**International Journal of Biology and Life Sciences**
ISSN: 2957-9511 | Vol. 10, No. 1, 2025

# Exploring the Research Progress of Traditional Chinese Medicine in Rheumatoid Arthritis based on the Nrf2/Keap1 Pathway

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**Abstract:** Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovitis and bone destruction. In recent years, the role of the Nrf2/Keap1 pathway in RA has received much attention. Research has shown that the Nrf2/Keap1 pathway plays an important role in RA by regulating oxidative stress and inflammatory response. Activation of Nrf2 can alleviate inflammation and bone destruction in RA, while overexpression of Keap1 may exacerbate RA symptoms. This article discusses the research progress of traditional Chinese medicine based on the Nrf2/Keap1 pathway in RA, including its molecular mechanism, role in the pathological process of RA, potential as a therapeutic target, and related drug development progress, providing new directions for drug development in the Nrf2/Keap1 pathway for RA treatment.

**Keywords:** Traditional Chinese Medicine; Rheumatoid Arthritis; Nrf2/Keap1 Signaling Pathway; Oxidative Stress.

## 1. Introduction:

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease characterized by symmetrical synovitis of the joints in the limbs, damaging cartilage, ligaments, tendons, and joints. In severe cases, it can lead to deformities and disabilities. A small number of patients may experience persistent extra articular symptoms such as systemic pain or stiffness, bilateral carpal tunnel syndrome, and inflammation causing multi organ involvement. RA can affect other organs such as the heart, brain, liver, and kidneys, and about 90% of RA patients die from cardiovascular disease [1-2]. It has always received widespread attention from the world medical community. Numerous studies have shown that activating the Nrf2 pathway can effectively restore redox homeostasis.

## 2. Current Research Status at Home and Abroad

### 2.1. Domestic Research Progress

In recent years, domestic scholars have conducted extensive research on the role of the Nrf2/Keap1 pathway in RA. Research has shown that activation of the Nrf2/Keap1 pathway can significantly alleviate joint inflammation and bone erosion in RA model animals. In addition, some traditional Chinese medicine ingredients such as rosmarinic acid and Tripterygium wilfordii glycosides, licorice chalcone A, and Angelica sinensis, as well as natural products such as resveratrol and curcumin, can activate this pathway to exert anti-inflammatory and antioxidant effects.

#### 2.1.1. Rosmarinic Acid

After treatment with rosmarinic acid, the fluorescence intensity of Nrf2 in the cell nucleus was significantly enhanced, indicating that rosmarinic acid can activate Nrf2. And it is precisely because Nrf2 is an important transcription factor that protects nerve cells from oxidative stress and inflammatory damage that rosmarinic acid exerts antioxidant effects by activating Nrf2.

#### 2.1.2. Tripterygium wilfordii

There are research results indicating that Tripterygium wilfordii glycosides may exert their therapeutic effects on RA by regulating multiple signaling pathways and key targets, especially in inflammation related pathways.

#### 2.1.3. Licorice Chalcone A (LCA)

Derived from licorice, it has antibacterial, anti-tumor, and anti-inflammatory activities. The relevant research results show that LCA activates Keap1-Nrf2 signaling and inhibits arthritis through phosphorylation of p62 at Ser349 site [3].

### 2.2. Foreign Research Progress

Foreign studies have also confirmed the important role of the Nrf2/Keap1 pathway in RA. Research has found that activation of Nrf2 can significantly alleviate joint inflammation and cartilage damage in RA model animals. In addition, gene therapy techniques such as siRNA [4] and CRISPR/Cas9 [5] have also been used to activate the Nrf2/Keap1 pathway, which is expected to achieve precise treatment of RA.

## 3. Structure and Function of Nrf2/Keap1 Pathway

### 3.1. Molecular Mechanism of Nrf2/Keap1 Pathway

Nrf2 is a soluble protein primarily present in the cytoplasm, belonging to the Cap ' n ' Collar (CNC) subfamily. It consists of 605 amino acids and contains seven specific functional protein homologous domains (Nrf2 ECH homologous domains, abbreviated as Neh). The Neh1 domain can interact with ubiquitin binding enzymes. Neh2 can be recognized and interact with Kelch like ECH related protein 1 (Keap1). Neh3, Neh4, and Neh5 function as transcriptional activation domains. Neh6 negatively regulates the activity of Nrf2 by binding to β - Transduction Protein Repeat Sequence Protein (β-TrCP), and the Neh6 domain also provides stability control for Nrf2 [6].

Keap1 protein was initially identified as a binding partner of Nrf2 and named Keap1 due to its structural similarity with Drosophila Kelch protein [7]. Keap1 is a member of the BTB Kelch protein family. BTB Kelch proteins are divided into two categories: KLHL proteins and KBTB proteins. KLHL proteins typically contain the following domains: the N-terminal Broadcomplex, Tramtrack, and Bricabarac (BTB) domains, as well as the C-terminal Kelch domain. The KBTB protein consists of a BTB domain and a repetitive C-terminal Kelch domain. Keap1 exerts its function through homodimerization of its BTB domain.

