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REVIEW

The Application Prospects and Future Outlook of *Kadsura coccinea* (Lem). A.C.Sm. in Rheumatoid Arthritis

Fan Ouyang[1,2,*], Xiuli Xi[2,*], Yun Liang[1,*], Min Wang[2,3], Mei Liu[2], Xiaoyan Jin[4], Hui Li[2], Jianxin Liu[2,3], Xuguang Hu[1]

[1]School of Chinese Materia Medica, Guangdong Pharmaceutical University, Guangzhou, Guangdong, 510080, People's Republic of China; [2]School of Pharmaceutical Sciences, China-Pakistan International Science and Technology Innovation Cooperation Base for Ethnic Medicine Development in Hunan Province, Sino-Pakistan Center on Traditional Chinese Medicine, Hunan University of Medicine, Huaihua, Hunan, 418000, People's Republic of China; [3]School of Pharmacy, Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang, People's Republic of China; [4]School of Pharmaceutical Sciences, Xinjiang Medical University, Wulumuqi, Xinjiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xuguang Hu, Guangdong Pharmaceutical University, 280 Outer Ring East Road, Guangzhou Higher Education Mega Center, Panyu District, Guangzhou, Guangdong, 510080, People's Republic of China, Email huxuguang@gdpu.edu.cn; Jianxin Liu, Hunan University of Medicine, 492 Jinxi South Road, Hecheng District, Huaihua, Hunan, 418000, People's Republic of China, Email jxliu@hnmu.edu.cn

Abstract: *Kadsura coccinea* (Lem). A.C.Sm. has a long history of use in traditional Dong medicine for activating Qi, relieving pain, and dispersing blood stasis. It has garnered increasing attention for treating rheumatoid arthritis (RA), a condition associated with synovial inflammation and tissue damage. *K. coccinea* L. effects anti-RA by eliminating reactive oxygen species and directly or indirectly inhibiting lipid peroxidation. This review summarizes its potential therapeutic effects on RA through regulating inflammatory cytokines, reducing oxidative stress, and targeting specific cells and pathways, forecasting its future application prospects.

Keywords: *Kadsura coccinea* Lem. A.C.Sm., rheumatoid arthritis, triterpenoids, sesquiterpenes, antioxidant, immunomodulatory

Introduction

K. coccinea L., an evergreen climbing shrub belonging to the pharmaceutically significant family Schisandraceae, is a notable species in traditional Chinese medicine. Ethnobotanically referred to as "Heilaohu" in China. *K. coccinea* L. is colloquially recognized as cold rice ball, bufuna, and chicken intestine wind.[1] This species is endemic to the subtropical regions of southwestern China, with its primary distribution encompassing Hunan, Guangxi, Guizhou, and Fujian provinces.[2] As a traditional Dong medicine with a long history, its roots, stems, and fruits have been widely used in ethnomedicinal practices for the management of gastrointestinal disorders, rheumatoid arthritis (RA), traumatic injuries, dysmenorrhea, and inflammatory edema.[1,3] Modern pharmacological studies have revealed extensive biological activities, including inhibition of NF-κB and JAK2/STAT3 signaling pathways to reduce RA-associated inflammation,[4] as well as inhibition of rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS) and RAW 264.7 cell proliferation and induction of apoptosis to ameliorate inflammation.[5] Meanwhile, *K. coccinea* L. is used in local ethnic hospitals to assist in clinical practice for reducing joint swelling and relieving pain.[6] This suggests that the important biological activities of *K. coccinea* L.-related extracts are equally worthy of our attention, and we can explore the role of *K. coccinea* L. in the treatment of diseases in a broader way, and explore the application prospects of *K. coccinea* L. from a deeper mechanistic study, which can provide a positive impact for exploring the wider research of botanicals in modern medicine.

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease, currently known to be characterized by persistent inflammation of the joints. Worldwide, it can affect approximately 0.5% to 1% of the population, and current research has shown that women are more affected than men.[7] RA is driven by immune system dysfunction, leading to

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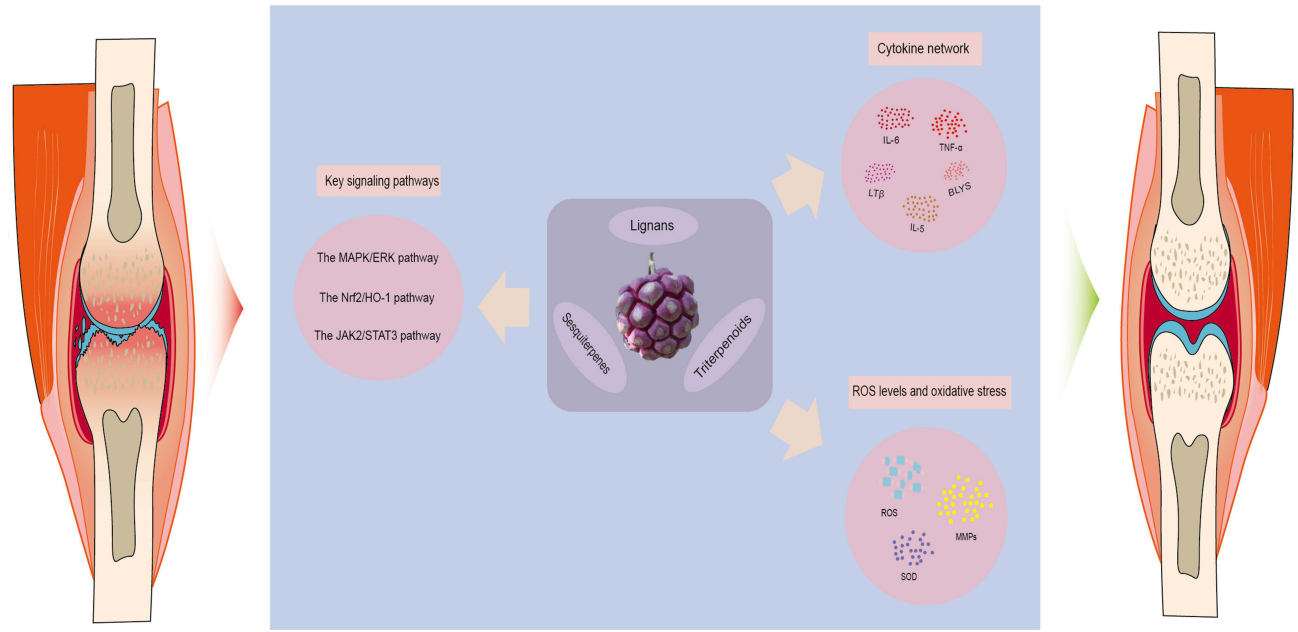
Graphical Abstract



abnormal tissue responses that result in joint damage and destruction. The disease can manifest at any age, with prevalence increasing with age, and is associated with a complex interplay of genetic, immunological, and environmental factors.[8] Chronic inflammation in RA not only impacts the joints but can also have systemic effects throughout the body.[9] Genetic and environmental triggers are the main influencing factors in the early stage of inflammation, which can lead to the production of anti-citrullinated protein antibodies (ACPAs) and pro-inflammatory cytokines, thereby initiating immune dysregulation.[10,11] During the progression phase, immune cells such as Th1 and Th17, T cells, B cells, and macrophages, along with pro-inflammatory cytokines such as TNF-α, IL-6, interleukin-17 (IL-17), drive synovial inflammation, cartilage degradation, and bone erosion.[10–12] Synovial hyperplasia and the formation of pannus further exacerbate tissue destruction.[7,13] In advanced stages, uncontrolled inflammation results in systemic complications, including cardiovascular diseases, osteoporosis, and interstitial lung disease, affecting multiple organ systems.[14–16] The pathogenesis is characterized by immune imbalance, such as dysregulation in Th17/Treg cell ratios and receptor activators of the nuclear factor kappa-B ligand (RANKL)-mediated osteoclast activation, ultimately causing irreversible joint damage and systemic dysfunction.[11,12]

Rheumatoid arthritis (RA) remains incurable, but contemporary medical advancements have enabled effective disease management through targeted therapeutic approaches.[7] Nonsteroidal anti-inflammatory drugs (NSAIDs) serve as primary agents for symptom control in RA patients, demonstrating notable efficacy in alleviating pain, stiffness, and inflammatory processes through their antipyretic and analgesic properties.[17] However, their clinical utility is constrained by significant systemic toxicity, with non-selective NSAIDs posing substantial gastrointestinal risks and selective COX-2 inhibitors exhibiting cardiovascular hazards including myocardial infarction and stroke.[18] Glucocorticoids demonstrate disease-modifying potential by slowing radiographic joint damage progression and modulating endothelial dysfunction in RA pathophysiology.[19,20] Nonetheless, it is also concerning that prolonged corticosteroid medication is associated with multi-system complications affecting gastrointestinal, cardiovascular and immune function.[21] In addition, approximately 30% of RA cases develop treatment resistance, a pattern similar to that observed in chronic inflammation.[22] Biologics targeting specific immune mediators offer new avenues for RA treatment. These include cytokine inhibitors such as TNF-α, IL-6, IL-17, T cell co-stimulation blockers such as abatacept, and B cell depleting therapies such as rituximab, which together modulate humoral and cellular inflammatory pathways.[23–25] Despite their "precision strike" nature, these biologics also increase the risk of

infection, including relapses of tuberculosis and opportunistic viral infections.[26] Conventional synthetic antirheumatic drugs (csDMARDs) remain the first-line treatment, although the remission rate is low, approximately 20–25%, due to the high risk of relapse after discontinuation of medication. However, the current guidelines still emphasize that treatment should continue to aim primarily at alleviating the condition of the patients.[27,28] This treatment situation highlights the need for the development of novel anti-RA drugs from natural sources, where the low toxicity and high safety profile of natural products make them promising candidates for the long-term treatment of RA to ameliorate the slight limitations that currently exist with disease-modifying antirheumatic drugs (DMARDs).

