing [43]. THSWD significantly decreases various pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α. Although the precise mechanisms are not fully understood, several components of THSWD contribute to its anti-inflammatory effects. Flavonoids in Flos Carthami reduce pro-inflammatory cytokines [44], while sodium ferritin in Radix Angelicae Sinensis decreases inflammation through the TNF-α signaling pathway. Additionally, angelica polysaccharides promote the biosynthesis of proteoglycans in the cartilage matrix [45], aiding in cartilage repair. Total glycosides in Radix Paeoniae Alba not only reduce the release of pro-inflammatory factors but also regulate adhesion factors to control inflammation [46]. Furthermore, THSWD plays a role in regulating hemorheology and blood cell composition. Treatment with THSWD significantly reduces blood and plasma viscosity, hematocrit, white blood cell count, and erythrocyte sedimentation rate [47]. According to traditional Chinese medicine theory, these effects align with the principles of promoting blood circulation and removing blood stasis, which are crucial in preventing thrombosis post-fracture surgery and mitigating the risk of DVT. Blood stasis is considered a core factor in the occurrence of DVT in traditional Chinese medicine.

THSWD has notable benefits in promoting osteogenesis, enhancing bone metabolism, and improving calcium and phosphorus metabolism after fracture surgery, thereby accelerating the recovery of joint function [48, 49]. Additionally, THSWD provides pain relief by inhibiting the expression of pain mediators such as nitric oxide (NO), serotonin (5-hydroxytryptamine), and prostaglandin E2 in the serum [50]. In traditional Chinese medicine, pain is understood to arise either from blockage or deficiency, with pain due to blood stasis falling under the former category. Modern medical research interprets this concept by demonstrating that THSWD can influence hemorheology and modulate levels of pro-inflammatory factors, coagulation factors, and pain mediators in the blood. These effects collectively promote blood circulation, relieve pain, and exhibit anti-inflammatory and anticoagulant properties. Moreover, it has been observed that elderly patients often develop mental disorders following fractures. Research indicates that serum levels of IL-8 peak before the onset of these disorders, while IL-6 peaks during the disorders [51]. THSWD has been shown to reduce serum levels of IL-6, IL-8, and other inflammatory factors, which might help prevent the development of mental disorders, although direct evidence for this effect is currently lacking.

The therapeutic effects of THSWD in fracture treatment are comprehensive, involving the regulation of cytokine production, transcellular transport, and bone cell metabolism in the affected area. During the initial stage of fracture healing, inflammatory cytokines such as TNF-α peak within 24 h to activate mesenchymal stem cells [52, 53]. This process is supported by macrophage inflammatory proteins-α (MIP-1α), which induce $CD8^+$ T cell adhesion and natural killer (NK) cell proliferation [54], playing a crucial role in repairing vascular injuries. THSWD enhances the migration of peripheral blood mesenchymal stem cells through neutrophil chemokines, promoting their orientation during the early stages of fracture [55]. It maintains the initial inflammatory response involving TNF-α and MIP-1α. The second stage, involving soft callus formation and revascularization, is vital for prognosis as hypoxia can lead to necrosis. Vascular endothelial growth factor (VEGF) is essential in this stage, enhancing vascular permeability, endothelial cell migration, proliferation, and angiogenesis. THSWD accelerates angiogenesis and callus reconstruction by increasing VEGF expression [56], activating the VEGF/focal adhesion kinase (FAK) signaling pathway, promoting osteogenic differentiation of bone marrow mesenchymal stem cells, and significantly increasing callus area and cartilage regeneration [57, 58]. In hypoxic tissues, THSWD promotes hypoxia-inducible factor-1 (HIF-1α) accumulation in endothelial cells by activating the HIF pathway. This factor binds to the vascular permeability factor (VPF) gene promoter, inducing its expression and promoting early-stage angiogenesis [59]. Additionally, THSWD reduces inflammation by inhibiting inflammatory cytokines and platelet activation markers [60], preventing excessive inflammatory reactions from hindering hard callus formation. During the hard callus formation stage, THSWD at a dosage of 300 $mg \cdot kg^{-1}$ enhances the local expression of insulin-like growth factor (IGF) 1 and bone morphogenetic protein (BMP) 2 at the growth plate, stimulating the proliferation of growth plate chondrocytes and new bone formation in adolescent rats [61]. Preoperatively, THSWD can reduce swelling quickly, shorten the waiting time for fracture patients, lower treatment costs, and improve prognosis by rapidly restoring blood supply [62].

