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Review

The prospect and underlying mechanisms of Chinese medicine in treating periodontitis

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ABSTRACT

Inflammation represents a critical immune response triggered by cellular activities and inflammatory mediators following tissue damage. It plays a central role in the pathological progression of diverse diseases, including psychiatric disorders, cancer, and immunological conditions, rendering it an essential target for therapeutic intervention. Periodontitis, a prevalent oral inflammatory disease, is a leading cause of tooth loss and poses significant health challenges globally. Traditionally, inflammatory diseases such as periodontitis have been treated with systemic administration of synthetic chemicals. However, recent years have witnessed challenges, including drug resistance and microbial dysbiosis associated with these treatments. In contrast, natural products derived from Chinese medicine offer numerous benefits, such as high safety profiles, minimal side effects, innovative pharmacological mechanisms, ease of extraction, and multiple targets, rendering them viable alternatives to conventional antibiotics for treating inflammatory conditions. Numerous effective anti-inflammatory natural products have been identified in traditional Chinese medicine (TCM), including alkaloids, flavonoids, terpenoids, lignans, and other natural products that exhibit inhibitory effects on inflammation and are potential therapeutic agents. Several studies have confirmed the substantial anti-inflammatory and immunomodulatory properties of these compounds. This comprehensive review examines the literature on the anti-inflammatory effects of TCM-derived natural products from databases such as PubMed, Web of Science, and CNKI, focusing on terms like "inflammation", "periodontitis", "pharmacology", and "traditional Chinese medicine". The analysis systematically summarizes the molecular pharmacology, chemical composition, and biological activities of these compounds in inflammatory responses, alongside their mechanisms of action. This research seeks to deepen understanding of the mechanisms and biological activities of herbal extracts in managing inflammatory diseases, potentially leading to the development of promising new anti-inflammatory drug candidates. Future applications could extend to the treatment of various inflammatory conditions, including periodontitis.

1. Introduction

Inflammation, a critical immune response, is initiated by cellular and inflammatory mediators following tissue damage. This response plays a vital role in containing pathogens at the site of inflammation, preventing their systemic spread, and promoting tissue repair and homeostasis under adverse conditions [1]. The body, in response to inflammation, activates defense mechanisms primarily involving the vascular system, where inflammatory transmitters and cytokines elicit a nonspecific immune response[2]. However, as inflammation progresses, a significant increase in proinflammatory cytokines occurs, leading to a cascade reaction. This surge can result in a "cytokine storm" and the onset of systemic inflammatory response syndrome [3]. As an inflammatory disease, periodontitis also exhibits this type of cascade reaction in the development of the condition. In periodontitis, the accumulation of local bacteria and their byproducts initiates the disease, while the progression is largely determined by the host's immune response [4]. Although dental plaque is a critical factor for the onset of periodontitis, the host's immune reaction to the bacteria and their byproducts plays a pivotal role in the degradation of periodontal tissue [5]. Furthermore, intense inflammation can lead to fatal hypersensitivity reactions in diseases such as cancer, rheumatoid arthritis, encephalomyelitis, systemic lupus erythematosus, rheumatic fever, allergic asthma, and immune complex glomerulonephritis [6-8]. Localized inflammation in specific organs can also have severe consequences. For instance, brain inflammation can compress critical centers, vocal cord inflammation can obstruct the larynx, leading to asphyxiation, and severe myocarditis can impair heart function. In these situations, anti-inflammatory medications are essential to suppress the response [9-11]. Uncontrolled inflammation can result in pathological, potentially

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life-threatening reactions. Therefore, controlling the inflammatory response through a complex molecular cascade is vital to eliminate proinflammatory cytokines and restore normal tissue homeostasis. Chinese medicine has demonstrated efficacy in treating inflammatory diseases and has been employed in routine treatments for infectious diseases, pandemics, and cancer over the past five millennia. The discovery of penicillin by Alexander Fleming in 1928 ushered in an era of synthetic pharmaceuticals. However, the escalating global incidence of epidemics, infectious diseases, and cancers has led to a surge in the reliance on antibiotics, often prescribed as the initial treatment for periodontitis. Recent years have witnessed the emergence of significant challenges, such as antibiotic resistance and bacterial imbalance. While the advent of antibiotics was revolutionary, their adverse effects have increasingly constrained their use. In response, researchers globally are exploring the potential of Chinese medicines, which have historically been utilized for their anti-inflammatory properties.

The "San Huang Xiao Yan Recipe" has been utilized for several decades in treating diabetic foot, effectively inhibiting high mobility group box-1 protein (HMGB1) expression and reducing inflammation through the AMP-activated protein kinase (AMPK)/nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway [12]. Similarly, the "Viola yedoensis Makino" formula mitigates atopic dermatitis by attenuating M2 macrophage polarization *via* the JAK2/STAT3 signaling pathway [13]. Sophoridine, a natural alkaloid, demonstrates antitumor and anti-inflammatory properties by promoting M1 polarization in RAW264.7 and THP-1-derived macrophages through the mitogen-activated protein kinase (MAPK) signaling pathway [14]. Xanthohumol significantly reduces hepatic iron accumulation and counters drug-induced hepatic ferroptosis by activating the Nrf2/xCT/GPX4 signaling pathway [15]. Natural products in Chinese medicine offer benefits including high safety, low toxicity, cost-effectiveness, ease of extraction, diverse targets, and bacterial resistance [16]. A considerable number of Chinese medicine extracts show promise for therapeutic applications.

This review provides a comprehensive analysis of Chinese medicinal compounds possessing anti-inflammatory properties, focusing primarily on alkaloids, flavonoids, terpenoids, lignans, and other active substances. The mechanisms of action of these active ingredients are explored in depth, with the aim of enhancing our understanding of their pharmacological effects. This research approach holds promise for addressing various inflammatory conditions, including periodontitis, in the future.