Natural products have been an invaluable and useful source of managing RA for their unique advantages.[29] Among natural remedies, *K. coccinea* L. has gained increasing attention as a plant with promising therapeutic potential for RA.[1,4,5,30] This plant contains bioactive compounds such as triterpenoids and lignans, which have been reported to exert immunomodulatory effects and inhibit the proliferation of fibroblast-like synoviocytes (FLS), a critical pathological feature of RA.[5,30] Meanwhile, compounds derived from *K. coccinea* L. effectively suppress inflammatory mediators, including TNF-α and IL-6, and mitigate oxidative stress, thus supporting its potential as a natural alternative for treating RA.[31] These phytochemical constituents have been demonstrated to exhibit potent anti-inflammatory and immunomodulatory properties through selective inhibition of key signaling pathways, particularly the NF-κB and JAK/STAT3 cascades.[4]

Based on the pathogenesis of RA, we further speculate that *K. coccinea* L. may exert anti-RA effects through multiple pathways. *K. coccinea* L. can exert anti-RA effects by targeting immune cells such as T cells and macrophages, and regulating the levels of inflammatory factors such as IL-6, interleukin-1 beta (IL-1β), and TNF-α. Meanwhile, *K. coccinea* L. can also exert anti-RA effects by reducing oxidative stress, affecting various signaling pathways such as the Nuclear factor erythroid 2-related factor 2/Heme Oxygenase-1 (Nrf2/HO-1) pathway, Janus Kinase-Signal Transducer and Activator of Transcription (JAK/STAT) pathway, Nuclear factor kappa-B (NF-κB) pathway, and mitogen-activated protein kinase/Extracellular signal-regulated kinases (MAPK/ERK) pathway. This review aims to provide a comprehensive analysis of the pharmacological properties of *K. coccinea* L., focusing on its active constituents and mechanisms of action in RA treatment. The possible ways in which *K. coccinea* L. may exert its anti-RA effects are shown in Figure 1.

Methods

Literature search was conducted on electronic databases PubMed, China National Knowledge Infrastructure (CNKI), and Google Scholar, using themes or keywords such as "Kadsura coccinea (Lem). A.C.Sm.", "*Kadsura coccinea"*, "K. coccinea", "Heilaohu", "inflammation", and "rheumatoid arthritis" to collect relevant literature information from 2025 and before. A total of 2567 articles related to *K. coccinea* L. were retrieved, and a total of 837 target documents were selected. Through detailed screening, it was found that compounds from "K. coccinea L." with "Triterpenoids", "Sesquiterpenes", and "Lignans" were closely related to "rheumatoid arthritis", so this was used as a theme or keyword for the search, and 619 target documents were selected, which were then classified and the content of the further documents was analyzed. The flowchart of the literature search is shown in Figure 2. "K. coccinea L." was adopted as the definitive plant name following comparison and confirmation on the World Flora Online website (http://www.worldfloraonline.org).

The Active Compounds of *K. coccinea* L. in Treating RA

Application of the Lignans from *K. coccinea* L. in Treating RA

Lignans have recently gained recognition as promising candidates for RA therapy due to their ability to modulate inflammation, oxidative stress, and aberrant synovial proliferation. These compounds, often extracted from various plants, exhibit significant anti-inflammatory effects by regulating several signaling pathways involved in RA pathogenesis.[32] While much of the current study has concentrated on describing their inhibitory effects on NF-κB signaling and related cytokine production, we consider that their therapeutic potential is linked with in the multi-dimensional regulatory roles they play within RA pathogenesis. *K. coccinea* L. is a group of lignan-rich medicinal plants with a wide range of pharmacological properties, among which the potential therapeutic effects in RA are particularly prominent.[33] These lignans, particularly dibenzocyclooctadiene and spirobenzofuranoid lignans, have shown anti-inflammatory, anti-cytotoxic, and antioxidative effects that could play a key role in modulating RA progression.[34,35]

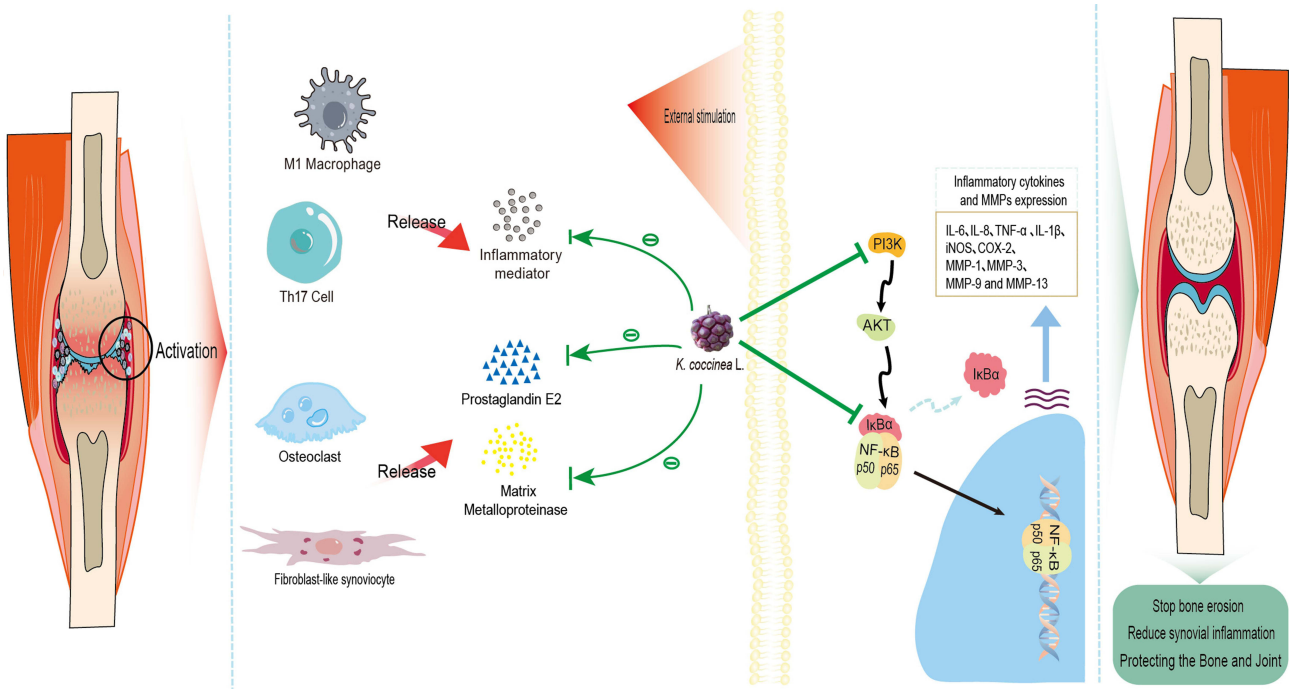


Figure 1 The possible way *K. coccinea* L. exerts its anti-RA effect. *K. coccinea* L. inhibits inflammatory cytokines and MMPs expression via the PI3K/AKT/NF-κB axis, thereby reducing synovial inflammation, osteoclast activity, and bone erosion.

Abbreviations: IL-6, Interleukin-6; IL-8, Interleukin-8; TNF-α, Tumour necrosis factor-alpha; IL-1β, Interleukin-1β; iNOS: Inducible ntric oxide synthase; COX-2, Cyclooxygenase-2; MMP-1, matrix metallopeptidase 1; MMP-3, matrix metallopeptidase 3; MMP-9, matrix metallopeptidase 9; MMP-13, matrix metallopeptidase 13; PI3K, Phosphatidyqinositol-3 kinase; NF-κB, nuclear factor kappa-B; IκBα, inhibitor kappa B alpha.