In summary, THSWD can be effectively utilized in the preoperative, intraoperative, and postoperative stages of fracture treatment, participating in the entire process of callus formation and significantly aiding in recovery (Fig. 3).

Joint replacement

The development of artificial joint replacement technology began in the 1940s, primarily addressing joint injuries, destruction, and deformities resulting from trauma, tumors, and bone diseases. Currently, hip and knee joint replacements are well-established, whereas shoulder, elbow, and wrist joint replacements remain areas of active research due to the limited understanding of the precise functions of tissues in these joints. Key challenges in joint replacement surgery include pain management, prevention of joint contracture, infection control, avoidance of nerve injury, and prevention of DVT. Complications arising from these challenges can significantly increase treatment costs, adding between 15 000 and 30 000 per patient per fracture [63]. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for postoperative pain relief. However, their use can lead to adverse effects, such as gastrointestinal injury [64]. Although the incidence of postoperative infection is relatively low at 1% [65], such infections can be severe, potentially necessitating repeated surgeries, causing tendon injuries, and even leading to death [66]. Additionally, within the biopsychosocial medical

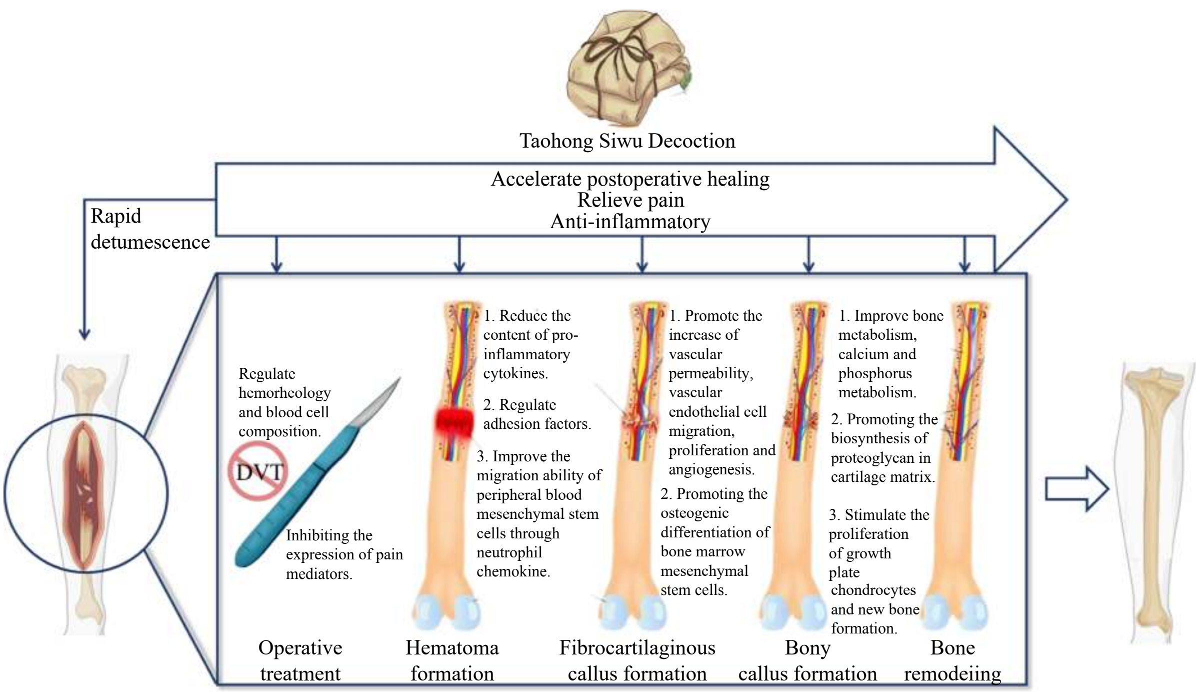

Fig. 3 Mechanism of Taohong Siwu Decoction in the treatment of bone fractures.

model, the anxiety and fear associated with long-term postoperative dysfunction are significant concerns.

According to the literature, THSWD has several therapeutic effects in the context of joint replacement, focusing on anti-inflammation, DVT prevention, pain relief, reduction in prosthesis loosening [67], and avoidance of complications, all while maintaining a high safety standard [68]. The Siwu Decoction component of THSWD effectively nourishes and generates blood, preventing anemia and nerve damage.