2. Signaling Pathways Involved in Periodontitis and Inflammation

Inflammation initially serves as a defensive mechanism of the body, aimed at eliminating pathogens. During an inflammatory response, the body activates various defense and protective mechanisms, generating inflammatory transmitters and cytokines that trigger nonspecific immune responses [2]. The progression of inflammation involves multiple stages and steps, evolving gradually. Both the onset and resolution of inflammation are governed by signaling processes, which are part of a complex biological network. This network features intricate "crosstalk" among numerous regulators and receptors. Various signaling pathways are intricately coordinated to mitigate inflammation and return inflamed tissues to their normal physiological state. Periodontitis, a prevalent inflammatory condition, stands as a primary contributor to tooth loss globally and poses a serious health problem to human society worldwide [17]. Bacteria elicit an immune response in periodontal tissues that includes the aggregation of inflammatory cells, cytokine production, osteoclast activation, and bone resorption [18]. Bacterial components, such as lipopolysaccharide (LPS), prompt the release of interleukins, including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), from periodontal tissue cells. These interleukins function as autocrine factors, perpetuating chronic inflammation in periodontal tissues. Such inflammation is marked by heightened levels of inflammatory mediators in the tissues, which contribute to alveolar bone resorption [19]. The induction of inflammatory gene expression is governed by various intracellular signaling mechanisms, pivotal in the development and progression of periodontal inflammation. This study specifically examines several signaling pathways integral to the onset and progression of inflammation.

2.1. The nuclear factor kappa-B (NF-κB) signaling pathway

NF-κB, a family of transcription factors, plays crucial roles in diverse physiological and pathological processes. The NF-κB family, including inducible transcription factors such as NF-κB1 p50 and RELA (also known as p65), is typically activated by various immune receptor stimuli through the NF-κB signaling pathway. The activation sequence begins with the kinase TAK1, which subsequently activates the IKK complex. The IKK complex then phosphorylates IκBα or other IκB family members, leading to their ubiquitination and proteasomal degradation. This facilitates the nuclear translocation and release of NF-κB family members, notably the NF-κB1 p50-p65 dimer. IKK-mediated phosphorylation of p105 also promotes the production of p105, i.e., NF-κB1 p50, aiding its nuclear translocation [20-23]. Recent research has revealed that dysregulation of NF-κB activity is linked to inflammation-related diseases and cancer, positioning NF-κB as a potential therapeutic target. The NF-κB signaling pathway is crucial for maintaining immune homeostasis and managing chronic inflammation, particularly in autoimmune diseases [24]. In macrophage inflammation induced by LPS, the NF-κB signaling pathway is a key mediator. Anti-inflammatory medications can target NF-κB by inhibiting this signaling pathway [25]. Numerous studies demonstrate that Chinese herbal extracts effectively block the NF-κB signaling pathway, thereby reducing inflammation (Fig. 1).

The NF-κB signaling pathway plays a crucial role in various inflammatory diseases, rendering it a vital therapeutic target. A study revealed that in gingival tissue samples from chronic periodontitis patients, NF-κB was commonly targeted by four microRNAs: miR-21, miR-100, miR-125b, and let-7a. This suggests a significant influence of the NF-κB signaling pathway on the development and progression of periodontitis [26]. Another study demonstrated that in an experimental periodontitis model, rats treated with gliclazide exhibited reduced inflammation and less linear bone loss compared to the control group. The expression levels of NF-κB p50, phosphoinositide 3-kinase (PI3K), protein kinase B (AKT), and F4/80 were downregulated, proving NF-κB's impact on periodontal inflammation [27]. Moreover, compared to pre-treatment levels, gingival tissue biopsies from treated periodontitis dogs showed decreased expression of TNF-α, receptor activator of nuclear factor kappa-B ligand (RANKL), osteopontin (OPG), matrix metalloproteinase-1 (MMP-1), IL-6, and interleukin-10 (IL-10), suggesting that NF-κB signaling pathway inhibition reduces periodontal inflammation, making it a potential therapeutic target [28].

Forsythoside A (FSA), a primary component of *Forsythia suspensa*, exhibits anti-inflammatory, antibacterial, antioxidant, and neuroprotective properties [29]. Research has examined the influence of different FSA concentrations on the expression of proteins related to the TLR/NF-κB signaling pathway. The findings indicate that FSA markedly reduces the expression of TLR and NF-κB p65 proteins, including NF-κB p65 in the nucleus, thereby impeding the NF-κB signaling pathway. ATG [30], a lignan-like compound derived from *Arctium lappa*, possesses diverse pharmaco-

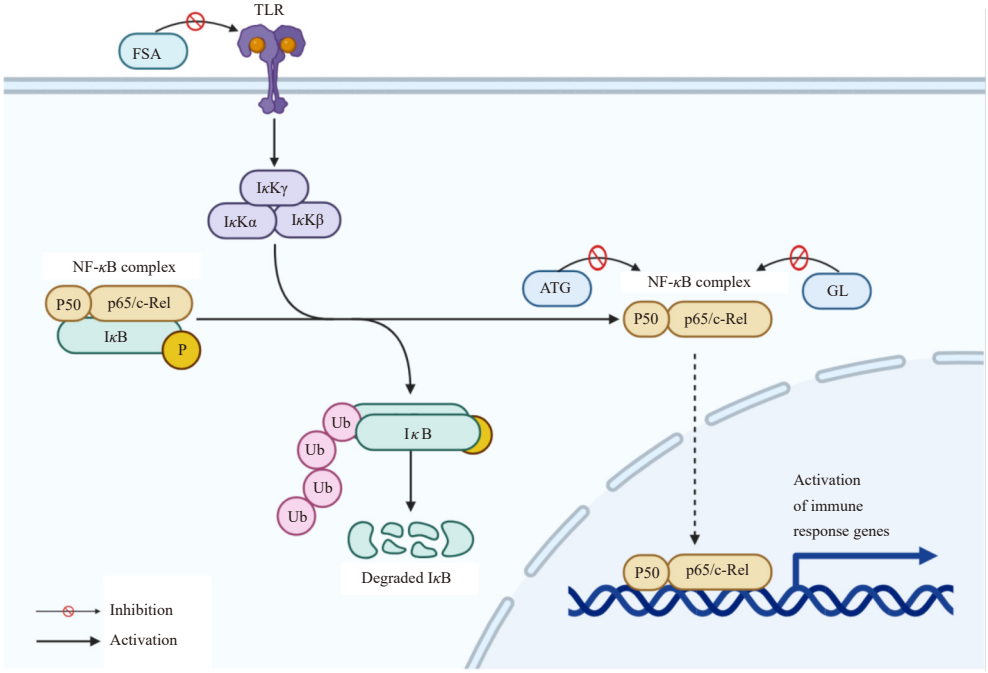

Fig. 1 Chinese medicines mitigate inflammation through the inhibition of the nuclear factor kappa-B (NF-κB) signaling pathway. Arctigenin (ATG) and Glycyrrhizin (GL) effectively impede the NF-κB signaling pathway by markedly reducing lipopolysaccharide (LPS)-induced NF-κB p65 phosphorylation, which in turn diminishes P65 expression. Similarly, Forsythoside A (FSA) attenuates the NF-κB signaling pathway by significantly decreasing both Toll-like receptors (TLR) and NF-κB p65 protein expression levels, as well as NF-κB p65's presence in the nucleus.