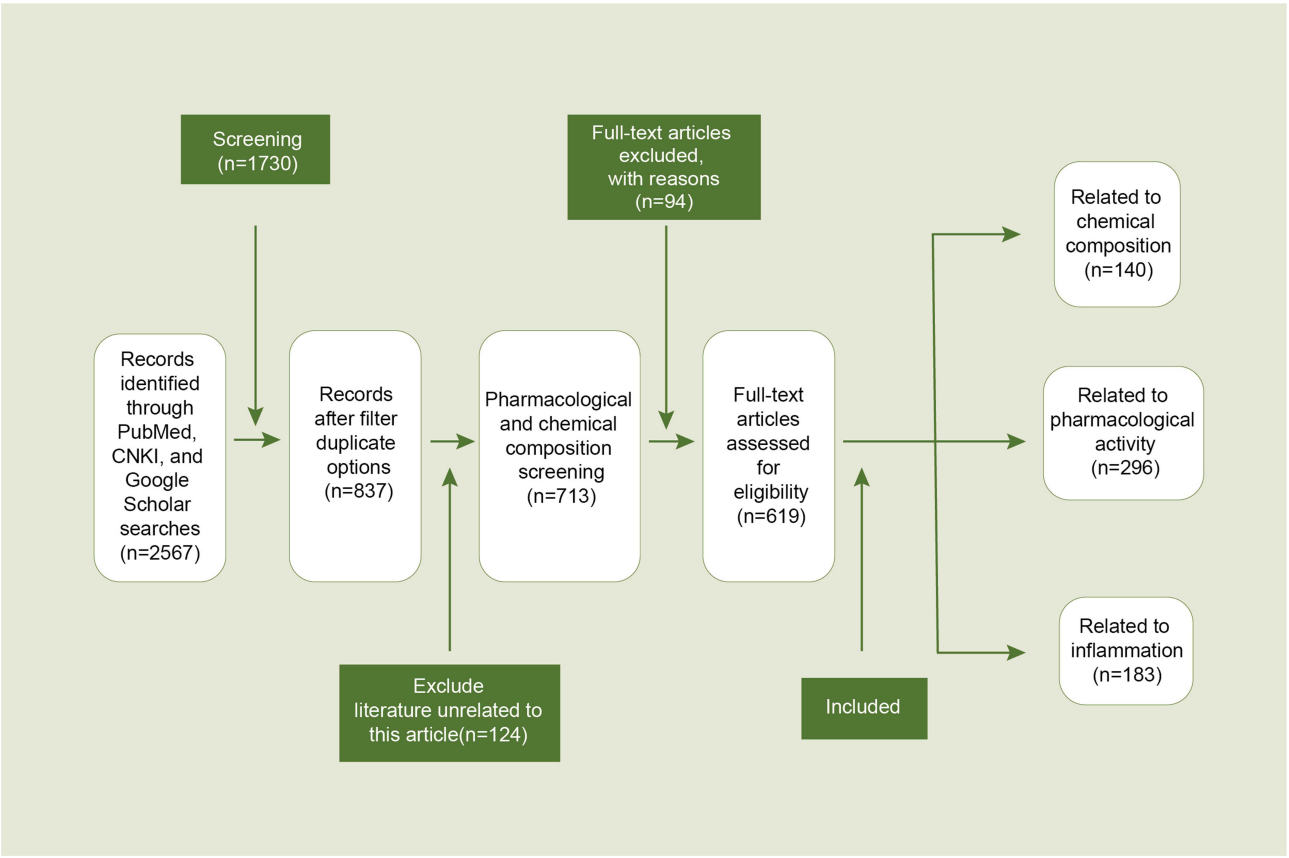


Figure 2 Literature screening process diagram.

For example, Lignans from *K. coccinea* L., such as those possessing the dibenzocyclooctadiene structure, exhibit inhibitory effects on inflammatory pathways by targeting key molecular pathways involved in RA. The lignans' impact on the NF-κB signaling pathway is particularly notable.[36] The NF-κB pathway is involved in the regulation of immune responses and inflammation, which are central to RA pathogenesis. Compounds like kadsuralignan H and heilaohusuins demonstrate inhibitory activity against the proliferation of RA fibroblast-like synovial (RA-FLS) cells, which play a crucial role in the development of RA.[32] These compounds effectively modulate the inflammatory process by down-regulating pro-inflammatory markers such as P-NF-κB p65, while promoting apoptosis in RA-FLS cells via upregulation of Bax and IκBα.[32] Furthermore, the dibenzocyclooctadiene lignans from *K. coccinea* L. have been shown to exhibit strong antioxidant properties, which help mitigate oxidative stress, another contributing factor in the pathogenesis of RA.[34] From this, we can observe that this convergence of anti-proliferative, anti-inflammatory, and antioxidative effects indicates that lignans could act as integrated modulators of disease progression, rather than functioning as simple anti-inflammatory agents. In addition to their anti-inflammatory and antioxidant properties, these lignans also display cytotoxic effects, selectively inhibiting RA-related cell proliferation without causing widespread cell damage.[37] This selective action makes the lignans from *K. coccinea* L. promising candidates for developing targeted treatments for RA, aiming to reduce inflammation and cellular damage while preserving healthy tissue.

One aspect of lignans that has not received enough attention is their influence on systemic pathways in addition to the classical cytokine signaling. In recent studies, lignan derivatives from Loranthus parasiticus have shown strong anti-arthritic activity by targeting key proteins and pathways such as sex hormone-binding globulin (SHBG) and NF-κB.[38] Specifically, the lignan monomer (-)-nortrachelogenin was identified as a potent inhibitor of NF-κB activity, a crucial factor in RA's inflammatory cascade.[38,39] The binding of lignans to SHBG helps elevate free androgen levels, which in turn inhibits NF-κB activity in macrophages.[38] It follows that the above process reduces joint inflammation, reduces synovial hyperplasia, and prevents cartilage damage in RA models. Also, we found that the therapeutic potential of lignans extends to their ability to modulate various immune responses. Lignan treatments have been found to inhibit the production of pro-inflammatory cytokines, including TNF-α and IL-6, which are central to developments in RA.[40] Furthermore, the mixed lignan derivatives from Loranthus parasiticus not only suppressed inflammatory cytokines but also promoted a higher level of androgens in the serum.[38] These mechanisms show a possible interaction between endocrine regulation and immune modulation, which may make lignans different from other phytochemicals. We believe that this dual function, combining local anti-inflammatory action with systemic hormone regulation, could offer a special therapeutic value, especially for RA patients who also have hormonal disorders. Otherwise, we argue that lignans, by regulating immune responses and specific signaling pathways, may contribute to the overall anti-inflammatory effect. This suggests that they could offer a novel approach to managing RA, potentially reducing the need for traditional anti-inflammatory medications and improving the overall therapeutic landscape. However, we also recognize that the practical use of lignans requires further clinical trials and research to fully understand their mechanisms and confirm their long-term efficacy and safety. Overall, we confidently predict that lignans isolated from *K. coccinea* L. may control the progression of RA by modulating inflammatory pathways, reducing oxidative stress, and inhibiting cell proliferation, and provide a potentially viable strategy for future therapies for RA. The anti-inflammatory mechanism diagram of *K. coccinea* L. is shown in Figure 2

Application of the Sesquiterpenes from *K. coccinea* L. in Treating RA

Sesquiterpenes derived from *K. coccinea* L., a traditional ethnic Dong medicine from China, exhibit significant anti-RA and anti-inflammatory activities.[41] Current phytochemical studies have identified a variety of novel sesquiterpenoids as well as the potential ability of known analogs for the treatment of RA.[42] Among these, gaultheriadiolide, a class of sesquiterpenoids from *K. coccinea* L., which the authors named compound 19, showed potent cytotoxicity against RA fibroblast-like synoviocytes (RA-FLS) with the half maximal inhibitory concentration (IC50) of 9.37μM, highlighting its role in inhibiting synovial proliferation, while we know that synovial hyperplasia is a marker of worsening RA.[43] In addition, several other sesquiterpenes have been shown to suppress TNF-α and IL-6 release in activated by LPS-induced RAW264.7 macrophages, suggesting a broader capacity to regulate cytokine-driven inflammation.[44] While these findings collectively confirm the pharmacological relevance of *K. coccinea* L.-derived metabolites, current literature often

emphasizes descriptive outcomes rather than drawing integrative insights into their therapeutic potential. Due to these cytokine drivers are implicated in RA-related inflammation and joint destruction, therefore, we predict that sesquiterpenes may attenuate disease severity by modulating inflammatory cascades. Otherwise, a study identified multiple RA-related targets by network pharmacological analysis, including MAPK3, JAK2, and STAT3, which are central to the NF-κB and JAK2/STAT3 pathways.[45] Experimental validation confirmed that gaultheriadiolide downregulated NF-κB p65, phosphorylated inhibitor of κB-α (IκBα), JAK2, and STAT3 protein levels in LPS-stimulated RAW 264.7 cells, thereby suppressing inflammatory signaling. The dual inhibition of NF-κB and JAK2/STAT3 pathways by sesquiterpenes disrupts cytokine-driven synovial inflammation and proliferation.[43] These signaling pathways play a pivotal role in the pathogenesis of RA by promoting the survival of synoviocytes, cartilage degradation, and immune dysregulation.[41,43,44] Furthermore, sesquiterpenes, such as compounds 2, 6, and 20 exhibited stronger inhibition of IL-6 production compared to methotrexate, with IC50 values of 1.34–1.66μM versus 4.51μM, respectively.[4] From our perspective, the significance of these studies lies not simply in the identification of new compounds, but in the pattern of activity that emerges across multiple sesquiterpenes. The fact that structurally diverse analogs converge on key inflammatory pathways, especially NF-κB and JAK2/STAT3, which indicates these metabolites may act as network regulators rather than single-target agents. This is an important distinction, because conventional DMARDs such as methotrexate often focus on one or a limited number of molecular targets, leaving other inflammatory cascades unchecked. Sesquiterpenes, by contrast, demonstrate simultaneous inhibition of synoviocyte proliferation, macrophage activation, and osteoclastogenesis. Such multi-layered modulation indicates that they may attenuate RA progression at several pathogenic checkpoints, rather than providing symptomatic relief only.

