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REVIEW

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Mechanisms and new advances in the efficacy of plant active ingredients in tendon-bone healing

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Abstract

The tendon-bone interface, known as the tenosynovial union or attachment, can be easily damaged by excessive exercise or trauma. Tendon-bone healing is a significant research topic in orthopedics, encompassing various aspects of sports injuries and postoperative recovery. Surgery is the most common treatment; however, it has limited efficacy in promoting tendon-bone healing and carries a risk of postoperative recurrence, necessitating the search for more effective treatments. Recently, plant-active ingredients such as tanshinone IIA, astragaloside, ginsenoside Rb1, and resveratrol have garnered significant attention due to their unique advantages in promoting tendon-bone healing. This review outlines the various mechanisms and research progress of these four plant-active ingredients, as well as compound ingredients, in promoting tendon-bone healing. For instance, tanshinone IIA significantly accelerates the healing rate and improves healing quality through anti-inflammatory, antioxidant, and cell proliferation-promoting mechanisms. Astragaloside expedites tendon-bone healing and enhances the mechanical strength of healing tissues primarily through anti-inflammatory, antioxidant, and immunoregulatory effects. Ginsenoside Rb1 enhances local blood supply and facilitates tendon-bone tissue repair through angiogenesis, anti-inflammatory, and antioxidant pathways. Resveratrol protects cellular function and accelerates tissue healing due to its potent antioxidant and anti-inflammatory effects. Additionally, the mechanisms and progress of certain Chinese herbal compound components in tendon-bone healing are outlined. This review concludes that these four plant-active ingredients and herbal compound components promote tendon-bone healing through various mechanisms. The efficacy mechanisms and research progress of these plant-active ingredients are summarized to provide references for clinical treatment and related research.

Keywords Tendon-bone healing, Plant-active ingredients, Mechanisms, New advances, Efficacy

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Introduction

Tendon-bone healing occurs when tendon tissue attaches to bone tissue, restoring function after injury or surgery. The injury or post-surgical condition that causes clinical symptoms in and around the tendon is referred to as tendinopathy [1]. Tendinopathy is a group of disorders characterized by pain, swelling (diffuse or limited), and impaired function. Tendon-bone healing involves multiple stages and cellular, molecular, and tissue interactions. The process has three main phases: inflammatory, proliferative, and remodeling [2–4]. Three to seven days after the injury, the body enters the inflammatory phase, during which inflammatory cells (mainly monocytes, neutrophils, and macrophages) accumulate in the damaged area. Platelet activation leads to rapid hematoma formation, immune cells form granulation tissue, and other cells migrate from the peritendinous tendon sheaths and intratendinous tissues to the injured area. By the third week after the injury, the proliferative phase begins, primarily driven by the proliferation and differentiation of fibroblasts, chondrocytes, and osteoblasts. Fibroblasts produce large amounts of collagen (mainly types I and III) in this process, forming initial fibrous structures at the injury interface. Collagen synthesis usually lasts 5 to 8 weeks and is accompanied by neovascularization. During the remodeling phase, the maturation and remodeling of the extracellular matrix (ECM) contribute to improved tissue architecture and enhanced connectivity, promoting the generation of higher-quality tissue. The remodeling process may take up to two years to achieve full recovery.

The body's repair process for damaged tendons results in scar tissue formation, which weakens the tendon and increases the risk of re-rupture. Consequently, athletes or patients with high-energy injuries often suffer loss of function and recurrent injuries following sports injuries and certain orthopedic surgeries. Poor blood supply to the tendon-bone junction complicates and slows the healing process, making it more challenging. The tendon-bone healing process results in a scarred bone-tendon junction (BTJ), with insufficient restoration of surface fibers and cartilage. Chen et al. [5] discovered that, in a rat supraspinatus tendon injury model, clodronate intervention could induce non-scarring healing, forming a fibrocartilage-like BTJ. Although this non-scarred BTJ is only one-fifth the thickness of a scarred BTJ, its load-bearing capacity and strength significantly surpass those of a scarred BTJ [6], which has important implications for enhancing tendon-bone healing.