logical effects such as antitumor, immunomodulatory, and, notably, anti-inflammatory properties. Research [31-33] demonstrates that ATG primarily targets the NF-κB signaling pathway for its anti-inflammatory action. Additionally, GL is recognized for its immune-modulating, anti-inflammatory, antiviral, and antiallergic properties. Studies indicate that LPS can significantly elevate the protein expressions of P65 and NF-κB p65, along with cyclooxygenase-2 (COX-2) [34, 35]. A study found that GL can reduce P65 expression by significantly decreasing COX-2 expression and inhibiting LPS-induced phosphorylation of NF-κB p65, contributing to its anti-inflammatory effect [36].

In conclusion, both theoretical and empirical evidence substantiates the employment of Chinese medicinal treatments for inflammatory disorders. Myriad Chinese medicine compounds exhibit anti-inflammatory properties by inhibiting the NF-κB signaling pathway.

2.2. The Janus kinase-signal transducers and activators of transcription (JAK/STAT) signaling pathway

The JAK/STAT signaling pathway is characterized by the formation of complexes involving ligands, receptors, JAKs, and STATs [37]. The JAK family consists of four distinct members: TYK2, JAK1, JAK2, and JAK3. Similarly, the STAT family is composed of seven entities: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. Upon cytokine-receptor binding, the JAK-TYK complex becomes activated, initiating regulatory signaling. This activation leads to the phosphorylation of receptor tyrosine residues, which in turn activates STAT binding sites. STAT1, through its Src homology domain 2, associates with the receptor, undergoing rapid activation and phosphorylation at tyrosine residues in its C-terminal domain. The phosphorylated STATs then dimerize and translocate to the nucleus, where they regulate gene expression, influencing various immune functions [38, 39].

The suppressor of cytokine signaling (SOCS) proteins, operating through the JAK/STAT signaling pathway, have been implicated in the pathogenesis of immune-related diseases [40]. This family consists of eight proteins, including CIS and SOCS1-SOCS7, with SOCS1-3 and CIS inhibiting JAK/STAT-related cytokine signaling *via* a negative feedback loop [41]. In periodontitis models, increased SOCS1 expression corresponds with activated STAT1 and nuclear factor-kappa B (NF-κB) signaling pathways [42]. SOCS1-3 also plays a role in regulating bone resorption in periodontitis [43]. Several studies have linked SOCS gene dysregulation to the development of periodontitis *via* the JAK/STAT signaling pathway [44], with additional research showing increased activation in infected gingival epithelial cells [45, 46]. Furthermore, 25-hydroxyvitamin D3 (25-OHD3) improved diabetic periodontitis by downregulating the JAK1/STAT3 signaling pathway in the gingival epithelium [47], indicating the JAK/STAT signaling pathway's close relation to periodontitis development, indicating the close relationship between the JAK/STAT signaling pathway and the development of periodontitis.

ATG effectively inhibits the movement of STAT1 and STAT3 into the nucleus by limiting the phosphorylation of JAK2, STAT1, and STAT3, thus hindering the anti-inflammatory functions of the JAK/STAT signaling pathway [48, 49]. Furthermore, research indicates that curcumin suppresses the JAK/STAT signaling pathway by blocking the phosphorylation of JAK1, JAK2, and their downstream molecules (STAT1 and STAT3). It acts as a cytokine signaling inhibitor, preventing the overactivation of JAK and STAT [50].

The findings demonstrate the potential of select Chinese medicine extracts to mitigate inflammation through modulation of the JAK/STAT signaling pathway (Fig. 2). This insight establishes a foundational basis for the incorporation of traditional Chinese herbs in the treatment of inflammatory diseases.

2.3. The MAPK signaling pathway

The MAPK signaling pathway, which involves a series of serine-threonine protein kinases, plays a crucial role in the treatment of inflammatory diseases [51]. The MAPK cascade in humans comprises three distinct and regulated branches: Extracellular signal-regulated kinase (ERK), c-Jun *N*-terminal kinase (JNK), and p38 MAPK. ERK activation is mediated by the upstream kinases MEK1 and MEK2, JNK by MKK4 and MKK7, and p38 MAPK by