Sesquiterpenes have shown significant promise as therapeutic agents in the treatment of RA due to their potent anti-inflammatory effects, which are primarily mediated through modulation of key molecular signaling pathways.[43] These compounds, particularly sesquiterpene lactones (SLs), have the potential to interfere with various inflammatory mechanisms, alleviating the symptoms of RA and potentially altering disease progression.[46] In RA, NF-κB activation leads to the expression of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, which are involved in the inflammatory cascade.[47] One of the key mechanisms through which sesquiterpenes exert their therapeutic effects is by inhibiting the NF-κB signaling pathway, a central regulator of inflammation and immune response.[48] Several studies have demonstrated that sesquiterpenes can effectively inhibit NF-κB activation, thus reducing the production of these cytokines and alleviating the inflammatory response in RA.[43,49] For instance, a type of sesquiterpene lactone from *K. coccinea* L. exerts anti-inflammatory effects, playing a crucial role in RA progression, characterized by inflammation, joint degradation, and fibroblast-like synovial cell proliferation. These compounds primarily target key inflammatory pathways, including the NF-κB and JAK2/STAT3 signaling pathways, which are involved in synovial inflammation and cartilage degradation.[4] Moreover, sesquiterpenes from *K. coccinea* L. may also influence the expression of genes linked to inflammation and immune responses. For example, a study indicates that compounds from *K. coccinea* L. target genes such as Janus kinase 1 (JAK1), Janus kinase 2 (JAK2), which are involved in cytokine signaling and immune cell activation.[50,51] This interaction highlights the compounds' multifaceted role in modulating immune responses and reducing inflammation, making them promising candidates for RA therapy. The ethnopharmacological background of *K. coccinea* L. adds further weight to this interpretation. Its long-standing application in Dong traditional medicine indicates not only efficacy but also potential tolerability in chronic use. Unlike synthetic immunosuppressants, natural products such as sesquiterpenes may provide a more favorable safety profile, which is critical for long-term RA management. Thus, these compounds should not be viewed solely as isolated chemical entities; instead, they represent a bridge between traditional medicine and modern pharmacology, offering a blueprint for the rational development of safer adjunctive therapies.

And same as sesquiterpene lactones from plants like Xanthium mongolicum have been found to regulate macrophage polarization, specifically regulating the inflammatory process by shifting M1 macrophages to the M2 phenotype.[52] This shift is critical for controlling chronic inflammation in RA. By targeting both the NF-κB and MAPK signaling pathways, sesquiterpenes not only diminish the activity of pro-inflammatory macrophages but also help to restore the balance of the immune environment within the synovial joint.[53] Additionally, sesquiterpenes have been noted for their ability to modulate osteoclastogenesis, and the process by which bone-resorbing cells are activated.[54] This is particularly important

in RA, as excessive osteoclast activity contributes to joint destruction. Natural germacrane sesquiterpenes, for example, have been shown to inhibit osteoclast formation and bone resorption by suppressing the RANKL-induced NF-κB activation.[43] This highlights their potential not only in controlling inflammation but also in preventing joint degradation in RA. The anti-inflammatory potential of sesquiterpenes also extends to their ability to modulate other key inflammatory molecules, such as matrix metalloproteinases (MMPs) and chemokines.[55] By reducing the expression of matrix metalloproteinases 3 (MMP-3), IL-1, and other markers of inflammation in synovial cells, sesquiterpenes help to alleviate joint swelling and cartilage degradation.[43] In light of these considerations, we propose a more integrative research framework for sesquiterpenes in RA. One, future studies should systematically evaluate subclass-specific mechanisms to identify synergistic combinations rather than relying on single-compound assessments. And then, in vivo validation, particularly in well-established RA models, is necessary to confirm whether the in vitro potency of sesquiterpenes can translate into meaningful therapeutic outcomes. Also, advances in structural modification and formulation science should be leveraged to improve the pharmacokinetic properties of these natural scaffolds. Last but not least, sesquiterpenes may be best positioned as adjunctive therapies rather than stand-alone agents, complementing DMARDs by providing multi-target regulation with potentially reduced toxicity.

In conclusion, sesquiterpenes from *K. coccinea* L. hold considerable promise for RA therapy, not only their potent anti-inflammatory activity but also they embody a multi-target, ethnopharmacologically grounded approach to drug-assisted therapeutic strategy. By regulating overlapping pathways involved in synovial proliferation, cytokine signaling, and bone resorption, they offer a paradigm for the development of natural product-based therapies that move beyond single-target inhibition. We therefore suggest that these compounds should be regarded as both therapeutic candidates for future multi-target strategies in the treatment of RA.

Application of the Triterpenoids from *K. coccinea* L. in Treating RA

Triterpenoids have shown a significant role in treating rheumatoid arthritis (RA). Of course, this is not only due to their confirmed anti-inflammatory activity and immunomodulatory properties, but also because their multi-target mechanism that align with the complex pathogenesis of RA. In previous studies, Yang et al (2021) and Faustino et al (2023) have provided detailed and extensive descriptions of its therapeutic potential. However, based on our relevant research, certain triterpenoids that have undergone structural modification or are derived from specific plant sources may offer new mechanism insights and have the potential to enhance therapeutic efficacy. For instance, ursolic acid (UA) and its derivative ursolic acid-3-acetate (UAA) have been proven to alleviate RA inflammation by inhibiting the expression of matrix metalloproteinases (MMPs), which are the main factors causing cartilage destruction, additionally, UAA administration in both in vitro and in vivo models resulted in decreased paw swelling, reduced joint destruction, and a lower clinical arthritis score in collagen-induced arthritis (CIA) mice.[56–58] Therefore, we suggest that the targeted molecular optimization of triterpenoids can make up for the deficiencies existing between the discovery of natural products and clinically relevant therapeutics. And, the triterpenoids also effectively downregulated the activation of nuclear factor-kappa B (NF-κB) and the production of pro-inflammatory cytokines like TNF-α and IL-1β.[5] Triterpenoids, due to their characteristics of natural origin and related mechanisms of action, provide promising adjuvant regimens for the traditional treatment of RA. We believe that these compounds may bring better therapeutic effects in the future, and their reliable safety is also worthy of exploration by researchers.

Triterpenoids from *K. coccinea* L., such as heilaohuacid G and other lanoxane derivatives, due to their anti-inflammatory and immunosuppressive properties, have shown significant potential in the treatment of RA.[5,33] Studies have shown that these triterpenoids inhibit the proliferation of RA fibroblast-like synoviocytes (RA-FLS) and induce apoptosis, addressing one of the key mechanisms behind RA progression.[59] For instance, Heilaohuacid G effectively inhibits the NF-κB pathway, which plays a core role in RA by regulating the production of pro-inflammatory cytokines and promoting the proliferation of RA-FLS.[5,32] Furthermore, compounds like heilaohuacid A and B, isolated from *K. coccinea* L., have been shown to reduce inflammation by downregulating inflammatory cytokines such as IL-6 and TNF-α in LPS-induced RA-FLS cells.[30] These actions hinder the inflammatory responses and prevent the excessive proliferation of FLS, which is critical for the development of joint damage in RA.[60] Thus, Triterpenoids from *K. coccinea* L. not only inhibit cellular proliferation but also modulate the immune response, making them promising candidates for

RA therapy.[30,32] In summary, we speculate that these triterpenoids from *K. coccinea* L. can alleviate the disease progression of RA by targeting inflammatory pathways and inducing apoptosis of FLS cells, highlighting the therapeutic potential of such compounds in RA diseases. Meanwhile, we believe that these compounds provide an ideal template for the development of safer targeted kinase inhibitors or NF-κB pathway regulators. Also, in the future, the specific mechanism of action of such compounds in the treatment of RA is also worthy of the attention of researchers. For example, how they induce apoptosis in FLS cells, and the stability and reliability of their targeted effect on inflammatory pathways, all of which are worthy of feasibility exploration by researchers.

The Mechanism Research of *K. coccinea* L. in RA

K. coccinea L. Modulates the Cytokine Network to Alleviate Inflammation in RA

Despite the pathogenesis of RA remaining unclear, studies have shown that its progression involves a complex network of cytokines and immune cells, which can trigger the proliferation of synovial cells, leading to damage to cartilage and bones.[61] The participation of pro-inflammatory cytokines such as tumor necrosis factor TNF-α and interleukin IL-6 is crucial for the pathogenesis of RA. The participation of pro-inflammatory cytokines such as tumor necrosis factor TNF-α and interleukin IL-6 is crucial for the pathogenesis of RA. Furthermore, the role of Th17 cell subsets in autoimmune diseases has also highlighted the role of relevant cytokines, including interleukin-12 (IL-12) and IL-17, in the pathogenesis of RA.[62] The evidence also implicates interleukin-4 (IL-4) and interleukin-13 (IL-13) in autoimmune disease pathogenesis.[63] We therefore hypothesize that these cytokines play a key role in regulating the inflammatory process and influencing the course of RA, and the interrelationships of cytokines in the occurrence and development of the disease are highly worthy of our further exploration.