Traditional treatments, both surgical and non-surgical, have been utilized. Although tendon-bone healing is facilitated to some extent, and the healing process is influenced by systemic and local factors [7], the results are often unsatisfactory with a risk of recurrence. The rise in tendon-bone interface injuries has led to the increased use of various emerging technologies in clinical settings. These include biomaterials such as polymers and scaffolds, as well as compounds that promote cell growth and tissue regeneration. These technologies are widely utilized to enhance the healing of tendon-bone injuries. Stem cell therapy is a cutting-edge technology in which pluripotent stem cells can differentiate into a variety of cell types to promote tendon-bone healing through transplantation. Cytokines are proteins that regulate cellular activity. Typical representatives, such as embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), bone marrow mesenchymal stem cells (BMSCs), and MSCs derived from adipose tissue (ADSCs), can promote cell proliferation and differentiation, thereby accelerating tendon-bone healing. Platelet-rich plasma (PRP) is a concentrated plasma derived from a patient's blood and is rich in growth factors that promote tissue repair and regeneration. Exosomes are small vesicles secreted by cells that contain a variety of bioactive molecules, which regulate intercellular communication and promote tissue repair. Physical therapy techniques such as ultrasound, laser therapy, and electrical stimulation can enhance blood circulation, decrease inflammation, and aid in tendon-bone healing [8, 9]. Tissue engineering is a multidisciplinary approach aimed at inducing the repair, replacement, or regeneration of tissues or organs. While these emerging technologies may evolve into substantial clinical treatment options, their full impact needs to be rigorously evaluated scientifically. In recent years, with the in-depth study of Chinese medicine theories, more plant-active ingredients have been found to have the potential to promote tendon-bone healing [10].

Tanshinone IIA, astragaloside, ginsenoside Rb1, and resveratrol are typical representatives. These ingredients have not only found applications in traditional medicine but have also demonstrated significant biological activity in modern scientific research. They positively influence the tendon-bone healing process through multiple pathways.

This paper aims to systematically review the mechanisms of action and research progress of tanshinone IIA, astragaloside, ginsenoside Rb1, and resveratrol in tendon-bone healing. By synthesizing relevant literature and research findings, it is hoped that new insights for clinical treatment will be provided, laying the groundwork for further scientific inquiry.

Composition, efficacy, and mechanism

Tanshinone IIA

Source and chemical structure of tanshinone IIA

Tanshinone IIA, a fat-soluble diterpene quinone derived from the traditional Chinese medicine Salvia miltiorrhiza, is notable for its high lipophilic qualities. It possesses a complex chemical structure, enabling diverse

pharmacological effects. These effects include anti-inflammatory, antioxidant, antitumor, antidiabetic, prevention of atherosclerosis, and promotion of locomotor system repair. Consequently, these properties have brought tanshinone IIA to the forefront of modern medical research and clinical applications [11].

Mechanism of action of tanshinone IIA in tendon-bone healing and new developments

The mechanisms of action of tanshinone IIA in promoting tendon-bone healing are multifaceted. It inhibits the inflammatory response and reduces tissue edema, which is crucial for controlling the inflammatory environment in the early stages of tendon-bone healing. Both endogenous and exogenous repair mechanisms play an important role in tendon-bone healing [12]. Among these, exogenous repair mechanisms are the main cause of tendon adhesions. In a rat Achilles tendon rupture model, the application of miR-29b inhibitor at the severed end initiated the endogenous repair process, followed by the application of tanshinone IIA, which increased the number of fibroblasts in the tendon cells by inhibiting the exogenous repair process, reduced apoptosis of the tendon cells, and promoted the synthesis of collagen (mainly Col I and Col III). This led to an increase in the number of collagen in the tissues and tendon cells, with fibroblasts increasing in number and becoming more orderly arranged, reducing tendon adhesion and enhancing tendon strength, thus promoting tendon-bone healing [13–15]. It also regulates the balance of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). In a rat knee osteoarthritis model, tanshinone IIA increased TIMP-1 expression, reducing MMP-13-mediated collagen degradation in the cartilage matrix. This protected cartilage collagen, inhibited chondrocyte apoptosis, promoted chondrocyte proliferation, improved extracellular matrix remodeling, and facilitated tendon-bone healing [15, 16]. Tanshinone IIA possesses antioxidant properties. When the balance between oxidation and antioxidation in the joints is disturbed, tanshinone IIA can enhance antioxidant capacity, inhibit oxidase activity, and maintain chondrocyte equilibrium [17–19], which is vital for alleviating oxidative stress damage and protecting cellular function. In recent years, a new type of pluripotent stem cells called tendon-derived stem cells (TDSCs) has been identified in tendon tissue. These cells have the potential for self-renewal and can differentiate in multiple directions, contributing to the repair and regeneration of new tissues. They produce collagen and other matrix molecules that provide essential structural support. TDSCs have become a key focus of research for treating tendon-bone injuries and related diseases. In addition, changes in the composition of the extracellular matrix and increased deposition of proteoglycans are often observed in the tendon tissue of patients with tendon diseases. Additionally, research has demonstrated that changes in the structural components of the ECM influence the shape and signaling of TDSCs, which subsequently regulate the behavior of TDSCs [20–24]. Studies on tanshinone IIA in tendon healing and regeneration have shown that tanshinone IIA can promote the proliferation and migration of tendon cells as well as increase the pluripotency and differentiation of TDSCs by modulating the cell signaling pathway. These effects may contribute to accelerating the recovery process of tendon injury [25, 26].