Regarding anti-inflammation, studies indicate that levels of inflammatory cytokines such as IL-1, IL-6, IL-8, TNF-α, and MIP increase in the affected area post-joint replacement, influenced by infection status [69]. Elevated metalloproteinases, activated by cytokines like IL-6, can lead to synovial dysfunction and postoperative articular cartilage loss [70, 71]. THSWD has been shown to reduce inflammatory cytokines and skin temperature after unilateral knee joint replacement [72]. Moreover, THSWD can modulate inflammation *via* the transforming growth factor-β (TGF-β) signaling pathway, which interacts with various inflammatory and immune response pathways, thereby accelerating bone healing and enhancing knee function [73].

For DVT prevention, THSWD can augment conventional anticoagulant treatments and reduce thromboelastogram maximum amplitude index, D-dimer levels, whole blood viscosity, and other DVT indicators such as limb swelling on the surgical side [74, 75].

In terms of pain relief, prostaglandin E2, an acute pain factor, significantly increases post-joint replacement. THSWD can significantly lower prostaglandin E2 levels in the serum and affected areas [76, 77], thereby alleviating pain.

Regarding complication prevention, THSWD's anti-fibrosis effects observed in other tissues suggest it may prevent joint contracture or motor function limitation caused by tendon or nerve fibrosis post-surgery [78]. Reports indicate that THSWD can control postoperative bleeding, reduce pain, and prevent occult blood loss (hemoglobin loss within the body) [79], thus reducing the incidence of postoperative anemia [80]. Additionally, THSWD has been reported to improve the health of depression patients with cerebral ischemia/reperfusion, aid in neural function recovery [81], and mitigate brain damage caused by cell necrosis and neuritis *via* inflammatory pathways [82]. This function could be beneficial for the psychological rehabilitation of patients following joint replacement.

Therefore, THSWD could play a synergistic role in preventing secondary infection, anemia, and DVT by promoting the recovery of blood supply and nerve function (Fig. 4).

Femoral head necrosis

Avascular necrosis of the femoral head, also known as ischemic necrosis, aseptic necrosis, or ischemic osteonecrosis, is a condition associated with bone destruction or end-stage arthritis of the femoral head, most commonly affecting the hip [83]. In Germany, the annual incidence of ischemic necrosis in middle-aged individuals is approximately 5000−7000 cases [84]. The onset typically begins with fat accumulation and bone marrow displacement, leading to compression that inhibits venous outflow, causing stagnation and eventually ischemia. The pathogenesis involves trabecular ischemia, increased bone marrow pressure, and compartment syndrome. In mainland China, 49% of patients with avascular necrosis receive surgical treatment (including total hip arthroplasty and hip preservation), 37% receive chemical therapy (including bisphosphonates, statins, prostacyclin, and anticoagulants), and up to 72% receive traditional Chinese medicine treatments [83, 85]. Given the chronic nature of the disease, traditional Chinese medicine holds significant potential for long-term management.

Clinical research reports indicate that THSWD effectively alleviates symptoms in patients with stage I and II femoral head necrosis, with an overall effective rate of 92.15%. Patients showed significant improvements in Harris Hip Score (HHS), bone mineral density, and serum osteocalcin levels, along with enhanced local blood coagulation status [86]. As an adjunct treatment, THSWD enhances the effects of anticoagulant, vasodilatory, and lipid-lowering therapies, improves femoral head microcirculation and hip function, and enhances the overall quality of life [87]. While previous attempts to systematically review the literature on THSWD in treating femoral head necrosis have been inconclusive, many studies have explored and verified its pharmacological mechanisms [88]. The promising clinical results underscore the potential of THSWD as a complementary treatment for managing avascular necrosis of the femoral head.