Cytokines such as TNF-α, IL-6, and IL-1β are central mediators in RA, promoting inflammation and driving joint destruction.[64] TNF-α activates immune cells and induces the production of additional inflammatory mediators, while IL-6 supports T and B cell differentiation, thereby enhancing autoimmune responses.[64,65] IL-1β accelerates cartilage degradation by upregulating matrix metalloproteinases (MMPs).[66] *K. coccinea* L. has demonstrated extraordinary potential in modulating the inflammatory cytokine network associated with RA.[30] Several bioactive compounds from *K. coccinea* L., including lignans, triterpenes, and flavonoids, play critical roles in regulating cytokine expression and immune cell activity, which are crucial in the pathogenesis of RA.[12] Jia et al conducted a study using the Complete Freund's Adjuvant (CFA) to induce the AA rat model and found that the total extract of *K. coccinea* L. (KCTE) could significantly inhibit primary and secondary joint swelling and improve ankle joint pathology in AA rats, and significantly reduce serum TNF-α, IL-6, and IL-1β levels.[67] Extracts from *K. coccinea* L. have been shown to suppress the production of pro-inflammatory cytokines, thereby reducing synovial inflammation, immune cell activation, and joint destruction.[33,68] In a study on triterpenoids, a compound from *K. coccinea* L., the authors named compounds 4 and 31, which could significantly inhibit the release level of IL-6. The IC50 values of the two compounds were 8.15 and 9.86μM,[30] respectively, which were sufficient to prove that the key components from *K. coccinea* L. could affect the production of inflammatory factors, which provided valuable experience for the treatment of RA. These cytokines contribute significantly to the progressive joint damage seen in RA. Buch et al emphasize the pivotal role of these pro-inflammatory cytokines in RA, noting that therapeutic strategies targeting cytokine pathways, such as TNF inhibitors and IL-6 antagonists, have shown clinical efficacy in reducing inflammation and preventing further joint damage.[69] The immunomodulatory network of *K. coccinea* L. in rheumatoid arthritis showed in Figure 3.

K. coccinea L. May Modulate Key Signaling Pathways to Alleviate Inflammation and Joint Damage in RA

The pathogenesis of RA involves complex interactions among multiple signal transduction pathways, which affect synovial inflammation, immune disorders and joint destruction.[70] Among them, the JAK/STAT pathway is the core signal transduction mechanism of pro-inflammatory cytokines. When cytokines such as IL-6, TNF-α and IFN-γ bind to receptors, this pathway is activated, triggering the phosphorylation of JAK kinase and subsequent dimerization of STAT protein.[71,72] These activated STAT proteins migrate to the nucleus and induce the transcription of inflammatory mediators and osteoclast-related factors.[73] Chikusetsusaponin IVa (CS-IVa), a natural compound, demonstrated a powerful anti-RA effect in the collagenic arthritis (CIA) model by inhibiting JAK/STAT activation,[74] thereby reducing

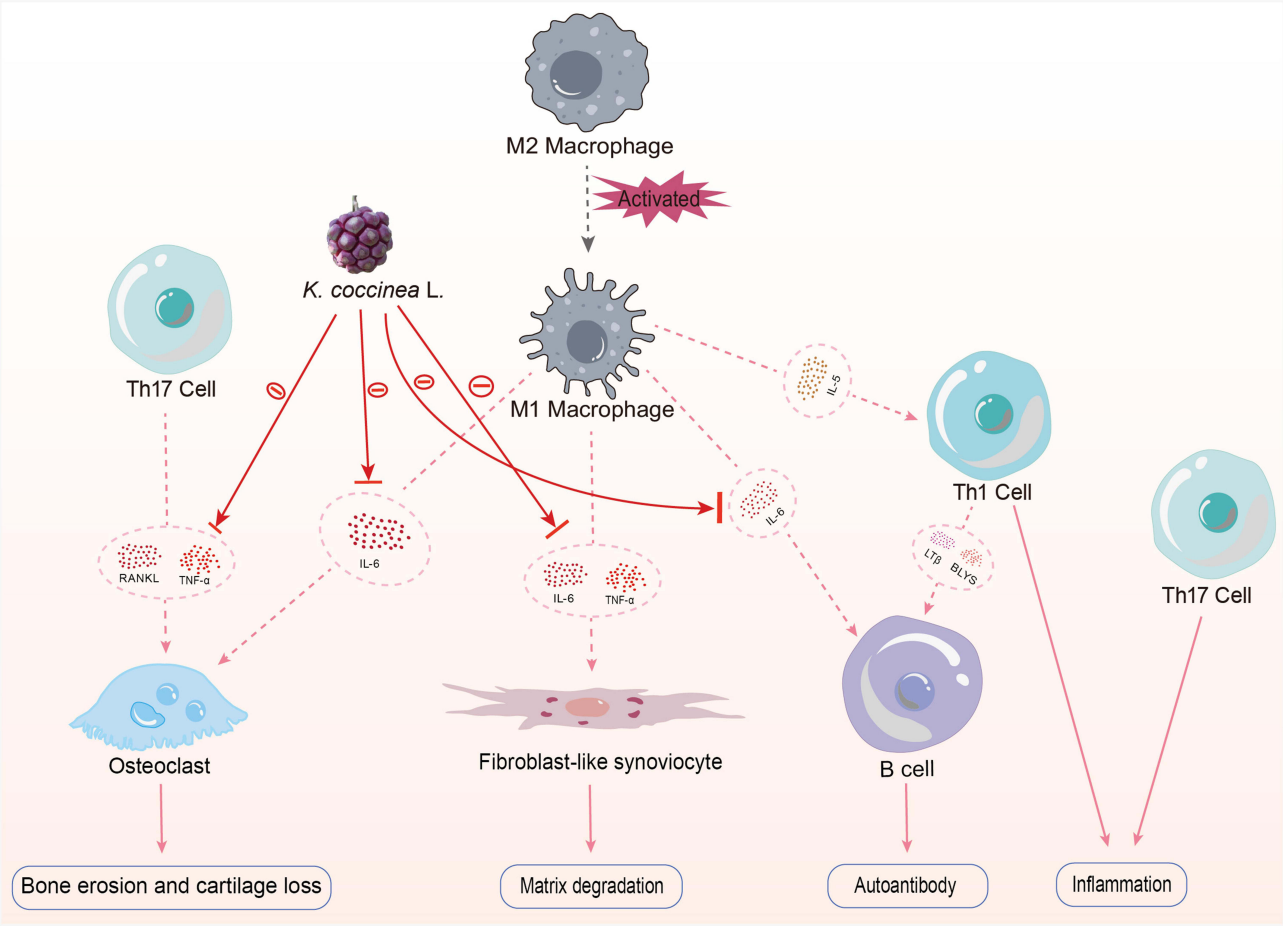


Figure 3 *K. coccinea* L. exerts therapeutic effects against RA by targeting multiple nodes within the pathological network, thereby suppressing the production of pro-inflammatory cytokines and osteoclastogenic factors. Solid arrows indicate an effect on, or the outcome for, the cell type or process being pointed to. Dashed arrows denote an action directed at the pointed-to cell type. Dashed circles surrounding a cell type signifies a potential modulatory influence from cytokines secreted by the upstream cell, as indicated by the preceding dashed arrow. Negative symbols (–) represent inhibition or blockade of the pointed-to process or interaction.
Abbreviations: IL-6, interleukin-6; IL-5, interleukin-5; TNF-α, tumor necrosis factor-α; RANKL, receptor activator of nuclear factor-κB ligand; BLYS, B lymphocyte stimulator; LTβ, Lymphotoxin Beta.

the levels of IL-1β, IL-6, TNF-α and IFN-γ in serum. Meanwhile, it alleviates synovial hyperplasia and bone destruction.[75] Similarly, Jolkinolide B (JB) alleviated the progression of RA in CIA rats by inhibiting the JAK2/STAT3 pathway, highlighting the dual role of this pathway in inflammation and osteoclast-mediated bone destruction.[72] Meanwhile, studies have shown that inhibiting NF-κB signal transduction can alleviate synovial inflammation and joint destruction in RA animal models, suggesting that this pathway may be a potential therapeutic target.[47,76] These findings undoubtedly all emphasize that influencing the release levels of related cytokines in RA by targeting JAK/STAT signaling is a promising therapeutic strategy.