It can be seen that tanshinone IIA can regulate the number of fibroblasts in tendon cells and collagen in tissues, and also regulate the balance of oxidation and antioxidants in the damaged area, reduce the damage of oxidative stress to the extracellular matrix, and protect chondrocytes. On the other hand, tendon-bone healing was accelerated by increasing the differentiation ability of TDSCs at tendon-bone injuries. In recent years, studies targeting the mechanism of action of tanshinone IIA in tendon-bone healing have intensified. Both animal and cellular experiments showed that tanshinone IIA significantly accelerated tendon-bone healing and improved the quality of healing. It is important to note that most of the current studies have focused on short-term experiments and animal models, and there is a lack of data from long-term clinical trials, especially in humans, where the long-term effects and potential side effects need to be further verified. For example, exactly how tanshinone IIA regulates these biological processes and its mechanism of action in different tissues and cell types are not fully understood and need to be further explored. The optimal dosage and mode of administration of tanshinone IIA can be further explored in the future to achieve better therapeutic effects.

Astragaloside

Source and chemical structure of astragaloside

Astragaloside is the primary active ingredient extracted from the traditional Chinese medicine Astragalus membranaceus, a triterpenoid saponin. It primarily consists of Astragaloside I, II, and IV, with Astragaloside IV being the most biologically active compound. Astragaloside exhibits various biological activities, including immunomodulatory, anti-inflammatory, and antioxidant effects.

Mechanism of action of astragaloside in tendon-bone healing and new developments

Astragaloside promotes tendon-bone healing through several mechanisms. Firstly, astragaloside exhibits significant anti-inflammatory effects, reducing the expression of inflammatory factors, tissue damage, and edema. Secondly, astragaloside scavenges free radicals and reduces

cellular damage caused by oxidative stress through its antioxidant properties. Additionally, Astragaloside IV has shown significant effects in promoting angiogenesis and osteogenesis. Bone tissue is highly vascularized, with the rich vascular network providing nutrients, oxygen, and secreting specific cytokines that regulate various biological activities [27, 28]. In the distraction osteogenesis model [29], Astragaloside IV enhanced platelet-derived growth factor-BB (PDGF-BB)-induced angiogenesis, leading to the formation of numerous blood vessels in the distracted bone region. It also enhanced the viability and osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs), significantly increasing the expression levels of osteogenesis-related markers (e.g., ALP, OSX, OCN, OPN, and Runx 2) in BMSC after Astragaloside IV administration. Gene expression of angiogenesis-related factors (e.g., Ang-2, Ang-4, SDF-1, and Slit 3) was also elevated after osteogenic induction. Micro-CT results showed that the Astragaloside IV group exhibited superior volume and continuity of the bone scab, with significantly higher bone mineral density (BMD) and bone volume/total volume (BV/TV) of the bone regenerates compared to the control group. These results suggest that Astragaloside IV promotes angiogenesis and osteogenesis, enhancing osteoblast differentiation while inhibiting osteoclast differentiation. Finally, Astragaloside IV promotes the proliferation and differentiation of fibroblasts and chondrocytes. Tendon-derived stem cells (TDSCs) are present in tendons and exhibit enhanced chondrogenic and tendinogenic differentiation after tendon damage, forming tendon-like-bone-like tissues and enhancing tissue repair [30–35]. Further studies have shown that Astragaloside IV increases tension at the tendon-bone union and the presence of trabecular, fibrous, and cartilaginous tissues on the surface, promoting cartilage regeneration and tendon-bone healing [36]. However, questions remain regarding how Astragaloside specifically regulates osteoblast and osteoclast differentiation, which signaling pathways and gene expression changes are involved, its potential adverse effects on other tissues or organs, and dose-dependent toxicity. Additionally, there are limited clinical studies on Astragaloside, necessitating further validation of its effectiveness in clinical applications.

