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Research Progress on the Mechanism of Action of Tanshinone IIA in the Prevention and Treatment of Osteoarthritis

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Abstract: ***Osteoarthritis (OA) is a chronic inflammatory degenerative disease that is difficult to cure due to its complex pathogenesis. Traditional Chinese Medicine (TCM), with its multi-component, multi-target, and multi-pathway characteristics, offers various mechanisms for the treatment of OA. Tanshinone IIA (Tan IIA), a primary active ingredient extracted from the herb Salvia miltiorrhiza (Danshen), has shown significant potential in the treatment of OA. Tan II A can participate in the development of OA by activating or inhibiting multiple signaling pathways. It has various effects, including the inhibition of chondrocyte apoptosis and degradation of the extracellular matrix, reduction of inflammatory factor production, promotion of chondrocyte autophagy, and antioxidative stress. This review summarizes the role and mechanisms of Tan II A in the prevention and treatment of OA, providing a theoretical basis for future research and clinical applications of Tan IIA in OA treatment.***

Keywords: Tanshinone IIA, Osteoarthritis, Chondrocytes, Mechanism of action.

1. Introduction

Osteoarthritis (OA) is a chronic degenerative change in joints caused by an imbalance between tissue repair and destruction, and it is one of the most common types of arthritis [1]. The affected tissues in OA include cartilage, subchondral bone, and synovium, and the condition is characterized by cartilage erosion, imbalance in subchondral bone remodeling, osteophyte formation, and synovial inflammation [2]. OA commonly occurs in middle-aged and elderly individuals, often accompanied by pathological changes such as cartilage degeneration, subchondral bone thickening, bone remodeling with osteophyte formation, synovitis, degenerative changes in ligaments and meniscus, and hypertrophy of the joint capsule. Clinically, it manifests as chronic joint swelling, pain, stiffness, limited mobility, joint deformity, and functional impairment [3, 4]. It is estimated that over 500 million people worldwide are affected by OA [5]. OA is incurable, and conventional treatment is primarily limited to the use of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid injections, and analgesics. However, long-term use of NSAIDs and analgesics such as acetaminophen can lead to adverse reactions, including gastrointestinal and cardiovascular diseases [6, 7]. OA is the most common cause of physical disability in the elderly worldwide and is also one of the major contributors to financial burdens. Therefore, there is an urgent need to develop new and more effective methods for the prevention and treatment of OA.

In recent years, traditional Chinese medicine (TCM) has been widely used in clinical treatment. An increasing body of research suggests that TCM is effective and has few side effects, making it a promising strategy for OA treatment. Danshen (Salvia miltiorrhiza Bge.), one of the most commonly used herbs in China, was first recorded in the "Shennong Ben Cao Jing" and is the dried root and rhizome of the Lamiaceae plant. The 2020 edition of the "Chinese Pharmacopoeia" describes its properties, including promoting blood circulation, relieving pain, clearing the heart, and cooling blood to resolve abscesses. It is widely used in the treatment of cardiovascular and cerebrovascular diseases [8]. Modern pharmacological studies show that Danshen has multiple therapeutic effects, including lipid regulation, antioxidant, anti-inflammatory, anticoagulant properties, and microcirculation improvement [9]. Tanshinone IIA (Tan IIA), a lipophilic diterpene compound extracted from Danshen [10], is widely available, low in toxicity, and has few adverse effects. It possesses anti-inflammatory, anti-apoptotic, and antioxidant activities, making it a potential treatment for various diseases, including cardiovascular diseases, cerebrovascular diseases, cancer, diabetes, obesity, and neurodegenerative diseases [11, 12].

This review aims to comprehensively summarize the current scientific evidence regarding the prevention and treatment of OA with Tan IIA. By focusing on the pharmacological actions and mechanisms of Tan IIA related to OA, the goal is to elucidate its contributions to OA and overall bone health, with the aim of providing new perspectives and evidence for OA treatment.