In a study on steroid-induced avascular necrosis of the femoral head in rabbits, THSWD significantly increased the density and number of bone trabeculae, improved microstructure, promoted the repair of necrotic tissue, and enhanced osteogenesis. The mechanism involved increasing the expression of VEGF to promote angiogenesis and restore blood sup-

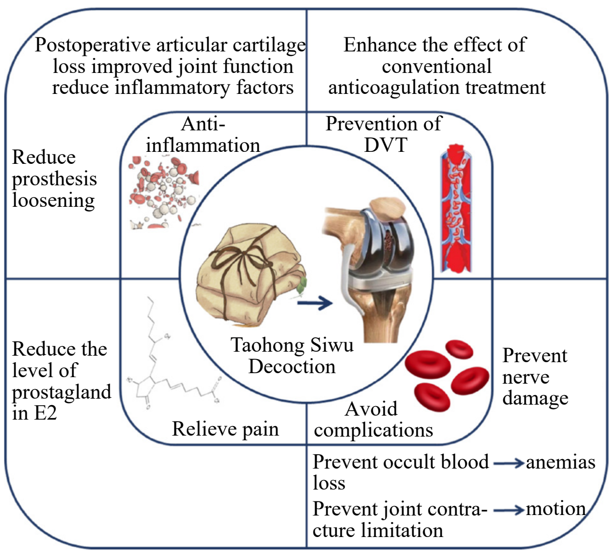

Fig. 4 Mechanism of Taohong Siwu Decoction in the treatment of joint replacement.

ply. Additionally, THSWD inhibited the expression of the adipogenic factor PPAR1, preventing steroid accumulation in osteoblasts, and inhibited osteoclast-related factors such as Receptor Activator of NF-KappaB (RANK) and RANKL. Simultaneously, it promoted osteogenic factors like Recombinant Runt Related Transcription Factor 2 (RUNX2), maintaining a balance between bone formation and resorption [89]. Previous research has shown that THSWD can regulate lipid signaling pathways in non-bone tissues [4], indicating its potential to inhibit fat accumulation. In another study on rats with traumatic femoral head necrosis, THSWD improved the pathological morphology of the femoral head by activating the BMP2/Smads/RUNX2 signaling pathway [90]. Recent studies have highlighted BMP2 as a target for inducing the proliferation and osteogenic differentiation of bone marrow stem cells [91].

Thus, THSWD's treatment of femoral head necrosis focuses on restoring tissue blood supply and promoting osteogenic differentiation, effectively preventing complete avascular necrosis of the femoral head (Fig. 5).

Osteoporosis

Osteoporosis is a common metabolic bone disease marked by decreased bone quality and the deterioration of bone tissue microstructure, leading to a heightened risk of fractures [92]. It is a major cause of morbidity and mortality among the elderly [93]. The imbalance between bone resorption and bone formation in osteoporosis results in reduced bone mass, strength, and density, increasing the risk of internal fixation failure, delayed fracture healing, and nonunion. With an aging global population, osteoporosis poses a significant healthcare burden worldwide [94]. In postmenopausal women, the primary cause of osteoporosis is calcium loss due to hormonal changes, with prevalence rates reaching 30%. Additionally, 50%−80% of middle-aged and elderly men suffer from secondary osteoporosis [95].

Bone cell activity is regulated by various cytokines, proteins, hormones, and vitamins, which maintain the balance between osteoblasts and osteoclasts [96]. The Wnt signaling pathway, a critical pathway for tissue regeneration, is one of the primary regulatory mechanisms. The RANK/RANKL signaling pathway is central to bone metabolism, primarily involved in the regulation of osteoclast activity by osteoblasts. RANKL and macrophage colony-stimulating factor (M-CSF), encoded by the *CSF1R* gene, are the only two factors known to directly promote osteoclast differentiation. Moreover, the phosphatidylinositide 3-kinases/protein kinase B (PI3K/Akt) signaling pathway can prevent osteoporotic bone loss by enhancing osteoblast function and promoting H-type angiogenesis [97]. In the past three decades, researchers have increasingly recognized the role of the adaptive immune system in the development of postmenopausal osteoporosis [98]. Adaptive immune cells, such as helper T cells and regulatory T cells, participate in the regulation of osteoblast and osteoclast activity, thus influencing bone remodeling.

The treatment of osteoporosis with THSWD focuses on regulating the bone remodeling process. Clinically, THSWD has been shown to increase bone mineral density, improve bone metabolism, promote the proliferation and differentiation of bone cells, and enhance the quality of life for patients with osteoporosis, particularly following a stroke [99]. After three months of treatment, osteoblasts are stimulated to proliferate and activate, while osteoclast activity is inhibited [100]. Network pharmacology research has demonstrated that THSWD can improve osteoporosis through multiple downstream pathways of the PI3K/Akt signaling pathway [101], which is essential for regulating the oxidative stress response [102]. In animal models, THSWD has been shown to treat osteoporosis *via* the RANK/RANKL and TGF-β signaling pathways. It enhances osteoblast activity, promotes new bone formation, shifts the balance towards osteogenesis over osteoclast activity, and significantly improves hemorheological indices [103] (Fig. 6). Plant hormones in derivatives, such as flavonoids (including isoflavones, *Lentinus edodes*, and propyl flavonoids) and non-flavonoids (like lignin), are considered effective for preventing osteoporosis [104]. THSWD is rich in flavonoids. Peony, a key component of THSWD, exhibits anti-inflammatory and immunomodulatory properties. After oral administration, paeoniflorin, a major active compound in peony, maintains a consistent presence in the blood, supporting the regulation of the adaptive immune system and promoting blood circulation [105, 106].