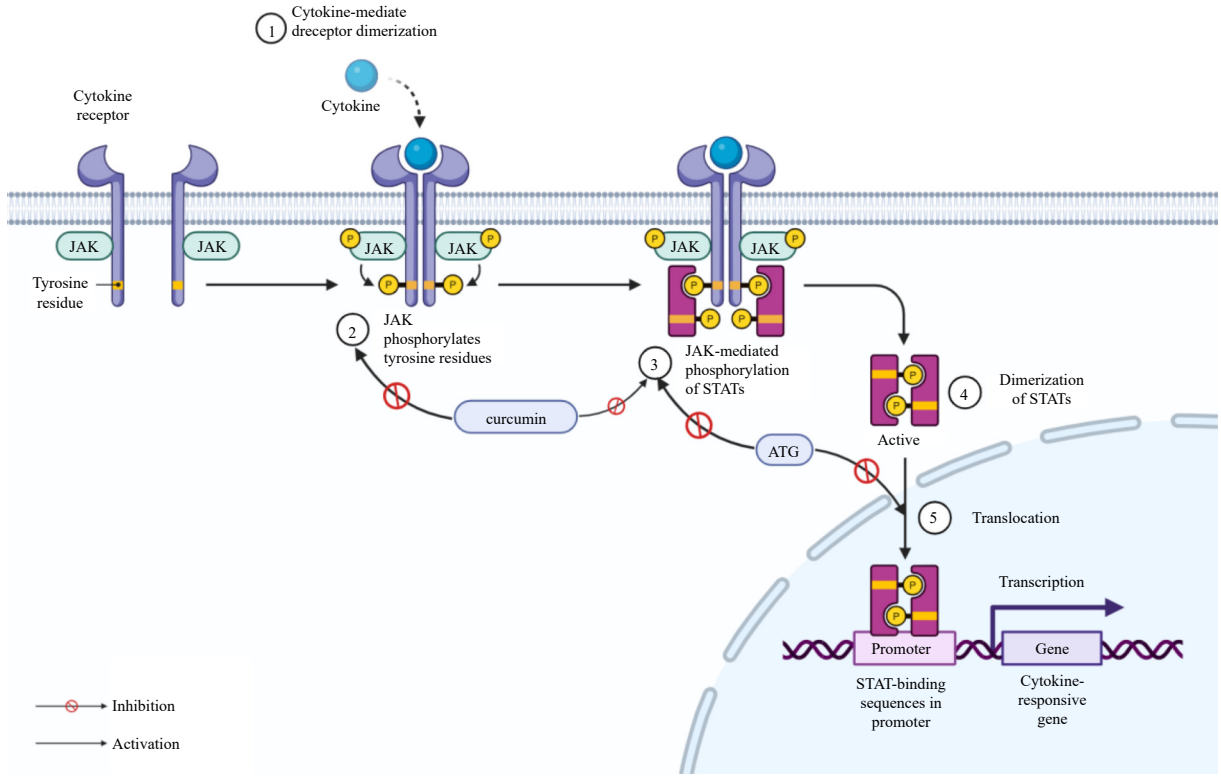

Fig. 2 Chinese herbs mitigate inflammation through the inhibition of the Janus kinase-signal transducer and activator of transcription (JAK/STAT) signaling pathway. Arctigenin (ATG) impedes the nuclear translocation of STAT1 and STAT3 by hindering the phosphorylation of STAT1, STAT3, and JAK2, thereby diminishing inflammatory responses. Curcumin suppresses the JAK/STAT signaling pathway by blocking the phosphorylation of JAK1, JAK2, and their downstream effectors (STAT1 and STAT3). It functions as a cytokine signaling inhibitor, curtailing the overactivation of JAK and STAT.

MKK3, MKK4, and MKK6. Upon activation, transcription factors such as activator protein 1, activating transcription factor 2, and T-lymphocyte chemotactic factor, which reside within the cytoplasm or nucleus, undergo phosphorylation and subsequent activation. This process ultimately triggers an inflammatory response [52].

MAPKs are recognized as key regulators of osteoclast activation and the expression of inflammatory mediators, including genes and proteins associated with osteogenesis, osteoclastogenesis, bone formation, and inflammation [53]. One study found that Ermiao Wan, a traditional Chinese herbal formula, prevented periodontitis by reducing alveolar bone loss and inflammation through the phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) and NF-κB/MAPK signaling pathways [54]. Additionally, SLIT2 overexpression in periodontitis may worsen inflammation and alveolar bone loss by activating the MAPK signaling pathway [55]. Erythropoietin can affect osteogenesis in healthy and periodontitis-derived periodontal mesenchymal stem cells by modulating the p38 MAPK signaling pathway [56]. Advanced glycation end-products (AGEs) increase intercellular adhesion molecule-1 (ICAM-1) and IL-6 expression in human gingival fibroblasts *via* the MAPK and NF-κB signaling pathways, accelerating the pathogenesis of periodontal diseases [57]. These findings indicate that the JAK/STAT signaling pathway represents a relevant target for the treatment of periodontitis.

Researchers have demonstrated that taraxsterol significantly diminishes LPS-induced activation of JNK, ERK, and p38 MAPK by inhibiting the activation of transforming growth factor-beta-activated kinase 1 (TAK1), thus suppressing the LPS-activated MAPK signaling pathway [58]. Additionally, studies indicate that forsythiaside A (FSA) can produce anti-migration and anti-inflammatory effects by modulating the JAK/STAT signaling pathway [59]. Furthermore, curcumin has been shown to suppress the MAPK signaling pathway by inhibiting p38 MAPK phosphorylation in macrophages, consequently reducing inflammation [50].

Extensive research has demonstrated that specific anti-inflammatory compounds in Chinese herbal medicines can mitigate inflammation by targeting the MAPK signaling pathway (Fig. 3).

2.4. The PI3K/AKT/mTOR signaling pathway

The PI3K/AKT signaling pathway plays a critical role in regulating diverse cellular processes. PI3Ks, classified as lipid kinases, consist of three classes: Class I (comprising isoforms α, β, γ, δ), Class II (including isoforms PI3KC2 α, β, γ), and Class III [60]. Structurally and functionally, PI3Ks are categorized into Class IA and IB, with Class IA consisting of p110α, p110β, and p110δ, which are associated with the p85 regulatory subunit containing the Src homology domain 2. Class I PI3K, found ubiquitously in cells, is activated by various proteins localized at the cell membrane, such as G protein-coupled receptors, receptor tyrosine kinases, and Ras family proteins [61]. Stimulation of receptor protein tyrosine kinase triggers the production of phosphatidylinositol 3,4,5-trisphosphate and phosphatidylinositol 4,5-bisphosphate by PI3K at the inner side of the plasma membrane [62]. Upon interacting with these phospholipids, AKT translocates to the inner membrane, where PDK1 and PDK2 phosphorylate and activate it. The activated AKT then modulates various substrates implicated in cell survival, cell cycle progression, and growth [63].

PI3K plays a critical role in the development of various inflammatory diseases [64]. Studies have demonstrated that PI3K contributes to the progression of LPS-induced chronic apical periodontitis by regulating the proliferation and differentiation of osteoclasts and osteoblasts [65]. KMUP-1, a xanthine derivative, exhibits inhibitory effects on phosphodiesterase and soluble guanylyl cyclase. Research has revealed that KMUP-1 can mitigate inflammation and osteoclast differentiation in periodontitis by targeting the PI3K/AKT signaling pathway [66]. Furthermore, another study has shown that C-reactive protein can impede osteogenesis and