2. Regulate Inflammatory Factors

Inflammatory factors play a key role in synovial inflammation and cartilage matrix degradation. The pro-inflammatory cytokine Interleukin-1β (IL-1β) activates the IKK complex through TRAF6, phosphorylates IκB, and releases Nuclear factor-κB (NF-κB) into the nucleus for transcription, regulating the expression of downstream target genes, and participating in the pathogenesis of OA. NF-κB is a central transcription factor in inflammation and immune responses, involved in infection, inflammation, immune responses, apoptosis, tumorigenesis, and cell cycle regulation and differentiation. It can be activated by various cytokines, such as IL-1β and tumor necrosis factor α (TNF-α) [13]. Studies have shown that Tan IIA can inhibit the expression of IL-1β mRNA and the activation of the NF-κB signaling pathway

induced by IL-1β, suppress inflammatory cytokine release, and delay the onset of OA [14]. TNF-α, secreted by macrophages, inhibits collagen II expression and extracellular matrix (ECM) synthesis, induces COX-2 expression, accelerates ECM degradation, and damages articular cartilage. Interleukin-6 (IL-6), an important pro-inflammatory factor, promotes the elevation of TNF-α levels and exacerbates cartilage damage. COX-2, an inducible cyclooxygenase, promotes the production of prostaglandin E2 (PGE2) from arachidonic acid, enhances matrix metalloproteinases (MMPs) synthesis, and degrades ECM [15]. Research has found that Tan IIA treatment significantly reduced the levels of TNF-α, IL-6, PGE2, and COX-2 expression in chondrocytes, indicating that Tan IIA can protect chondrocytes by reducing the expression of inflammatory mediators [16].

Numerous studies have shown that the Toll-like receptor 4/myeloid differentiation factor 88/nuclear factor-κB (TLR4/MyD88/NF-κB) inflammatory signaling pathway plays an important role in OA [17, 18]. Increasing evidence confirms that Toll-like receptors are widely involved in recognizing endogenous damage-associated molecular patterns (DAMPs), which can trigger non-infectious innate immune responses. The TLR4 signaling pathway includes both MyD88-dependent and independent pathways [19]. Transforming growth factor-β-activated kinase 1 (TAK1) plays a key role in the MyD88-dependent signaling network. It activates the IKK complex, specifically IKKβ, to promote the nuclear translocation of NF-κB, initiating the transcription and protein synthesis of various inflammatory cytokines, leading to or exacerbating the inflammatory response in articular cartilage. Blocking the TLR4/MyD88/NF-κB signaling pathway can significantly alleviate inflammation [20]. Studies have found that Tan IIA significantly reduced the expression of inflammatory cytokines such as IL-1β, TNF-α, and IL-6 in rat joint tissues and serum, inhibited the expression of TLR4, MyD88, and NF-κB proteins in cartilage tissue, and suppressed the nuclear translocation of NF-κB p65, exhibiting significant anti-inflammatory activity [21]. β-arrestin2 is an upstream cytokine of NF-κB, and its overexpression can inhibit NF-κB activation. Research indicates that Tan IIA at 25, 50 μmol/L can promote the expression of β-arrestin2, thereby exerting anti-inflammatory effects [22].

The PI3K/AKT/NF-κB signaling cascade can be activated by IL-1β. Research has confirmed that IL-1β activates PI3K and AKT phosphorylation, downregulates the PI3K/AKT signaling pathway, and releases various inflammatory cytokines, which are closely associated with the pathological progression of OA [23]. Studies have shown that Tan IIA can reduce the expression levels of p-PI3K, p-AKT, and p-P65 proteins, inhibit the activation of the PI3K/AKT/NF-κB signaling pathway, lower phosphorylation levels, and suppress the OA inflammatory response, delaying chondrocyte degeneration [16]. Tan IIA also suppresses the PI3K/Akt and NF-κB pathways by downregulating the expression of FBXO11, reducing chondrocyte apoptosis and inflammation in OA [24].

3. Inhibit Cell Apoptosis

Chondrocyte apoptosis leads to the degradation of articular cartilage and is a major factor in the development of OA [25]. Studies have found that Tan IIA inhibits the expression of inflammatory cytokines such as MMP-13, iNOS, IL-1β, and TNF-α, and increases the expression of collagen regulatory factors TGF-β and BMP-2, effectively suppressing chondrocyte apoptosis and articular cartilage degradation in rat models induced by anterior cruciate ligament transection (ACLT) and medial meniscectomy (MMx) [26].