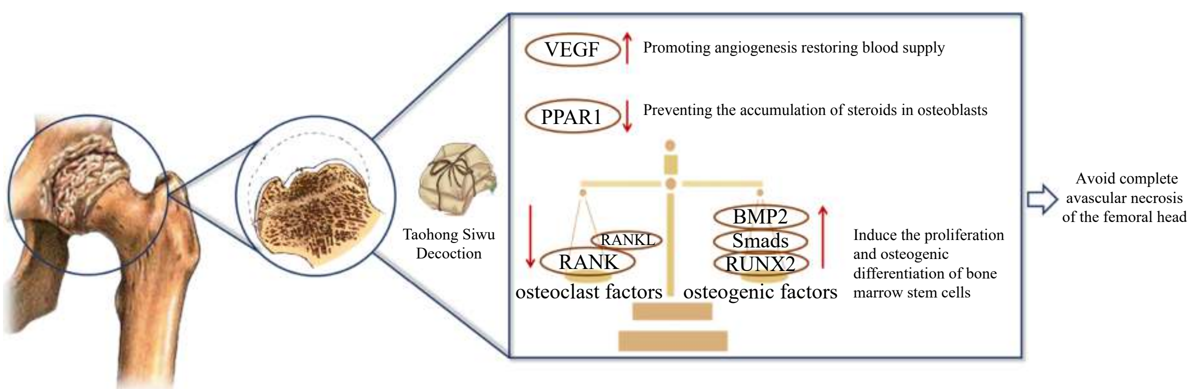

Fig. 5 Mechanism of Taohong Siwu Decoction in the treatment of femoral head necrosis.

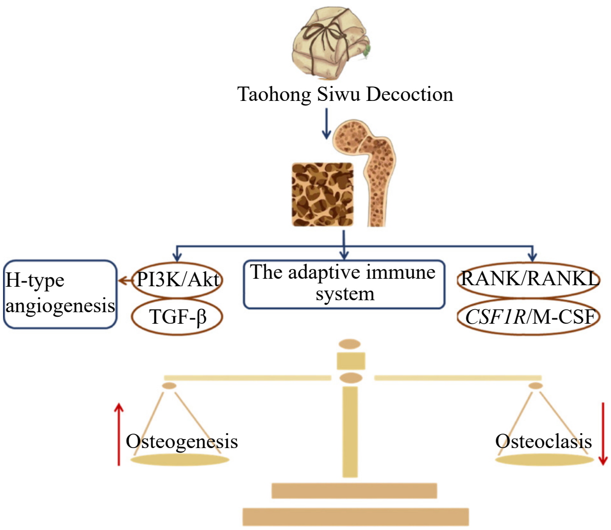

Fig. 6 Mechanism of Taohong Siwu Decoction in the treatment of osteoporosis.

Athletic injuries

Rotator cuff injury is a common injury in the process of exercise, which is manifested by shoulder pain, shoulder joint weakness and difficulty in movement. Clinical studies have found that THSWD can reduce the inflammatory response of rotator cuff injury and significantly relieve the symptoms. Meanwhile, in the rabbit rotator cuff injury model, the treatment mechanism is related to inhibiting the PI3K/Akt/mTOR signaling pathway, activating autophagy and inhibiting inflammatory response [107, 108]. For patients with acute ankle injury, THSWD can reduce pain mediators in serum, reduce inflammatory factor levels, and improve ankle function [109]. In the model of exercise-induced blood stasis syndrome, THSWD can reduce tissue damage and protect ischemic tissue by reducing cell apoptosis and necrosis [110] (Fig. 7). THSWD combined with surgery or modern therapies often improves efficiency and reduces adverse reactions.