### 3.2. Physiological Functions of Nrf2/Keap1 Pathway

The Keap1-Nrf2-ARE pathway is a key mechanism by which cells respond to oxidative stress. The activation of Nrf2 activity is a method for treating oxidative stress-related (OS) diseases, and the antioxidant system involved is mainly composed of various endogenous antioxidants, almost all of which are regulated by Nrf2 [8]. When cells are exposed to oxidative stress (such as ROS) or electrophilic substances, key cysteine residues in Keap1 are modified, causing conformational changes that prevent Nrf2 from being ubiquitinated and degraded, leading to Nrf2 transfer to the nucleus. In the nucleus, Nrf2 forms heterodimers with small Maf proteins and binds to antioxidant response elements (ARE), regulating the expression of downstream antioxidant genes. The activation of Nrf2 not only plays a protective role in oxidative stress, but also has therapeutic potential in various diseases. Therefore, the Keap1-Nrf2-ARE pathway has become a potential therapeutic target for various diseases.

## 4. Experimental Study on Nrf2 Keap1 Pathway in Rheumatoid Arthritis

Sun Yue intervened with Xin feng capsules in adjuvant arthritis rats and observed the effects on their cardiorespiratory function, oxidative stress status, and cytokine levels to evaluate their therapeutic efficacy. Research has shown that can protect the heart and lung function of rats by regulating the expression of the Keap1-Nrf2/ARE signaling pathway, clearing free radicals and redox products, increasing levels of anti-inflammatory factors, downregulating levels of pro-inflammatory factors, inhibiting joint and heart/lung tissue inflammatory responses, reducing the deposition of immune complexes in tissues, and minimizing tissue damage; At the same time, it can improve oxidative stress damage to endothelial cells, alleviate microvascular sclerosis, thereby improving joint inflammation and enhancing heart and lung function[9].

## 5. Clinical study of Nrf2 Keap1 Pathway in Rheumatoid Arthritis

After activation, the Keap1-Nrf2-ARE signaling pathway plays an anti-inflammatory and antioxidant role in RA, while also participating in cell apoptosis, immune regulation, and cartilage metabolism regulation, and is closely related to autophagy. This pathway may provide a new direction and therapeutic observation point for clinical treatment of RA [10].

### 5.1. Study on Xinfeng Capsule in the Treatment of Cardiovascular and Pulmonary Function in RA Patients

Sun Yue improved the cardiorespiratory function of RA patients by taking Xinfeng capsules based on the Nrf2/Keap1/ARE pathway in clinical practice. The clinical results are as follows: Xin feng capsules can significantly improve the symptom and sign scores, SF-36 scores, SAS and SDS scores of patients with rheumatoid arthritis; Increase the expression frequency of CD19+BTLA+Bcell and CD24+BTLA+Bcell in peripheral blood of rheumatoid arthritis patients, reduce laboratory indicators such as CDP, ESR, and thus inhibit immune responses; Increase the levels of antioxidant substances SOD and GSH in patients with rheumatoid arthritis, reduce the levels of free radicals and redox products ROS and MDA, enhance the body's antioxidant capacity, promote free radical clearance, and alleviate oxidative stress damage to heart and lung tissues;

## 6. Conclusion and Prospect

In recent years, traditional Chinese medicine has shown unique potential in the treatment of rheumatoid arthritis (RA) by regulating the Nrf2/Keap1 pathway. Research has found that active ingredients in traditional Chinese medicine, such as resveratrol, curcumin, piperonymus, rosmarinic acid, and triptolide, can activate Nrf2, inhibit Keap1 mediated oxidative stress and NF-κB inflammatory pathways, thereby reducing synovitis and bone destruction. However, existing research mostly focuses on single drugs or individual components, and the synergistic mechanism and clinical translation of compound prescriptions still need to be further explored. In the future, it is necessary to combine network pharmacology, metabolomics, and molecular docking technology to systematically analyze the dynamic network of multi-target regulation of the Nrf2/Keap1 pathway in traditional Chinese medicine; Meanwhile, based on organoid models or artificial intelligence screening, optimize the compatibility of traditional Chinese medicine formulas to enhance targeting and safety. In addition, exploring the association between Nrf2/Keap1 mediated immune metabolism reprogramming and traditional Chinese medicine intervention is expected to provide new strategies for personalized treatment of RA and promote the scientific and international integration of traditional Chinese and Western medicine therapy.

## Acknowledgments

**Fund project:** Shaanxi Province College Student Innovation Project (S202310716035);

Natural Science Foundation Project of Shaanxi Province (2023-JC-YB-693);

Project supported by An kang Science and Technology Bureau (AK2023-SF-13).

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