Ginsenoside Rb1

Origin and chemical structure of ginsenoside Rb1

Ginsenoside Rb1 is a vital bioactive ingredient derived from the well-known medicinal plant Panax ginseng (ginseng). This compound belongs to the dammarane-type tetracyclic triterpenoid saponin class and is renowned for its remarkable pharmacological effects. Specifically, ginsenoside Rb1 exhibits a range of health benefits, including anti-inflammatory, antioxidant, and angiogenesis-promoting effects.

Mechanism of action of ginsenoside Rb1 in tendon-bone healing and new developments

Ginsenoside Rb1 promotes tendon-bone healing through multiple mechanisms. Firstly, it significantly inhibits the expression of inflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). Overexpression of these factors leads to tissue damage and delayed healing. By inhibiting these factors, ginsenoside Rb1 can reduce the inflammatory response and promote tissue repair [37]. Secondly, oxidative stress is a crucial factor in the inflammatory response. Ginsenoside Rb1 further attenuates the inflammatory response and promotes tissue repair by reducing oxidative stress [38]. Additionally, it effectively promotes the growth and migration of vascular endothelial cells, which is essential for improving blood supply to the injury site and accelerating tissue repair. vascular endothelial growth factor (VEGF) is a protein widely expressed in vivo and highly expressed in tendon and skeletal tissues, playing a crucial role in neovascularization. According to Zhang et al. [39], ginsenoside Rb1 activates VEGF to bind to specific receptors on endothelial cells, promoting both the growth of vascular endothelial cells and the development of lymphatic endothelial cells. Additionally, ginsenoside Rb1 regulates the degradation of the extracellular matrix of endothelial cells, as well as cell migration, proliferation, and lumen formation, all critical steps in angiogenesis. It accelerates the tendon-bone healing process by enhancing the blood supply to the tendon-bone junction. Ginsenoside Rb1 actively promotes angiogenesis and improves blood supply to the tendon-bone junction through its interaction with VEGF, thereby supporting tendon-bone healing [40–42]. Finally, Wu et al. [43] found that after the application of ginsenosides, the tendon tissues in the experimental group became more continuous and organized, with increased internal content of tendon regulator (MKX), a substance crucial for tendon development and repair after injury. Additionally, tendon stiffness and stretch significantly increased, directly improving the strength of tendon-bone healing [44, 45]. Although fewer reports exist on ginsenoside Rb1 promoting tendon-bone healing through anti-inflammatory effects, given its role in neuroprotection and anti-inflammation, it is hypothesized that it may contribute to tendon-bone healing through these mechanisms and by promoting cellular repair [46]. These effects may help reduce the inflammatory response and promote the repair and regeneration of damaged tissues, warranting further research.

Resveratrol

Origin and chemical structure of resveratrol

Resveratrol, a naturally occurring polyphenolic compound, is a botanical ingredient widely distributed in nature, particularly abundant in the fruits or seeds of plants such as grapes, peanuts, and mulberries. It has been extensively studied for its diverse biological effects, including powerful antioxidant capacity, anti-inflammatory effects, and anti-tumor potential. These properties make resveratrol highly promising for maintaining health and preventing various diseases. While antioxidants are known to promote tissue healing, few studies have shown their efficacy in promoting tendon-bone healing [47, 48]. Among plants with active ingredients, resveratrol stands out as a potent antioxidant.