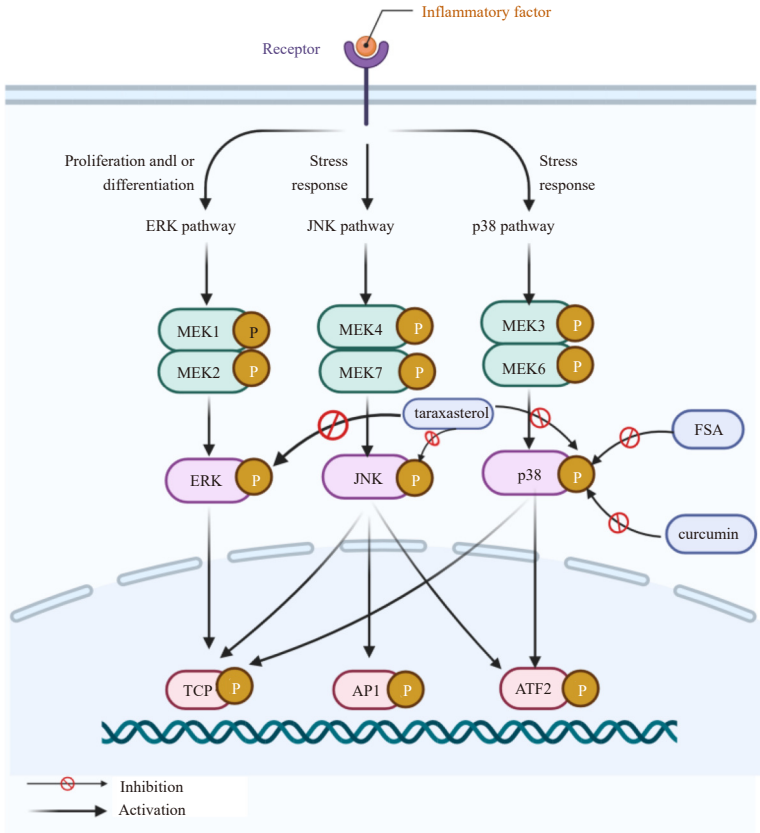

Fig. 3 Chinese medicines demonstrate anti-inflammatory properties through the inhibition of the mitogen-activated protein kinase (MAPK) signaling pathway. Tarasasterol effectively suppresses the activation of extracellular signal-regulated protein kinases (ERKs), c-Jun N-terminal kinase (JNK), and p38. Similarly, Forsythoside A (FSA) specifically inhibits p38 phosphorylation. Furthermore, curcumin targets p38 phosphorylation, thereby impeding the MAPK signaling pathway and consequently reducing inflammation.

enhance osteoclastogenesis *via* the PI3K/AKT signaling pathway under diabetic and proinflammatory conditions, thereby aggravating diabetic periodontitis [67]. Salidroside has also been found to stimulate the proliferation of human periodontal ligament cells through the PI3K/AKT signaling pathway [68]. These findings collectively suggest that the JAK/STAT signaling pathway is intricately linked to the development of periodontitis.

Paeoniflorin, the principal active compound of *Paeonia* L., has been demonstrated to significantly reduce the expression of PI3K, phosphorylated AKT, and mTOR, thereby inhibiting the PI3K/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathway [69]. Furthermore, rhodopsin acts as an anti-inflammatory agent by suppressing this signaling pathway [70]. Additionally, Tanshinone IIA, a natural compound extracted from Salvia miltiorrhiza Bunge, exerts anti-inflammatory properties by impeding the properties by targeting the PI3K/AKT/mTOR signaling pathway [71] (Fig. 4).

2.5. The high mobility group box-1 protein (HMGB1) signaling pathway

HMGB1 is a member of the chromatin structural protein family and plays a vital role in DNA binding and regulation of gene expression within the nucleus. As a critical cytokine, it mediates responses to infection, injury, and inflammation [72]. HMGB1 is a member of the chromatin structural protein family and plays a vital role in DNA binding and regulation of gene expression within the nucleus. As a critical cytokine, it mediates responses to infection, injury, and inflammation [73]. Upon cellular damage or infection, extracellularly released HMGB1 binds to specific receptors like the advanced glycosylation end product-specific receptor and TLR4 on immune cells. This interaction triggers immune cell activation and inflammatory responses [74]. HMGB1 is recognized as a key proinflammatory factor, orchestrating the migration and activation of immune cells and amplifying the inflammatory response, thereby playing a pivotal role in immune response and tissue repair [75].

HMGB1 is secreted extracellularly in response to inflammatory stimuli and is involved in various inflammatory diseases, including periodontitis [76]. The release of HMGB1 has been detected in the gingival sulcus fluid of patients with periodontitis, and TNF-α has been observed to increase HMGB1 secretion in gingival epithelial cells [77,78]. Additionally, in periodontal ligament fibroblasts, LPS and IL-1β have been discovered to boost HMGB1 secretion, and they also elevate the number of HMGB1-positive cells in a rat model of periodontitis [79]. Another study indicated that HMGB1 secretion in periodontal tissues is stimulated by infection, and anti-HMGB1 antibodies can reduce the secretion of various inflammatory cytokines, thus inhibiting the progression of periodontitis [80]. An investigation into 26 differentially expressed periodontitis-related genes identified a strong positive correlation between HMGB1 and SR-associated CTD-related factor 11 [81]. In conclusion, HMGB1 is significantly associated with and essential to the progression of periodontitis.

GL has been demonstrated to inhibit the translocation of HMGB1 from the nucleus to the cytoplasm and reduce the expression and synthesis of HMGB1. ATG effectively suppresses the HMGB1 signaling pathway by diminishing HMGB1 expression, thereby exerting an anti-inflammatory effect [82,83] (Fig. 5).

2.6. The Keap1-Nrf2 signaling pathway

The Keap1-Nrf2 signaling pathway is crucial in the cellular response to oxidative stress. It plays a vital role in protecting cells from oxidative damage and maintaining homeostasis through redox processes. Keap1 is composed of four domains: BTB