Acute soft tissue injury

Soft tissue injury refers to trauma caused by direct or indirect forces to soft tissue or skeletal muscles, or long-term chronic strain. Following tissue injury, microcirculation disorders and aseptic inflammation occur, leading to local swelling and pain. THSWD aids in the repair of acute soft tissue injuries in rats by reducing the inflammatory response and inhibiting oxidative stress through the TGF-β signaling pathway [111]. After surgical repair of soft tissue defects in the limbs, THSWD has been shown to increase the survival rate of skin flaps, elevate hemoglobin and red blood cell counts, and improve systemic symptoms [112, 113]. The therapeutic effects of THSWD on soft tissue injury are primarily attributed to its anti-inflammatory properties and its ability to restore blood supply.

In summary, THSWD functions by promoting blood circulation and nourishing the blood in orthopedic conditions. The promotion of blood circulation involves altering hemorheology and blood components, leading to anticoagulation, pain relief, and prevention of joint contracture. The blood-nourishing function of THSWD is reflected in its ability to promote angiogenesis, enhance bone formation, and prevent occult blood loss (Fig. 8).

Conclusion and Prospects

THSWD has been validated as an effective adjunctive therapy for orthopedic diseases through pharmacological, molecular biological, and clinical evidence. Recent studies have particularly emphasized THSWD's role in fracture treatment, focusing on its anti-inflammatory and anticoagulant properties, pain relief, DVT prevention, enhancement of tissue function, and promotion of tissue recovery.

However, current research has identified several issues: a) There is considerable variability in the dosages and administration methods of THSWD, leading to inconsistencies across studies. This heterogeneity impedes the ability to derive clinically applicable findings. b) There is a scarcity of standardized studies and large-scale randomized controlled trials on the use of THSWD in orthopedic treatments. Most existing reports are based on clinical observations, which lim-

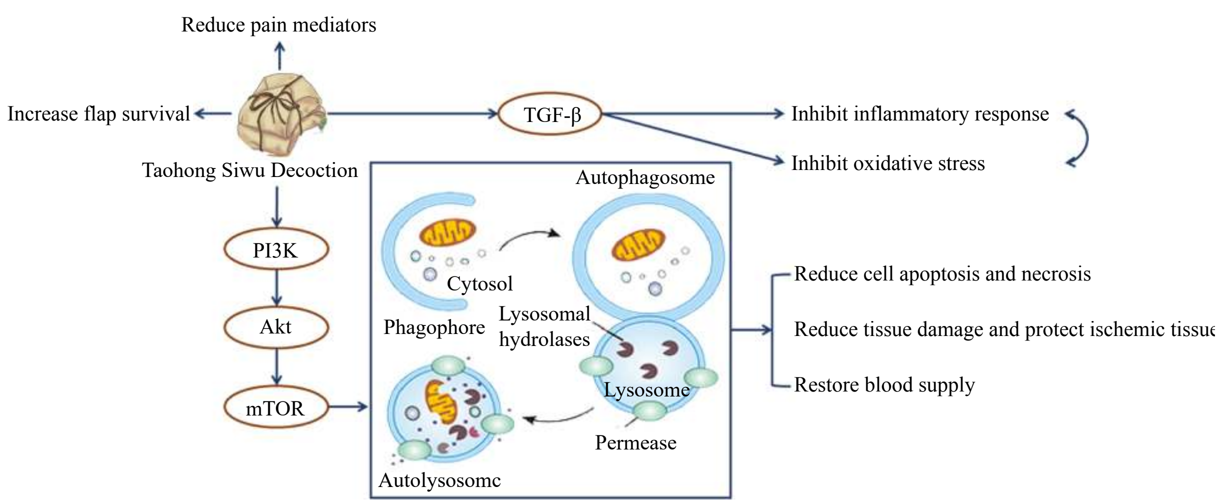

Fig. 7 Mechanism of Taohong Siwu Decoction in the treatment of athletic injuries and acute soft tissue injury.