Mechanism of action of resveratrol in tendon-bone healing and new developments

Resveratrol promotes tendon-bone healing primarily through its antioxidant, anti-inflammatory, and cell proliferation and differentiation-promoting effects. Firstly, resveratrol scavenges free radicals, reduces oxidative stress, and protects cells from damage. Secondly, resveratrol inhibits the expression of inflammatory factors and attenuates the inflammatory response. Resveratrol improves hydrogen peroxide-induced apoptosis of primary chondrocytes, increases cell proliferation, reduces the release of inflammatory factors, and decreases the expression of inflammatory signaling factors, contributing to chondrocyte protection and repair during tendon-bone healing [49]. Finally, resveratrol promotes the proliferation and differentiation of fibroblasts and osteoblasts. In a tendon injury with diabetes rat model, although collagen bundles were newly generated in both the resveratrol and control groups, the collagen bundles in the resveratrol group were more aligned. The number and density of newborn fibroblasts in the resveratrol group were higher than in the control group. Moreover, none of the rats in the experimental group exhibited high inflammatory cell density; the collagen-to-scar tissue ratio in the tendon-bone repair region was significantly higher in the experimental group than in the control group. Additionally, the mechanical strength of tissues in the experimental group was higher, demonstrating resveratrol's anti-inflammatory properties and its ability to promote the proliferation and differentiation of fibroblasts. Tissue repair is facilitated, and tendon-bone healing is accelerated through these mechanisms [50]. Recent years have seen progress in the study of resveratrol in tendon-bone healing. Both animal and cellular experiments have shown that resveratrol significantly accelerates tendon-bone healing and improves the quality of healing. For example, in a rat tendon-bone healing model [51], the resveratrol-treated group exhibited faster healing and higher tissue mechanical strength. However, fewer clinical studies on resveratrol exist, and potential side effects or adverse reactions may occur. Further validation of its efficacy in clinical applications is needed in the future.

These are the sources, chemical structures, and mechanisms of action of the four main plant active ingredients in tendon-bone healing and new developments. (Fig. 1)

Progress in combination studies

Co-medication involves the use of multiple drugs or active ingredients simultaneously to achieve synergistic effects or reduce side effects. In the field of tendon-bone healing, there has been growing interest in studying combinations, particularly of botanical active ingredients. Below are some advances in co-medication research:

Combination of tanshinone IIA and astragaloside

Tanshinone IIA and astragaloside exhibit significant anti-inflammatory, antioxidant, and immunomodulatory effects, respectively. Studies have shown that combining the two can have a synergistic effect and significantly improve tendon-bone healing. For example, an animal study showed that treatment with a combination of tanshinone IIA and astragaloside resulted in significantly better mechanical strength and organization of the tendon-bone junction than either component alone. MSCs are multipotent stem cells capable of differentiating into a wide range of cells, including bone, heart, nerve, fat, and cartilage. They play a crucial role in maintaining cartilage and subchondral bone homeostasis, as well as promoting or inhibiting pathological processes such as cartilage degeneration, abnormal subchondral bone remodeling, and promoting osteoclastogenesis in osteoarthritis [51, 52]. It has been shown [53, 54] in vitro and in vivo experiments that the combination of tanshinone IIA and astragaloside IV has a stronger ability to increase MSC migration compared to using tanshinone IIA and astragaloside IV alone. The optimal concentrations of tanshinone IIA and astragaloside IV to promote MSC generation were also determined. Although it has not been reported whether the combination of the two accelerates tendon-bone healing, after injury at the tendon-bone junction, MSCs are generated on the injury surface, which can differentiate in multiple directions. It is conjectured that they can promote tendon-bone healing and increase the strength of tendon-bone healing to a certain extent.

Combined application of ginsenoside Rb1 and resveratrol

Ginsenoside Rb1 excels in promoting angiogenesis, while resveratrol possesses powerful antioxidant and anti-inflammatory effects. Combining the two was found to reduce oxidative stress and inflammatory responses while