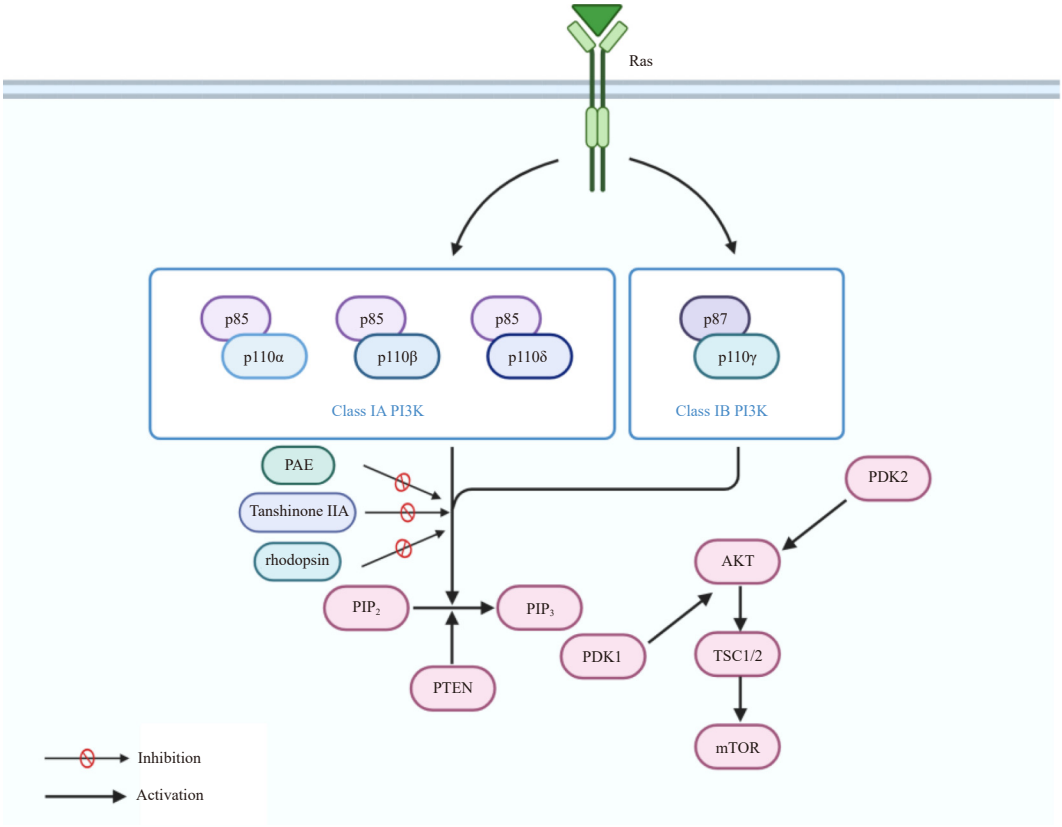

Fig. 4 Chinese medicinal compounds demonstrate anti-inflammatory properties by targeting the phosphatidylinositol-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathway. Paeoniflorin (PAE), rhodopsin, and tanshinone IIA effectively inhibit this signaling pathway, resulting in a reduction of inflammation.

(amino acids 61–179), IVR (amino acids 180–314), DGR (amino acids 315–598), and CTR (amino acids 599–624), with the DGR and CTR domains collectively referred to as the DC domain [84]. Nrf2, a 605-amino acid transcription factor, includes seven functional domains (Neh1-7). The Neh1 domain enables Nrf2 to bind to antioxidant response elements (ARE) [85]. Neh2 serves as the binding site for Keap1, which forms homodimers upon binding [86]. The Neh3 domain's *C*-terminal interacts with the transcription coactivator CHD6, while Neh4 and Neh5 function as transcriptional activation domains that enhance NRF2 transcription and amplify NRF2-targeted ARE gene expression [87]. The Neh7 domain interacts with retinoic acid X receptor alpha, inhibiting Nrf2 [88]. The BTB domain facilitates Keap1 dimerization, allowing ubiquitin attachment to a specific lysine in Nrf2's Neh2 domain. The IVR domain promotes Nrf2 ubiquitination *via* interaction with Cul3, and the DC domain physically associates with Nrf2's Neh2 domain [84]. Under normal conditions, most Nrf2 is bound to Keap1; however, during oxidative stress, reactive oxygen species (ROS) stimulate the dissociation of the NRF2-Keap1 interaction in a dose-dependent manner. Newly synthesized Nrf2 then translocates to the nucleus, forming a heterodimer with a small MAF protein [89]. This Nrf2/Maf complex initiates the expression of ARE-dependent genes encoding antioxidant and cytoprotective proteins, thereby exerting anti-inflammatory, antioxidant, detoxifica-

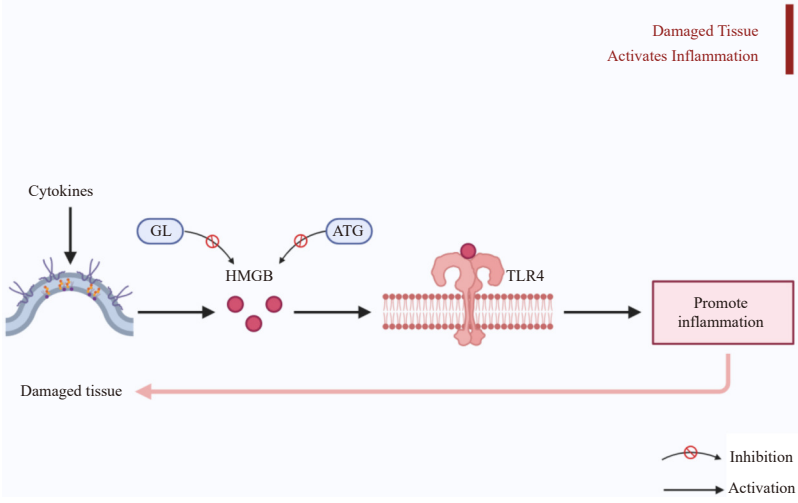

Fig. 5 Chinese medicines achieve anti-inflammatory effects by suppressing the high mobility group box-1 protein (HMGB1) signaling pathway. Glycyrrhizin (GL) impedes the translocation of HMGB1 from the nucleus to the cytoplasm, as well as its expression and synthesis, thereby inhibiting the HMGB1 signaling pathway. Forsythoside A (FSA) curtails the upregulation and release of HMGB1, effectively inhibiting the HMGB1 signaling pathway.

tion, and autophagy effects.

The Kelch-like ECH-associated protein 1/Nrf2 (Keap1/Nrf2) signaling pathway primarily regulates the expression of anti-inflammatory genes, mitigating inflammation progression, and indirectly influencing associated NF-κB and MAPK signaling pathways along with other inflammatory control networks *via* negative regulation [89,90]. Research demonstrates that a novel *N*-acetyl-L-cysteine-derived red fluorescent carbonized polymer dot can regulate REDOX homeostasis in the periodontitis microenvironment and promote bone formation by modulating the Keap1/Nrf2 signaling pathway [91]. Additional studies have revealed significant inhibition of Nrf2 regulatory proteins in periodontal tissues of patients with advanced periodontitis, alongside a marked increase in inflammatory proteins. Overexpression of NRF2 and puerarin has been shown to significantly reduce osteoclast numbers during periodontitis progression [92]. Furthermore, activation of the KEAP1-NRF2 signaling pathway has been found to delay aging in PDLSC [93]. Collectively, these findings suggest a critical role of the Keap1/Nrf2 signaling pathway in the onset and progression of periodontitis.