Additionally, existing research shows that the occurrence and development of OA are closely related to the immune imbalance between regulatory T cells (Treg) and helper T cells 17 (Th17). Under normal physiological conditions, Treg/Th17 maintains a continuous dynamic balance. During OA, under the stimulation of inflammatory stress, the proportion of Th17 increases, the expression of anti-apoptotic B-cell lymphoma-2 (Bcl-2) in cartilage tissue decreases, the expression of pro-apoptotic Bcl-2-associated X protein (Bax) increases, and cell apoptosis in knee joint cartilage tissue dramatically increases, leading to cartilage tissue structural and functional impairment [27]. Studies have found that Tan IIA intervention in OA rats significantly alleviated the imbalance of Treg/Th17 in spleen tissue, significantly increased the expression of Foxp3 in cartilage tissue, and significantly reduced the expression of IL-17, indicating that Tan IIA can significantly intervene in the Treg/Th17 immune imbalance in OA rats and reduce the apoptosis rate in cartilage tissue [28].

Recent research data suggests that ferroptosis, a newly discovered form of cell death, is triggered by iron-dependent lipid peroxidation and is closely related to the progression of OA [29, 30]. Lipid peroxidation caused by glutathione depletion or glutathione peroxidase 4 (GPX4) inactivation is a hallmark of ferroptosis, and ROS can also trigger ferroptosis in various types of cells [31]. Studies have shown that Tan IIA effectively reversed the increased ROS levels, MDA levels, and iron concentration in LPS-induced chondrocytes, as well as the decreased GSH levels and Gpx4 expression. By inhibiting ferroptosis in chondrocytes, Tan IIA alleviates chondrocyte damage [32].

4. Anti-oxidative Stress

Previous studies have shown that oxidative stress plays a key role in promoting chondrocyte apoptosis, catabolic processes, and matrix degradation, leading to telomere shortening in chondrocytes, a reduction in the number and function of mitochondria, imbalance in redox status, and impaired ECM synthesis. It is a crucial factor in the progression of OA [33, 34]. Mitochondrial dysfunction can cause an increase in reactive oxygen species (ROS), leading to oxidative imbalance in chondrocytes and oxidative damage to various joint components. Pro-inflammatory factors can induce the synthesis of inducible nitric oxide synthase (iNOS), generating large amounts of NO that react with O2 to form peroxynitrite (ONOO-), which then produces nitrotyrosine, triggering oxidative stress. This affects downstream inflammatory mediators, ECM homeostasis, and cell activity, causing joint cartilage damage [35]. Studies have found that Tan IIA can reduce NO and iNOS levels in inflammatory cartilage, decrease the release of inflammatory factors, inhibit ECM degradation and cell apoptosis, and prevent oxidative

stress damage to cartilage [26].

5. Inhibit the Degradation of Cartilage Matrix

Articular cartilage is composed of ECM and chondrocytes, and the balance between ECM degradation and synthesis is crucial for maintaining normal cartilage physiology. The ECM protects chondrocytes, and when degradation exceeds synthesis, it can lead to cartilage defects, subchondral bone hyperplasia, and cartilage damage. Previous studies have suggested that the onset of OA is associated with ECM imbalance and degradation [36]. Aggrecan and type II collagen (Col II) are the main components of ECM, which promote chondrocyte proliferation and differentiation while maintaining ECM balance. A decrease in these components disrupts ECM balance and leads to the development of OA [37]. Aggrecan is an essential substance for maintaining cartilage activity, and its loss can damage articular cartilage. Aggrecan-degrading enzymes (ADAMTS) participate in the degradation of cartilage matrix, and the activity of ADAMTS-4 and ADAMTS-5 can be triggered by pro-inflammatory factors, making them the main active enzymes for Aggrecan degradation [38]. Cartilage-degrading factors such as MMPs and tissue inhibitors of metalloproteinases (TIMPs) regulate the balance between bone synthesis metabolism and degradation [39]. Among them, MMP-13 is the most effective enzyme for degrading Col II, which reduces the anti-inflammatory ability of articular cartilage and promotes cartilage degeneration [40]. Inflammatory factors repeatedly act on the cartilage matrix, accelerating ECM degradation and causing cartilage degeneration [41].