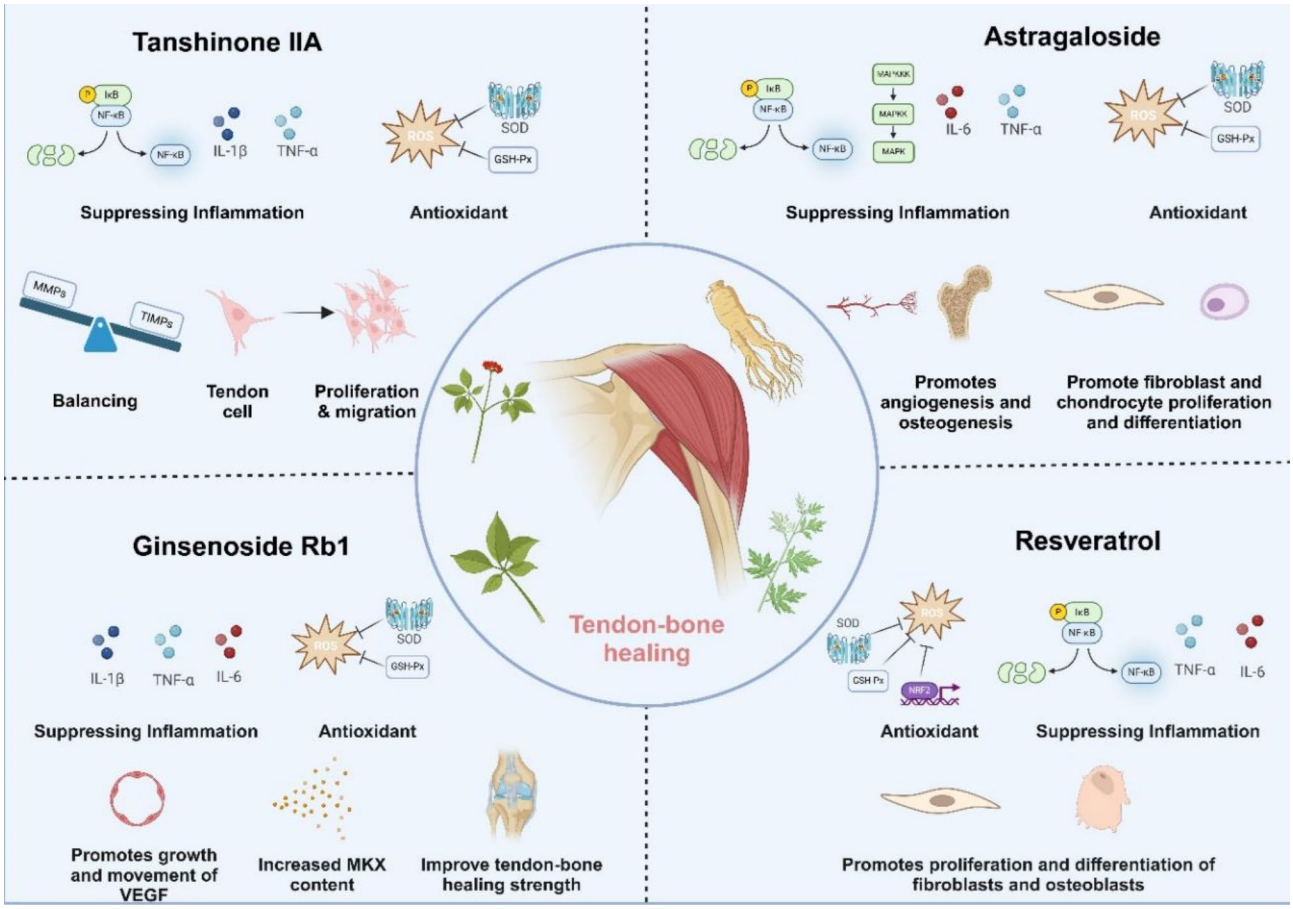

Fig. 1 Mechanisms associated with the promotion of tendon-bone healing by four major plant active ingredients

improving local blood supply. Qian et al. [55] found in a rat experiment that combining ginsenosides with resveratrol increased NO and superoxide dismutase (SOD) activity, decreased inducible nitric oxide synthase (iNOS) activity, and increased endothelial nitric oxide synthase (eNOS) activity in cardiomyocytes. This enhanced the ability to scavenge free radicals, reduced endothelial dysfunction and inflammatory damage, and protected the cardiomyocytes. The application of ginsenosides or resveratrol alone had a promotional effect on tendon-bone healing, but the effects of the two together on tendon cells as well as osteocytes have not been reported, and the mechanism of tendon-bone healing is not yet clear. This may be a direction for future research.

Combined application of multiple plant active ingredients

Several studies have explored the effects of combining multiple plant-derived active ingredients. For example, studies of the combination of tanshinone IIA, astragaloside, and ginsenoside Rb1 have shown complementary effects in promoting cell proliferation, anti-inflammation, and angiogenesis, significantly improving tendon-bone healing. Specific mechanisms include: tanshinone IIA primarily acts through anti-inflammatory and cell proliferation-promoting effects; astragaloside acts through anti-inflammatory and immunomodulatory effects; and ginsenoside Rb1 promotes angiogenesis and antioxidant effects.