Another study determined that Licochalcone B (LCB) exhibits its anti-inflammatory properties by counteracting the inhibitory impact of ROS on the Keap1/Nrf2 signaling pathway, thereby reactivating it [93,94]. Furthermore, baicalin has been demonstrated to mitigate oxidative stress and exert anti-inflammatory effects by diminishing ROS's inhibitory action on the Keap1/Nrf2 signaling pathway and enhancing its expression, thus alleviating fatty liver disease associated with metabolic dysfunction [95] (Fig. 6).

2.7. The AhR signaling pathway

The AhR is a basic helix-loop-helix (bHLH) Per-AhR nuclear transporters (ARNT)-Sim (PAS) homologous domain protein belonging to the bHLH transcription factor superfamily. The AhR signaling pathway encompasses both genomic and non-genomic signaling pathways. In the genomic signaling pathway, the functional domains of the AhR protein include the bHLH domain, PAS domain, and a glutamate-rich domain [96]. The bHLH domain facilitates AhR binding to target gene promoters and protein dimerization, while the PAS domain aids in forming protein complexes with ARNT and binding ligands. The *C*-terminal, a glutamate-rich region, is essential for recruitment and transcriptional activation [97]. The AhR repressor (AHRR) protein, a crucial target gene of activation, acts as an AhR suppressor with a structure similar to AhR [98]. In AhR and ARNT, activation 97. The AhR repressor (AHRR) serves as a transinhibitory domain, inhibiting AhR activity by binding to ARNT and forming AHRR-ARNT complexes. In the nucleus, activation of the AHRR-ARNT complex involves the hydroxylases CYP1A1, CYP1B1, and AHRR, regulating the transcription of AHR-dependent genes [99]. The non-genomic signaling pathway of AhR, triggered by TCDD binding, leads to calcium influx into the cytoplasm, initiating PKCα activation, phospholipase A2 phosphorylation, and arachidonic acid production [100]. Concurrently, TCDD binding releases tyrosine kinase Src from the AhR complex [101], activating Src along with Focal Adhesion Kinase (FAK) [102]. Furthermore, Src activation stimulates the MAPK signaling pathway, culminating in the transcription of COX-2 and ultimately promoting inflammation [103].

The AhR signaling pathway plays a critical role in the onset and progression of various inflammatory diseases. Research has demonstrated that vitamin D3 can significantly mitigate alveolar bone loss in mouse models of periodontitis and suppress inflammation *via* the AhR/NF-κB/NLRP3 signaling pathway [104]. Additionally, Porphyromonas gingivalis is reported to exacerbate the inflammatory response in periodontitis by suppressing the AhR signaling pathway [105]. The AhR-ligand axis is also implicated in inflammatory diseases and bone homeostasis, with findings indicating that inhibition of the AhR signaling pathway in periodontitis can be counteracted by the AhR ligand 6-formylindolo (3,2-b) carbazole, which exhibits preventive effects against periodontitis [106]. Collectively, these studies underscore the significant association of AhR with the development and management of periodontitis.

Baicalein is known to modulate the anti-inflammatory actions of the AhR/interleukin-22 (IL-22) pathway and ameliorate colitis by enhancing the expression of cytochrome P450 1A1 (CYP1A1), a downstream target protein of AhR, and facilitating AhR nuclear translocation [107]. BBR regulates the expression of

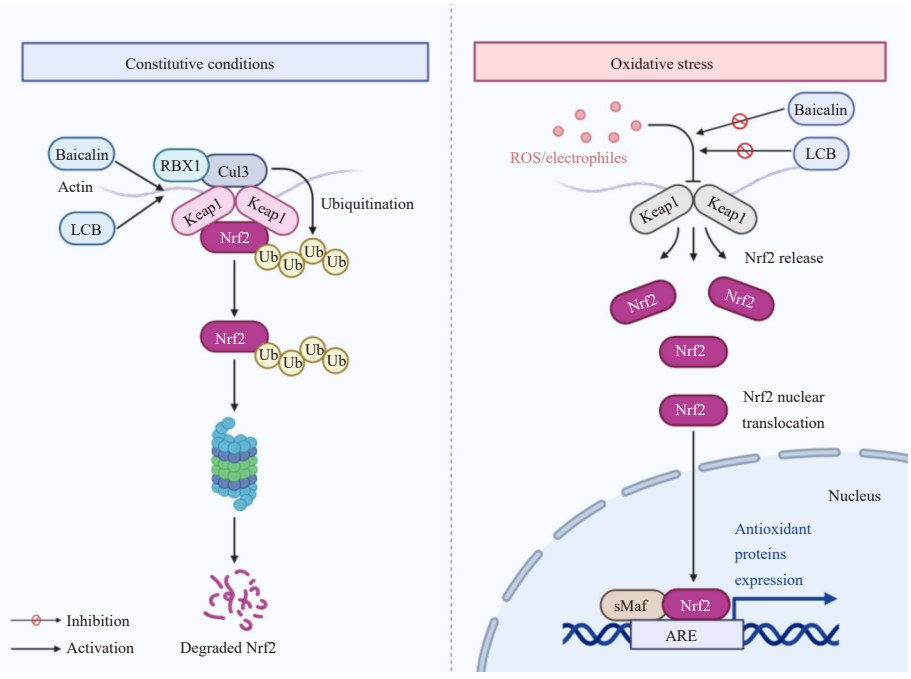

Fig. 6 Chinese medicines, such as licochalcone B (LCB) and baicalin, achieve anti-inflammatory effects by activating the kelch-like ECH-associated protein 1/nuclear factor erythroid 2-related factor 2 (Keap1/Nrf2) signaling pathway. These compounds counteract the inhibitory effects of reactive oxygen species (ROS) on this signaling pathway, thereby reactivating it.

CYP1A1 through intestinal flora-related tryptophan metabolites, activating the AhR signaling pathway to treat colitis in rats, reduce inflammation, and restore damaged intestinal barrier function [108] (Fig. 7).