The MAPK/ERK signaling pathway is a key regulatory pathway for regulating the activation of fibroblast-like cells (FLS) in RA. This pathway is involved in the transmission of cell surface signals to the nucleus and promotes the gene expression of cell proliferation and migration.[77] The MAPK/ERK pathway is activated by a variety of cytokines in RA, including IL-6 and TNF-α, which are abundant in the synovial fluid of RA patients.[78] The activation of this pathway leads to an increase in the proliferation and migration of RA-FLS, thereby promoting synovial hyperplasia and joint injury.[16] Thus, it is of great significance to explore the therapeutic potential of RA by targeting the MAPK/ERK pathway. Through research, it has been found that the Nrf2/HO-1 signaling pathway plays a key role in the pathophysiology and therapeutic regulation of RA. Recent preclinical studies have confirmed that activating the Nrf2/HO-1 pathway is a beneficial mechanism for the treatment of RA.[79] For instance, it is known that the Nrf2 activator dimethylfumaric acid (DMF) significantly exhibits anti-

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arthritis effects in animal models by increasing the levels of Nrf2 and HO-1, thereby alleviating oxidative stress and inflammation.[80] Similarly, another natural compound, coumaric acid (AA), has been proven to inhibit the proliferation of fibroblast-like synovial cells (RA-FLS) in RA, promote apoptosis, and regulate NF-κB signaling through the Nrf2/HO-1 pathway.[81] The flavonoid isoglycyrrhizin (ISL) can also regulate this pathway, thereby protecting RA chondrocytes from apoptosis and reducing oxidative stress.[82] Furthermore, salicylate in Alangium chinense (Lour). Harms have also been found to activate Nrf2 and HO-1, thereby inhibiting reactive oxygen species (ROS) and improving inflammatory markers.[83] It can be seen from this that by up-regulating Nrf2 and HO-1, cartilage degeneration can be prevented, the infiltration of inflammatory cells can be reduced, and the damage of oxidative stress to joints can be alleviated, thereby delaying the disease progression of RA and providing new inspirations for the exploration of clinical efficacy.

The bioactive compounds of *K. coccinea* L. have been confirmed to have significant effects in regulating inflammation and cell proliferation in RA.[30,84] The key signaling pathways identified in these studies include NF-κB and JAK2/STAT3 pathways, which are crucial in the inflammatory processes of RA.[4,85] Some studies have pointed out that the NF-κB pathway regulates inflammatory responses by activating pro-inflammatory cytokines, such as TNF-α and IL-6, which in turn contribute to the proliferation of fibroblast-like synoviocytes (RA-FLS) and the destruction of cartilage in RA.[30,32] Several compounds isolated from *K. coccinea* L., such as Heilaohuacid G and Heilaohutriterpene B, have been shown to inhibit the activation of this pathway.[5,32] For instance, Heilaohuacid G significantly reduced the levels of NF-κB p65 and increased the expression of IκBα, suggesting its role in blocking NF-κB activation and reducing inflammation. In addition to NF-κB, the JAK2/STAT3 pathway also plays a critical role in mediating the inflammatory response in RA.[5] This pathway is activated by cytokines like IL-6 and TNF-α, which are elevated during RA progression.[61] Compounds from *K. coccinea* L., particularly sesquiterpenes like gaultheriadiolide, have demonstrated inhibitory effects on the JAK2/STAT3 signaling, further supporting their anti-inflammatory properties. These signaling pathways regulate the expression of genes involved in cell survival, proliferation, and apoptosis, processes that are dysregulated in RA.[4] By modulating these pathways, the relevant compounds from *K. coccinea* L. help to inhibit RA-FLS cell proliferation, promote apoptosis, and reduce inflammatory cytokine production.[30] Additionally, *K. coccinea* L. modulates the mitogen-activated protein kinase (MAPK) signaling pathway, further suppressing the activation of inflammatory mediators.[43,86] The latest research has found that the remarkable anti-inflammatory properties of *K. coccinea* L. can be attributed to its ability to activate the Nrf2/HO-1 signaling pathway. Root extracts of this plant, particularly ethyl acetate extract (ET5), have shown excellent results in inhibiting inflammatory indicators by LPS in RAW264.7 cells such as NO, TNF-α, IL-6 and monocyte chemoattractant protein 1 (MCP-1) in vitro. Reliable research has shown that kelch-1ike ECH- associated protein (Keap1) can continuously target Nrf2 for degradation and inhibit its activity under normal conditions. When exposed to oxidative stress, such as ROS, the sensing function of Keap1 is activated, the degradation process of Nrf2 is controlled, and Nrf2 accumulates and translocates into the nucleus. In the nucleus, Nrf2 forms heterodimers with small Maf proteins (sMaf). The Nrf2-sMaf dimer recognizes and binds to the ARE in the enhancer region of the target gene, recruits co-activators, and initiates the transcription of a series of downstream cell-protective genes.[87] Notably, ET5 stimulated Nrf2 nuclear translocation and up-regulated the transcription of Nrf2 target genes, including HO-1 and NAD(P)H quinone dehydrogenase 1 (NQO1), which play crucial roles in reducing oxidative stress and inflammatory responses.[88] Thus, the compounds from *K. coccinea* L. provide a promising avenue for RA treatment by targeting key inflammatory signaling pathways. These findings not only highlight the therapeutic potential of *K. coccinea* L. but also suggest that it can serve as a natural source for the development of new anti-RA agents, especially given the persistent challenge of managing chronic inflammation in autoimmune diseases like RA. The regulatory effect of *K. coccinea* L. on the Nrf2/HO-1 pathway is shown in Figure 4.

K. coccinea L. May Reduce Inflammation and Tissue Damage in RA by Regulating ROS Levels and Oxidative Stress

Reactive oxygen species (ROS) are generated during inflammation in RA, especially in immune cells such as neutrophils and macrophages.[89] When they are released in the synovium and synovial fluid, high levels of ROS intensify oxidative stress, thereby damaging cellular components such as proteins, lipids and DNA, and ultimately leading to the deterioration of RA.[90] One of the main roles of ROS in RA is its influence on the polarization of macrophages. ROS promotes the differentiation of macrophages into the pro-inflammatory M1 phenotype by activating the NF-κB signaling pathway.[91]