IL-1β induces the expression and release of TNF-α, IL-6, nitric oxide (NO), and PGE2, leading to the production of MMPs and aggrecanases, which cleave Col II and aggrecan [42]. Studies have found that Tan IIA can reverse the high expression of MMP-1, MMP-3, MMP-13, and ADAMTS-5 induced by IL-1β stimulation in chondrocytes, as well as the low expression of Col II and aggrecan, significantly inhibiting cartilage matrix degradation and reducing joint cartilage damage [16, 22]. In an OA rat model established by anterior cruciate ligament transection and medial meniscus removal, treatment with 0.25–0.5 mg/kg of Tan IIA significantly inhibited the expression of TNF-α, IL-1β, and iNOS, downregulated MMP-13 expression in the cartilage matrix, increased the levels of TIMP-1, TGF-β, and bone morphogenetic protein 2 (BMP-2), and promoted chondrocyte proliferation, effectively delaying the degradation of cartilage matrix during OA development [26]. SOX-9 promotes ECM generation and differentiation in cartilage, and its target transcription factor, SOX-6, is closely related to chondrocyte proliferation [43]. Recent research shows that a concentration of 100–200 μg/mL of Tan IIA significantly upregulates the expression of SOX-6 and Col II in chondrocytes of osteoarthritis rats, promoting chondrocyte proliferation [44].

The Wnt/β-catenin signaling pathway is closely related to chondrocyte metabolism, influencing both chondrocyte growth and development, as well as degeneration and apoptosis [45]. Research has shown that Tan IIA can inhibit the expression of β-catenin protein, downregulating the Wnt/β-catenin signaling pathway, thereby inhibiting chondrocyte degeneration and protecting chondrocytes [46].

6. Inhibit Chondrocyte Senescence

An increasing body of research points to cellular senescence as a common molecular mechanism driving age-related osteoarthritis (OA) [47, 48]. The repair capacity of adult cartilage is limited, and due to aging and mechanical stress, chondrocytes gradually lose their ability to maintain cartilage integrity and survival [49]. Additionally, senescent cells produce a pro-inflammatory phenotype known as the senescence-associated secretory phenotype (SASP), which induces structural and functional changes in surrounding cells and tissues. These harmful changes further reduce the mechanical integrity and lubrication of cartilage, accelerating its wear and damage, and also negatively affecting adjacent healthy chondrocytes [50]. Reports have shown that two proteins, CCN1 (cell communication network factor 1) and connexin 43, which promote cell-to-cell communication, are upregulated on the surface membrane of senescent chondrocytes [51].

Studies have found that Tan IIA can inhibit the secretion of endogenous CCN1 and CCN1-induced chondrocyte clustering, senescence, and OA progression [52]. This inhibition reverses the senescent phenotype of chondrocytes and promotes dedifferentiation and redifferentiation. The suppression of CCN1 by Tan IIA inhibits communication between senescent chondrocytes and surrounding cells, weakening intercellular signaling and preventing age-related morphological changes. In the absence of Tan IIA-mediated regulation, growth signals from damaged cartilage may induce senescence in adjacent healthy cells [53, 54].

7. Regulate the Secretion of Non-coding RNA

MicroRNAs (miRNAs) are a class of evolutionarily conserved, small single-stranded non-coding RNA molecules that regulate gene expression post-transcriptionally and play crucial roles in various biological processes [55-57]. Multiple studies have shown that miRNAs are key regulators of cartilage homeostasis, with miR-155, miR-106a-5p, and several other miRNAs being involved in the onset and progression of osteoarthritis (OA) [58, 59].Recent research data indicate that miR-155 is significantly upregulated in OA chondrocytes, and miR-155 can directly target the 3'-UTR of FOXO3 to downregulate its expression [60].Furthermore, Tan IIA can reduce miR-155 expression and exert anti-inflammatory effects on LPS-stimulated RAW264.7 cells [61]. Overexpression of miR-155 can reverse the anti-inflammatory effects of tanshinone II A and the expression of FOXO3. Studies have found that lipopolysaccharide (LPS) can induce the secretion of various inflammatory factors such as TNF-α, IL-1β, and IL-6 in human primary joint chondrocytes, upregulating miR-155-5p and downregulating FOXO3, further promoting cell apoptosis. Intervention with tanshinone II A at concentrations of 1, 10, and 100 μmol/L reversed the high expression of inflammatory factors, upregulated miR-155-5p expression, and suppressed FOXO3 expression, indicating that tanshinone II A directly acts on the miR-155/FOXO3 axis to exert anti-inflammatory and anti-apoptotic effects [58].