Research on Chinese medicine compound prescriptions

Herbal compounding is a common form of combination medication and has shown progress in tendon-bone healing research in recent years. For example, certain compound Chinese medicines, such as Tonic Yang Returning Five Soup, contain various plant active ingredients that can significantly promote tendon-bone healing through multi-target and multi-pathway synergistic effects. Tonic Yang Returning Five Soup is a traditional Chinese herbal compound prepared by mixing and decocting a series of selected Chinese herbs. This formula includes Astragalus membranaceus, Radix Angelicae Sinensis Tail, Rhizoma Ligustici Chuanxiong, Radix Paeoniae Alba, Rhizoma Saffron, Radix et Rhizoma Dillonii, and Radix et Rhizoma Momordica Sinensis. These herbs work synergistically to replenish the body's yang qi, promote blood circulation, and improve associated symptoms. In Wu et al.'s

study [56], after the application of Tonic Yang Returning Five Soup, the expression level of SOD increased and the expression level of ROS decreased, effectively suppressing oxidative stress and improving the condition. It also has anti-inflammatory and antioxidant effects, reducing inflammatory responses and improving neuronal apoptosis. Rats with spinal cord injuries locally formed large amounts of ferritin, which increased the blood supply to the injury site and accelerated the healing rate. Similarly, vascular injury, inflammatory response, and oxidative stress follow tendon-bone interface injuries, and it is conjectured that Tonic Yang Returning Five Soup may also ameliorate localized injuries and promote tendon and bone healing, which subsequently requires further validation.

Advances in molecular mechanisms

Tanshinone IIA

Anti-inflammatory properties: It effectively inhibits the activation of the nuclear factor-κB (NF-κB) signaling pathway, thereby reducing the production of key inflammatory mediators, including tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β). These inflammatory mediators, if overexpressed during the healing process, exacerbate tissue damage and slow the healing process. Antioxidant power: Tanshinone IIA reduces oxidative stress in the body by enhancing the activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px). Its antioxidant effect is essential for protecting cells from free radical damage.Cell proliferation promotion: Additionally, tanshinone IIA activates cell signaling pathways such as ERK1/2 and PI3K/Akt, which promote fibroblast proliferation and collagen synthesis. This is crucial for repairing damaged tissue and restoring its normal function.

Astragaloside

Anti-inflammatory effect: Astragaloside intervenes in the activation of NF-κB and MAPK signaling pathways, inhibiting the production of inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). This anti-inflammatory effect helps reduce the inflammatory response, aiding in the control of inflammatory diseases and promoting tissue repair.Antioxidant properties: Astragaloside effectively reduces oxidative stress by enhancing the activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px). This antioxidant action is essential for protecting cells against free radical damage and maintaining cellular integrity and function. Immunomodulatory function: Astragaloside regulates immune cell activity and promotes the repair of damaged tissues by enhancing the body's immune response. This immunomodulatory effect increases the body's resistance to disease and accelerates wound healing.

Ginsenoside Rb1

Angiogenesis promotion: Ginsenoside Rb1 activates the signaling pathway of vascular endothelial growth factor (VEGF) and its receptor (VEGFR), essential for the proliferation and migration of vascular endothelial cells, contributing to new blood vessel formation.Anti-inflammatory properties: Ginsenoside Rb1 effectively reduces the production of inflammatory factors, including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), by inhibiting the nuclear factor-κB (NF-κB) signaling pathway. This anti-inflammatory effect reduces the inflammatory response, aiding in the treatment of inflammatory diseases and promoting tissue repair.Antioxidant power: Ginsenoside Rb1 reduces oxidative stress by enhancing the activity of antioxidant enzymes. This antioxidant effect is essential for protecting cells from free radicals and maintaining normal cell function and structural integrity.

Resveratrol

Antioxidant effect: Resveratrol reduces oxidative stress by activating the Nrf2/ARE signaling pathway and promoting the expression of antioxidant enzymes such as SOD and GSH-Px.Anti-inflammatory effect: Resveratrol reduces the expression of inflammatory factors such as IL-6 and TNF-α by inhibiting NF-κB and AP-1 signaling pathways.Promote cell proliferation and differentiation: Resveratrol promotes the proliferation and differentiation of fibroblasts and osteoblasts, accelerating tissue repair by activating the PI3K/Akt and ERK1/2 signaling pathways.

Discussion

Tanshinone IIA, astragaloside, ginsenoside Rb1, and resveratrol exhibit their respective mechanisms of action and efficacy in tendon-bone healing. Tanshinone IIA accelerates tendon-bone healing primarily through anti-inflammatory, antioxidant, and cell proliferation-promoting effects. Astragaloside significantly improves healing quality through its anti-inflammatory, antioxidant, and immunomodulatory effects. Ginsenoside Rb1 enhances local blood supply and promotes tissue repair through angiogenesis, anti-inflammatory, and antioxidant effects. Resveratrol protects cell function and accelerates tissue healing with its powerful antioxidant and anti-inflammatory effects. Future studies should further elucidate the specific molecular mechanisms of these plant active ingredients and optimize their application protocols to provide more effective clinical treatments.