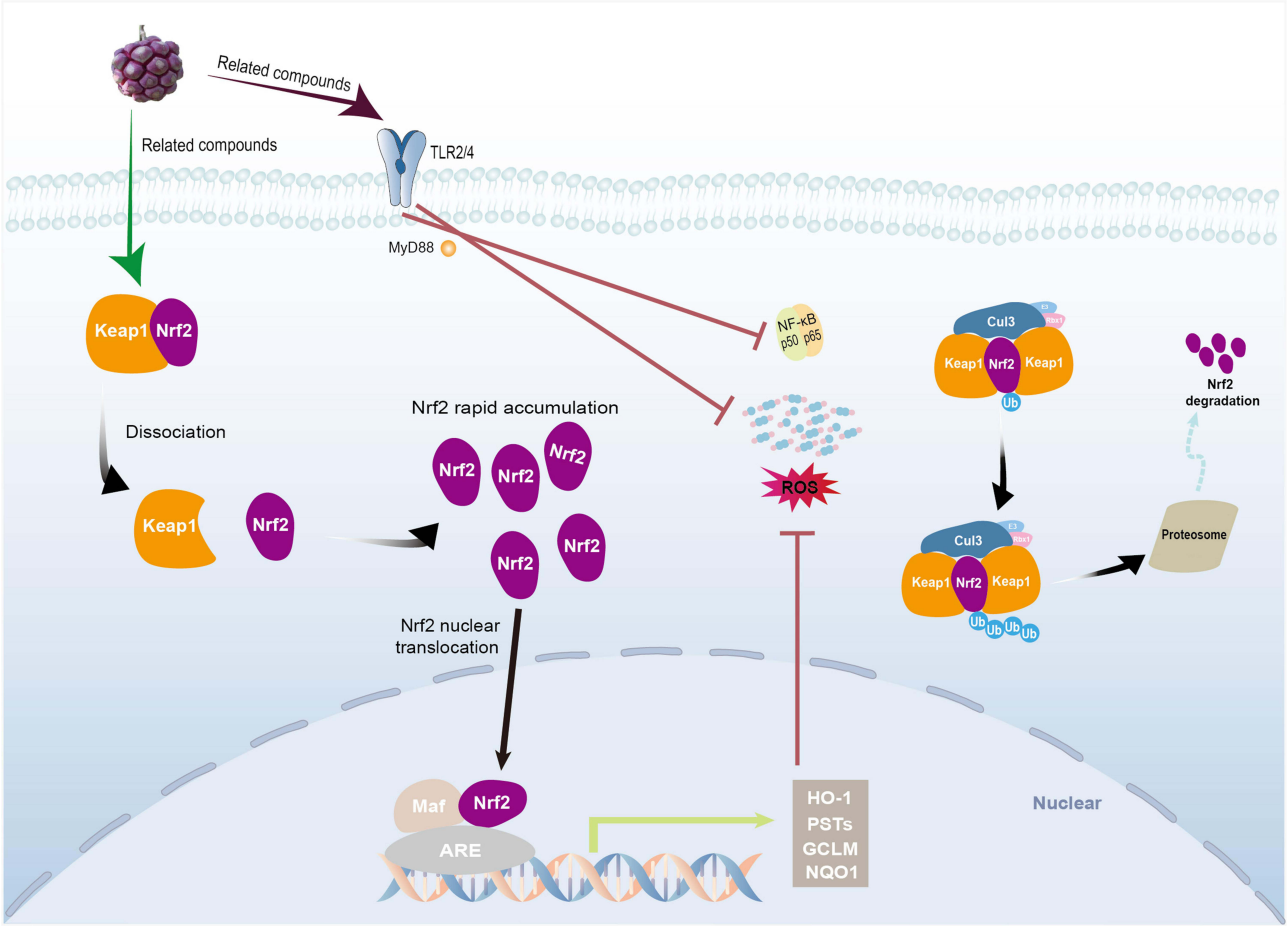

Figure 4 *K. coccinea* L. targets the Nrf2/HO-1 pathway to exert anti-RA effects. *K. coccinea* L. can activate Nrf2 and HO-1, leading to the suppression of ROS and improvement of inflammation. Reduce the infiltration of inflammatory cells; and attenuate the damage of oxidative stress on the joints, thus slowing down the progression of RA.
Abbreviations: Nrf2, nuclearfactor erythroidderived 2-like 2; HO-1, heme oxygenase 1; NQO1, NAD(P)H quinone oxidoreductase 1; Keap-1, Kelch-like ECH-associated protein 1; MyD88, Myeloid differentiation primary response protein 88; Maf, small Maf protein; PSTs, posterior superior temporal sulcus; GCLM, recombinant glutamate cysteine ligase, modifier subunit; ARE, antioxidant response element; ROS, reactive oxygen species; Cul3, cullin 3 protein; Rbx1, RING-box protein 1; Ub, Ubiquitin; TLR, Toll like receptor; NF-κB, nuclear factor kappa-B.

ROS can also promote the production of chemokines, attracting more immune cells to the inflamed area; thus, the inflammation cannot be effectively alleviated, and the chemokines would continuously affect the inflamed area.[89,92] In addition, ROS can also mediate the formation of neutrophil extracellular capture substances (NETs), which are structures containing DNA and other components released by neutrophils.[93] NETs play a crucial role in RA. They can amplify local inflammation and the development of autoimmunity by generating autoantibodies, especially anti-citrullinated peptide antibodies (ACPA). The persistent presence of NET in the synovial fluid of RA patients can lead to further tissue damage and promote the deterioration of the disease.[94] Furthermore, ROS can directly affect joint injury through lipid peroxidation. The elevated ROS level in RA promotes lipid oxidation, leading to the death of chondrocytes and fibroblast-like synovial cells (FLS), thereby causing cartilage destruction.[95,96] Oxidative stress has been shown to aggravate bone resorption through reactive oxygen species (ROS) mediated activation of matrix metalloproteinases (MMPs), which are a type of proteolytic enzyme responsible for degrading extracellular matrix components.[97] Meanwhile, ROS not only affects the inflammatory response but also the remission of the inflammatory response. Antioxidants that eliminate ROS can inhibit the activation of pro-inflammatory pathways and transform the polarization of macrophages from the M1 phenotype to the anti-inflammatory M2 phenotype. This transformation is crucial for alleviating inflammation and repairing tissue damage in patients with RA.[92,98] In summary, ROS are central to RA pathogenesis by exacerbating inflammation, promoting immune cell recruitment and activation, inducing tissue damage, and influencing macrophage

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polarization.[89,92] These findings highlight the potential of targeting ROS as a therapeutic strategy for RA treatment, aiming to alleviate inflammation, prevent joint damage, and potentially induce disease remission.[94,97]

Through relevant research, it has been found that *K. coccinea* L. contains dibenzocyclooctadiene lignans, which have antioxidant properties. These compounds can reduce reactive oxygen species (ROS) levels, thereby preventing cellular damage and tissue degeneration in RA.[34] Phenolic compounds isolated from the peels of *K. coccinea* L. have strong antioxidant activity.[99] These compounds effectively alleviate oxidative stress by scavenging free radicals and enhancing the activity of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione reductase (GR).[92] This antioxidant effect can reduce the excessive production of reactive oxygen species (ROS). As found in cellular inflammation models, it can also simultaneously inhibit the production of related lipid peroxidation markers such as malondialdehyde (MDA).[100] The antioxidant effect of *K. coccinea* L. is also reflected in its protective effect on RA, among which reactive oxygen species (ROS) play an important role in joint inflammation and tissue damage.[36,101] The related compounds from *K. coccinea* L. can help reduce the activation of inflammatory pathways and immune cell dysfunction by inhibiting reactive oxygen species (ROS), both of which are key factors in the progression of RA disease.[43] Moreover, the relevant compounds have been proven to enhance the defense system of cells against oxidative damage by promoting the activity of antioxidant enzymes, thereby maintaining cell integrity under oxidative stress conditions.[34,99] At the same time, the bioactive compounds of *K. coccinea* L. target key signaling pathways related to RA, such as the NF-κB and Nrf2 pathways.[5] These pathways regulate the response of cells to oxidative stress and inflammation. By regulating these pathways, *K. coccinea* L. can not only reduce the production of reactive oxygen species (ROS) but also promote the transformation to the anti-inflammatory macrophage phenotype, further alleviating the inflammatory process of RA.[5,91]

In conclusion, the rich composition of antioxidant compounds from *K. coccinea* L., including lignans and phenolics, contributes to its ability to modulate ROS levels and combat oxidative stress.[89,99,102] These properties make it a promising candidate for the treatment of RA, potentially alleviating inflammation, preventing joint damage, and improving overall therapeutic outcomes in RA patients.

Results

K. coccinea L. exhibits broad pharmacological potential against rheumatoid arthritis (RA), including anti-fibrotic, anti-inflammatory and antioxidant. Its three major bioactive components, namely triterpenoids, sesquiterpenes, and lignans, demonstrate significant anti-inflammatory effects. The plant exerts anti-RA effects by directly or indirectly inhibiting lipid peroxidation through reactive oxygen species scavenging. Furthermore, studies confirm that *K. coccinea* L. suppresses inflammatory mediators such as nitric oxide (NO), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), downregulates inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) protein expression, and modulates Nuclear factor-kappa B (NF-κB) and Nuclear factor erythroid 2-related factor/Heme Oxygenase-1 (2Nrf2/HO-1) signaling pathways. As a promising Dong ethnic medicine, its development into a novel anti-RA drug represents a prospective therapeutic strategy and a key focus for future research.

Discussion

This review comprehensively summarizes the possible mechanisms of *K. coccinea* L. in the treatment of RA, indicating that, as a natural plant, its related compounds have great potential in the development of anti-RA drugs (Table 1). Since it was first reported in Thailand in 1972, *K. coccinea* L. has been mentioned as a fruit rich in nutritional value. Its edible part has high energy, protein, and fat, and therefore can be used as a potential healthy fruit for future food applications.[103] In China, some plants of the *Kadsura* genus are often used in folk medicine with activating blood circulation, relieving pain, dispelling wind, and dehumidifying effects.[104] Modern pharmacological studies have shown that *K. coccinea* L. demonstrates therapeutic potential in diabetes, rheumatoid arthritis, inflammatory liver disease and gastrointestinal related diseases, and is applied to other types of diseases.[4,102,105,106] Therefore, *K. coccinea* L. represents an emerging functional food with significant medicinal and economic value. It has a wide range of exploitable application prospects and deserves our attention.

Through a large number of clinical studies, it has been found that the related chemical drugs for treating RA may have certain adverse reactions during the period when patients take them, which is not conducive to the prognosis of

Table 1 Compounds in *K. coccinea* L. May Have an Impact on RA

Active Ingredient	Classifications	Compounds	Source	Pharmacological Action	Reference
Triterpenoids	Intact lanostane triterpenoids	3-hydroxy-12-acetoxycoccinic acid, 3-hydroxy-12-hydroxyl coccinic acid, 3-hydroxy-neo-kadsuranic acid, 24(E)-3-oxo-9β-lanosta-7, 24-dien-26-oic acid, Coccinone A-D, Coccinic acid, Kadcoccinone F, Kadcoccinones G-Q	Roots	↓pro-inflammatory cytokines such as IL-6 and TNF-α	[5, 30, 107–110]
	3,4-seco-lanostane	Coccinilactone B, Coccinilactone A, Seco-coccinic acids A-K, Kadsuracoccinic acids A-C, Kadsuric acid, Micranoic acid A, Kadcoccilactones R	Plants	↓inflammatory factors such as IL-6, TNF-α; MMP-1, and MMP-3	
	14 (13→12)-abeolanostane	Kadcoccinone A, Kadcoccinone B, 6/6/5/6-fused triterpenoid acids A-N	Stems	Anti-platelet aggregation induced by colloid, anticoagulant	
	Kadlongilactoe Triterpenoids	Kadcoccilactones K-P, kadlongilactones A-B, D, Longipedlactones A-C, E-F	Stems	↓pro-inflammatory mediators (NO and PEG2); ↓pro-inflammatory cytokines (TNF-α, IL-1β, IL-6)	
	Intact cycloartane triterpenoids	24-methylenecycloartenone	Stems	↓reactive oxygen species (ROS); ↓nitric oxide (NO); ↓inflammatory factors (TNF-α, IL-6, IL-18)	
	3,4- secocycloartane triterpenoids	Kadcoccilactone Q, Kadsudilacton, Coccinetane A-H	Plants	Neuroprotective, hepatoprotective, immunosuppressive, antiviral activity (HIV-1, DV3, RSV and H1N1)	
	Schinortriterpenoids	Kadcoccilactones B, D, E-F, H-J, Micrandiactone H	Stems, Rhizome	↓arachidonate 5-lipoxygenase (5-LO); ↓human leukocyte elastase (HLE); ↓inflammatory factors (I L-1a, IL-1b, TNF-a, IL-6, IL-8)	
Lignans	Dibenzocyclooctadiene lignan	14-O-demethyl polysperlignan D, Kadsurindutin E, Coccilignan A. et al	Roots	↓nitric oxide; (NO); ↓iNOS and COX-2; ↓expression of pro-inflammatory genes in RA FLS	[1, 111]
	Spirobenzofuranoid dibenzocyclooctadiene lignans	Schiarisanrin B, Heteroclitin D, Kadsulignans H-I, Schiarisanrin A, Kadsulignans E, F	Roots, Stems		
	Arylnaphthalene lignan	Kadsuralignan C, Kadsuralignan H, Kadsurindutin E, Coccilignan A,	Roots		
	Diarylbutanes lignans	Mesodihydroguaiaretic acid, Kadcoccilignan	Roots		