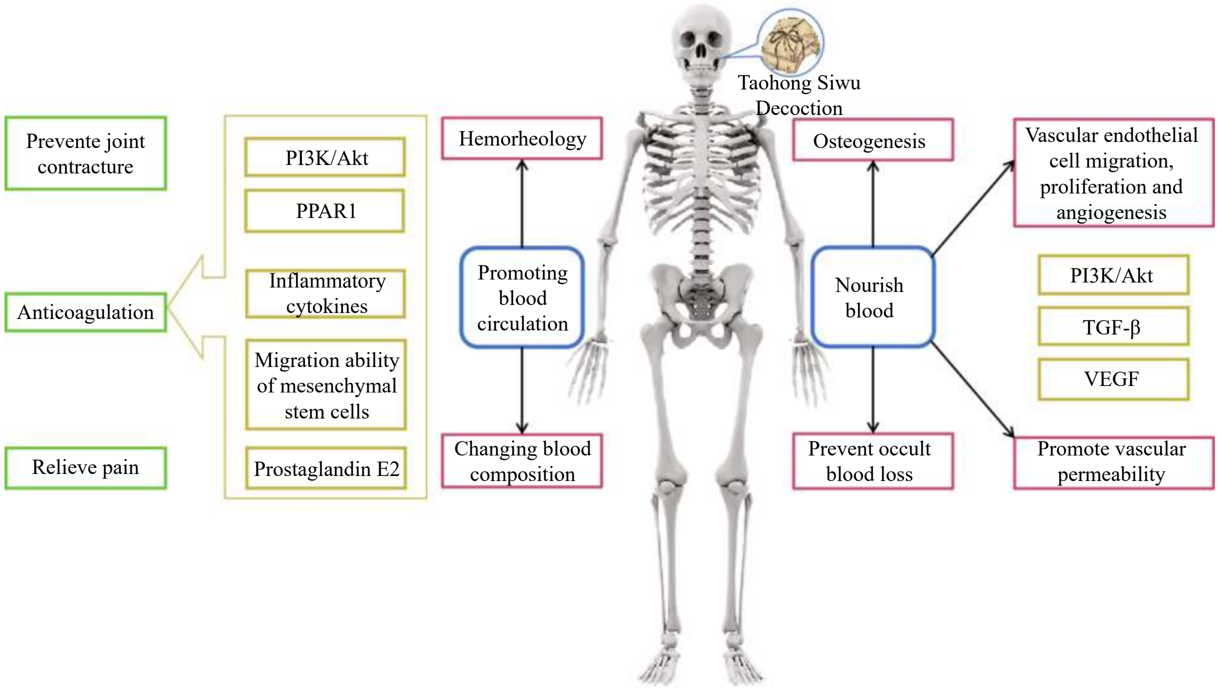

Fig. 8 Mechanism of THSWD for orthopedic diseases.

its the strength of the evidence supporting its use. In treating refractory orthopedic conditions (such as joint necrosis and joint replacement), the application of THSWD remains relatively limited. Current research often involves combining THSWD with other treatments, leading to significant variability in protocols. c) While some studies have explored the mechanisms of THSWD, the research has primarily focused on immune and gut microbiota mechanisms, which remain underexplored. d) DVT is a common and high-risk complication after orthopedic surgery. Although THSWD has shown excellent preventive effects, the understanding of its mechanism is superficial, and treatment protocols are not standardized.

This article makes several key recommendations to enhance the clinical application and research of THSWD in orthopedic treatment: a) It is essential to conduct standardized clinical trials to determine the optimal dosage, modifications, and administration methods of THSWD in orthopedic treatment. These trials will ensure consistency and efficacy across various patient populations. b) Large-scale randomized controlled trials with extensive subgroup analyses should be implemented to evaluate the efficacy of THSWD in combination with other treatments. These trials should also assess drug tolerance in different age groups, particularly elderly patients, whose bone metabolism differs significantly from younger individuals. It is necessary to provide tailored recommendations for refractory orthopedic diseases based on syndrome types, patient age, and disease severity to achieve uniform clinical treatment. c) Conducting in-depth mechanistic research is crucial to improve treatment precision and optimize drug delivery methods, thereby expanding the clinical applications of THSWD. Current research should focus on the modulation of gut microbiota and the role of the immune system, as these areas are closely related to established mechanisms such as inflammation and cell migration. d) Currently, THSWD is primarily administered as a decoction in clinical settings. While postoperative anticoagulants are routinely used after orthopedic surgery, they often have significant gastrointestinal side effects or bleeding risks. Although THSWD has not shown significant side effects in reports, there is a lack of focused research on its safety, especially when combined with anticoagulants. Additionally, the active ingredient amygdalin in Semen Persicae can produce toxicity when taken orally. Therefore, improving THSWD formulations to enhance safety and efficacy is a critical issue that needs to be addressed in clinical practice.

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