Recent studies have also highlighted the significant role of long non-coding RNAs (lncRNAs) in OA [62, 63], with nuclear enriched abundant transcript 1 (NEAT1) interacting with miRNAs to influence chondrocyte proliferation, migration, apoptosis, and ECM secretion, thus affecting OA. NEAT1_2 is one of the two isoform transcripts of NEAT1, playing a crucial role in the response of chondrocytes to stress and dedifferentiation induced by inflammatory factors [64]. Research has shown that under IL-1β stress, NEAT1_2 levels significantly decrease, leading to the downregulation of chondrocyte phenotype-related genes such as SRY-box transcription factor 9 (SOX9) and aggrecan (ACAN), causing dedifferentiation of chondrocytes [65]. Studies have indicated that Tan IIA upregulates the expression of lncRNA NEAT1_2 under IL-1β stress conditions, significantly reversing the downregulation of chondrocyte phenotype-related genes induced by IL-1β, thereby maintaining the chondrocyte phenotype [66].

8. Inhibit Chondrocyte Dedifferentiation

Clinical studies have shown that the dedifferentiation of chondrocytes plays an important role in the pathogenesis of OA [67]. Dedifferentiated chondrocytes exhibit dysregulated matrix metabolism, which is mainly characterized by increased expression of type I collagen (Col I) and type X collagen (Col X), decreased expression of type II collagen, glycosaminoglycans (GAGs), and cartilage-related transcription factor Sox9. The cell phenotype gradually changes from polygonal or oval-shaped to fibroblast-like spindle-shaped [68, 69]. Research has found that Tan IIA at concentrations of 100 μg/ml and 200 μg/ml can effectively reduce the expression of type I and type X collagen, thereby inhibiting the dedifferentiation of chondrocytes [70]. Col II is an early marker of cartilage formation and can protect chondrocytes and ECM by reversing cartilage degeneration. Col X is a marker of chondrocyte hypertrophy and is closely related to dedifferentiation [71]. The SOX transcription factor family is also considered to be closely associated with cartilage formation and development, with SOX9 being a key regulator of cartilage development and SOX6 being highly homologous to SOX9 [72]. Studies have shown that Tan IIA at concentrations of 100–200 μg/ml can upregulate the expression of Col II and SOX6 genes, while downregulating the expression of Col I and Col X genes. This inhibits chondrocyte hypertrophy, promotes chondrocyte proliferation, maintains the chondrocyte phenotype, and prevents chondrocyte dedifferentiation [44].

9. Inhibit Abnormal Blood Vessel Formation

The formation of abnormal blood vessels in subchondral bone disrupts bone remodeling and leads to subchondral bone sclerosis, which is a key driving factor in the pathogenesis of OA [73]. The use of the vascular endothelial growth factor (VEGF) inhibitor bevacizumab effectively suppresses angiogenesis and slows the progression of OA [74]. Studies have found that CD31hiEmcnhi blood vessels are significantly increased in the subchondral bone of OA rats or patients [75]. Vascular endothelial growth factor A (VEGFA) is a major regulator of angiogenesis, primarily activating signaling through VEGF receptor 2 (VEGFR2). Research shows that intra-articular injection of VEGFA accelerates OA progression in mice, whereas anti-VEGFA treatment alleviates cartilage degeneration [76].

Tan IIA is an important angiogenesis inhibitor that can reduce the secretion of VEGFA in vitro and inhibit the proliferation, migration, and lumen formation of endothelial cells. Danshenol IIA treatment downregulated the expression of VEGFA and VEGFR2 in the human non-small cell lung cancer cell line A549 [77]. Studies have shown that Danshenol IIA treatment leads to downregulation of VEGFR2 expression in CD31hiEMCNhi endothelial cells, reduces VEGFA secretion from hypertrophic chondrocytes, inhibits MAPK signaling activation, and reduces the growth of abnormal blood vessels in the subchondral bone, effectively alleviating OA progression [78].

10. Conclusions

In conclusion, an increasing number of studies support the multifaceted potential of Tan IIA in the treatment of OA. This study explores the mechanisms of action of Tan IIA in preventing and treating OA from multiple aspects, including inflammatory response, cell apoptosis, oxidative stress, cartilage degradation, cellular senescence, non-coding RNAs, cell dedifferentiation, and abnormal angiogenesis, making it a promising candidate for the prevention and treatment of OA. However, most of the research on Tan IIA in OA remains at the basic experimental stage, and its efficacy and mechanisms of action in humans are still unclear. Strict clinical studies are needed to translate these findings into safe and effective therapeutic approaches. A deeper understanding of the mechanisms, synergistic effects, and effective bioavailability of Tan IIA may provide new options for promoting bone health and treating OA.

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