(*Continued*)

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Table 1 (Continued).

Active Ingredient	Classifications	Compounds	Source	Pharmacological Action	Reference
Flavonoids	Flavan-3-ols	Procyanidin B1, Catechin, Procyanidin B2, Procyanidin, Procyanidin C-type, Procyanidin B-type, Catechin-hexoside, Epicatechin	Leaves	Antioxidant; ↑glutathione reductase antioxidant; ↑glutathione reductase (GR); ↑superoxide dismutase (SOD); ↑glutathione (GSH); ↓reactive oxygen species (ROS); ↓malondialdehyde (MDA)	[99, 112]
	Flavanones	Eriodictyol, Naringenin	Leaves		
	Flavonols	Rutin, Isoquercitrin, Kaempferol-3-rutinoside, Quercetin, Kaempferol, Isorhamnetin	Leaves		
	Flavanonols	Dihydroisorhamnetin, Taxifolin	Leaves		
	Dihydrochalcones	Phloridzin, Phloretin	Leaves		
Phenolic Acids		D-Galacturonic acid, Quinic acid, Malic acid, Citric acid, Gallic acid, Neochlorogenic acid, Chlorogenic acid, Caffeic acid, 1,3-Dicaffeoylquinic acid, Suberic acid, 4-Coumaric acid, Ferulic Acid, Salicylic acid, Azelaic acid, Isochlorogenic acid A, Abscisic acid. et al	Leaves	↑glutathione reductase (GR); ↑superoxide dismutase (SOD); ↓reactive oxygen species (ROS) ; ↓malondialdehyde (MDA); Regulating Th17/Treg cell imbalance	[99, 112, 113]

Notes: ↓, decrease; ↑: increase.

patients.[114] Therefore, exploring the pharmacological effects of *K. coccinea* L. and developing it as an anti-RA drug is a promising strategy. Meanwhile, although there are certain limitations in the current research on the anti-RA mechanism of *K. coccinea* L., and the safety of drug application has not been clearly explored, the related applications and studies of *K. coccinea* L. in the treatment of RA have been widely reported. It indicates that the application of *K. coccinea* L. in the future treatment of RA is very promising. However, it is worth noting that we still need subsequent preclinical and clinical studies to determine the safety of *K. coccinea* L. in the application of RA. However, the application of *K. coccinea* L. in the treatment of RA among the Tujia ethnic group in China has a long history. Meanwhile, some reports indicate that the polysaccharides from the fruits of *K. coccinea* L. have antioxidant and lipid-lowering activities,[115] and the compound component dibenzocycloctyl plays a prominent role in liver protection.[34] It can be seen from this that *K. coccinea* L. still has relative safety in the application of disease treatment.

Relevant progress has been made in the component research of *K. coccinea* L.; the mechanism research of related active components remains the focus of future exploration. We predicted the therapeutic and improvement potential of the main components in *K. coccinea* L. for RA. However, it is currently unclear how the active ingredients in *K. coccinea* L. act alone and have the effect of improving the disease progression of RA. Therefore, in future research, comprehensive pharmacological experiments should be conducted to verify how various components specifically function. Meanwhile, we also discussed the research progress of its key active ingredients for treating RA. *K. coccinea* L. can exert its anti-RA effect by targeting immune cells such as T cells and macrophages, regulating the levels of inflammatory factors, and simultaneously reducing oxidative stress, thereby affecting multiple signaling pathways such as the Nrf2/HO-1 pathway, JAK/STAT pathway, NF-κB pathway, and MAPK/ERK pathway. Ultimately, alleviate the symptoms of RA patients and improve their quality of life. Therefore, *K. coccinea* L. can be a promising natural medicinal plant and a complementary therapy for RA. Based on these, in the study of the disease progression of RA, *K. coccinea* L. has non-negligible potential for action and broad application prospects. Although the deep pharmacological mechanism of *K. coccinea* L. is not sufficiently explored at present, reliable studies have shown its therapeutic effect on inflammation. Further exploration of its anti-RA mechanism is an urgent task for future research.

To sum up, *K. coccinea* L. has good anti-inflammatory activity and may play a corresponding therapeutic role in RA by regulating the cytokine network, eliminating reactive oxygen species, reducing oxidative stress and inhibiting inflammatory pathways. All of these may become favorable factors for improving the prognosis of RA patients. Meanwhile, when developing drugs related to *K. coccinea* L., chronic toxicity needs to be evaluated, and clinical trials should be conducted during the development of related products to further assess the possible adverse reactions and related safety in RA patients.

Conclusion

K. coccinea L., a traditional Dong ethnic medicine with a long history of medicine food homology in China, has been proven to have excellent anti-inflammatory effects through the practical experience of the working people and extensive modern pharmacological research. These findings provide a solid theoretical basis for applications in the treatment of autoimmune diseases and other aspects, and we look forward to their future clinical application prospects. However, there are limitations in the research on its pharmacokinetic and toxicological effects, indicating that further rigorous and systematic studies are needed to ensure the safety and sustainability of *K. coccinea* L. in future disease applications.

Abbreviations

RA, Rheumatoid arthritis; CNKI, National Knowledge Infrastructure; ACPAs, anti-citrullinated protein antibodies; NSAIDs, Nonsteroidal anti-inflammatory drugs; DMARDs, disease-modifying antirheumatic drugs; FLS, fibroblast-like synoviocytes; UA, Ursolic acid; MMPs, matrix metalloproteinases; UAA, ursolic acid-3-acetate; CIA, Collagen induced arthritis; NF-κB, nuclear factor-kappa B; SLs, sesquiterpene lactones; NO, nitric oxide; NOS, nitric oxide synthase; TNF-α, Tumor necrosis factor-α; SHBG, Sex hormone-binding globulin; CS-IVa, Chikusetsusaponin IVa; CFA, Complete Freund's Adjuvant; JB, Jolkinolide B; ISL, isoglycyrrhizin; DMF, Dimethylfumaric acid; AA, coumaric acid; ROS, reactive oxygen species; Nrf2, nuclearfactor erythroidderived 2-like 2; HO-1, heme oxygenase 1; NQO-1, NAD(P)H quinone oxidoreductase 1; Keap-1, Kelch-like ECH-associated protein 1; Maf, small Maf protein; PSTs, posterior superior temporal sulcus; GCLM, recombinant glutamate cysteine ligase, modifier subunit; ARE, antioxidant response element; Cul3, cullin 3 protein; Rbx1, RING-box protein 1; Ub, Ubiquitin; ET5, ethyl acetate extract; sMaf, small Maf proteins; NETs, neutrophil extracellular capture substances; ACPA, anti-citrullinated peptide antibodies; MMPs, matrix metalloproteinases; SOD, superoxide dismutase; GR, glutathione reductase; IL-1β, Interleukin-1β; IL-6, Interleukin-6; IL-5; interleukin-5; TNF-α, Tumour necrosis factor-alpha; iNOS, Inducible ntric oxide synthase; COX-2, Cyclooxygenase-2; RANKL, receptor activator of nuclear factor-κB ligand; BLYS, B lymphocyte stimulator; LTβ, Lymphotoxin beta.

Author Contributions

F-OY: Conceptualization, Data curation, Investigation, Writing–original draft, Methodology, Software. XL-X: Writing–original draft, Conceptualization. YL: Writing–original draft, Conceptualization. MW: Writing–original draft, Data curation. ML: Writing–original draft, Investigation. J-YG: Writing–original draft, Investigation. X-YJ: Writing–original draft, Investigation. B-BH: Writing–review and editing, Supervision. X-BF: Writing–review and editing, Supervision. HL: Writing–review and editing, Supervision. J-XL: Writing–review and editing, Writing–original draft, Supervision. X-GH: Writing–review and editing, Supervision. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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