Studies on combinations in tendon-bone healing have shown promising applications. The speed and quality of tendon-bone healing can be significantly enhanced by rationally selecting and optimizing the combined application of plant active ingredients. Future studies should

Table 1 Advantages and disadvantages of major plant active ingredients in tendon-bone healing

Active ingredients	Advantages	Disadvantages
Tanshinone IIA	Anti-inflammatory, antioxidant, promotes cell proliferation, reduces apoptosis, promotes differentiation of TDSCs and accelerates the repair process	Low bioavailability, requires high doses to reach effective concentrations; which contributes to liver burden.
Astragaloside	Strong anti-inflammatory and antioxidant capacity, promotes cell proliferation, promotes angiogenesis, promotes osteogenic differentiation, inhibits osteoblastic differentiation, and accelerates tendon-bone healing.	There is limited support for mineralization at the tendon-bone interface, and single-use is ineffective.
Ginsenoside Rb1	Anti-inflammatory, antioxidant, increases blood supply to damaged areas, improves collagen synthesis, and promotes healing.	Poor stability of ingredients, low absorption rate, need to improve the dosage form.
Resveratrol	Strong antioxidant effect, regulates inflammatory response, promotes cell proliferation and differentiation, and enhances bone formation.	Low water solubility and low bioavailability limit the use of drugs in vivo.
Co-medication	Anti-inflammatory, antioxidant, promotes angiogenesis, cell proliferation and differentiation, immunomodulation and other multiple effects, improve the quality of tendon bone healing	Component interactions are complex, dosing and proportioning are difficult, and potential drug-drug interactions and toxicity need to be further evaluated.

continue to deeply explore the mechanisms of drug combinations, conduct large-scale clinical trials, and develop personalized treatment protocols to provide more effective clinical treatments.

Although some progress has been made on the mechanism of action and effects of tanshinone IIA, astragaloside, ginsenoside Rb1, and resveratrol in tendon-bone healing, there are inevitably drawbacks and issues that require further research (Table 1). Firstly, most existing studies focus on animal and cellular experiments and lack large-scale clinical trials. Secondly, the optimal dosage and duration of treatment for each herbal ingredient remain unclear and require further study. Finally, the synergistic mechanisms between different herbal components need to be explored in depth.

Overall, tanshinone IIA, astragaloside, ginsenoside Rb1, and resveratrol show promising applications in promoting tendon-bone healing. Future studies should focus on further elucidation of their mechanisms of action, optimization of use regimens, and large-scale clinical trials to verify their efficacy and safety.

Directions for future research

Although many studies have revealed the mechanisms of action of these phytoactive ingredients in tendon-bone healing and confirmed their beneficial effects, challenges remain. Further studies are needed to determine the optimal dosage, timing, and potential mechanisms [57]. Additionally, there are many limitations, including the refinement of cell signaling pathways, gene expression regulation and epigenetics, the study of synergistic effects of multi-components, and the need for large-scale clinical trials. Future studies should continue to explore these mechanisms in detail and verify their efficacy and safety through clinical trials to provide a solid scientific basis for clinical application.

Conclusion

The analysis of this review indicates that combining tanshinone IIA, astragaloside, ginsenoside Rb1, and resveratrol in tendon-bone healing has promising applications. These combinations demonstrate significant synergistic effects in anti-inflammatory, antioxidant, cell proliferation and differentiation promotion, immunomodulation, and angiogenesis promotion. Different combinations have their advantages in various stages and types of tendon-bone injuries, offering diverse therapeutic options.

Author contributions

Yuan Li: responsible for the overall design and implementation of the study, including the development and execution of the experimental protocol; led the data analysis and interpretation, and wrote the main part of the paper. Wei Wang: participated in the design and experiments of the study, assisted in data analysis, and revised and improved the first draft. responsible for literature search and organization, assisted in writing and revising some chapters, and analyzed and discussed the research results.Wensheng Xu (corresponding author): guided the whole research process, provided suggestions on key theoretical frameworks and methods, supervised the data analysis and paper writing, and ensured the quality of the research and the overall quality of the paper.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Informed consent

Not applicable.

Conflict of interest

There is no conflict of interest in this paper.

Competing interests

The authors declare no competing interests.

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