3. Anti-inflammatory Effects of Natural Products in Chinese Medicine

3.1. Alkaloids

Alkaloids, a class of nitrogenous organic compounds with significant biological activity, are crucial active ingredients in Chinese medicine. These compounds play a vital role in regulating metabolic processes within the body. Furthermore, alkaloids exhibit antibacterial and anti-inflammatory properties, promote blood circulation, eliminate blood stasis, and function as diuretics, thereby reducing swelling (Table 1).

3.1.1. Berberine

BBR can be isolated from the root of *Coptis chinensis* Franch, a prominent natural benzylisoquinoline alkaloid in this Chinese medicinal plant. Clinically, BBR hydrochloride is extensively used to treat gastroenteritis, bacillary dysentery, hyperlipidemia, diabetes mellitus, cancer, and inflammatory diseases [111]. BBR's primary effects in inflammatory conditions are as follows: (a) Inhibition of cytokine generation: BBR markedly diminishes the LPS-triggered secretion of proinflammatory agents like TNF-α, IL-1β, IL-6, and monocyte chemoattractant protein-1 (MCP-1), alongside genes related to endoplasmic reticulum stress such as CCAAT/enhancer-binding protein homologous protein (C/EBP homologous protein), COX-2, inducible nitric oxide synthase (iNOS), transforming growth factor-beta 1 (TGF-β1), connective tissue growth factor, intercellular adhesion molecule-1 (ICAM-1), activating transcription factor 4 (ATF4), and X-box binding protein 1 (XBP1) [109, 110, 112]. (b) Inflammatory signaling pathway regulation. BBR inhibits the Toll-like receptor 4 (TLR4)-myeloid differentiation primary response 88 (MyD88)-NF-κB signaling pathway by downregulating TLR4 and MyD88 protein expression, inhibiting inhibitor of kappa B alpha (I-κBα) phosphorylation, and preventing the translocation of NF-κB p65 from the cytoplasm to the nucleus [113]. Additionally, BBR regulates the Wnt/beta-catenin

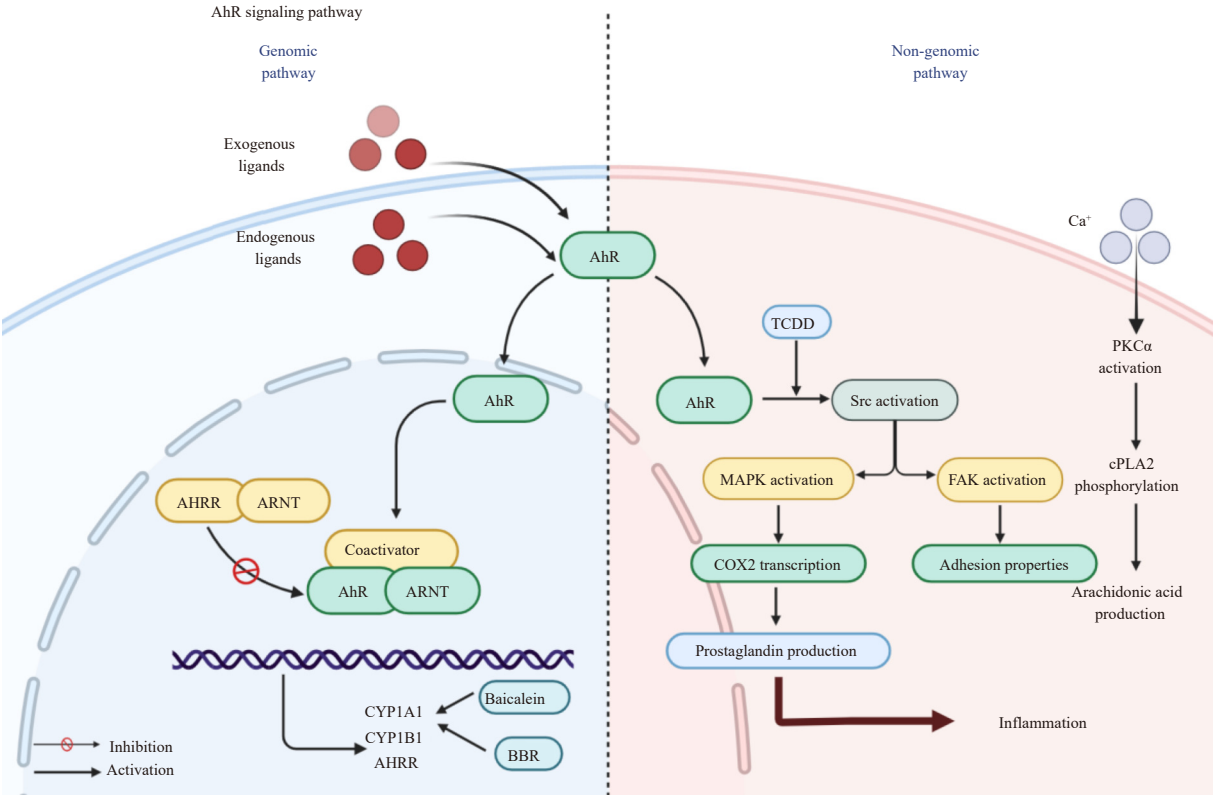

Fig. 7 Chinese medicines like baicalein and berberine (BBR) achieve anti-inflammatory effects by upregulating the expression of the downstream target protein cytochrome p450 family 1 subfamily A member 1 (CYP1A1) and activating the aryl hydrocarbon receptor (AhR) signaling pathway.

Table 1 Construction and anti-inflammatory mechanisms of alkaloids

Alkaloids	Models	Mechanisms of action	Ref.
Berberine	Mice RAW264.7, IPECs, and hepatocytes Rabbit CL model DSS-induced colitis mice Dry eye mice	↓ TNF-α, IL-1β, IL-6, MCP-1 ↓ C/EBP, COX-2, iNOS, TGF-β1, ICAM-1, ATF4, XBP1 ↓ TLR4, MyD88, NF-κB, PI3K, AKT, MAPK	109–115
Matrine	Intestinal epithelial cell Heart transplantation mice ALI and SAP Mice Sepsis-induced myocardial injury mice AIN mice	↓ IL-2, IL-6, IL-1β, TNF-α, NO ↓ p-JAK2, p-JAK2, p-STAT3, p-STAT ↓ NF-κB, MAPK, JAK/STAT ↑ ERK1/2, UCP2/SIRT3/PGC1α	116–122
Leonurine	TNF-α-HUVEC H9c2 cells and rat cardiomyocytes OA mice CAR-induced pleurisy-mice CIA mice	↓ IL-6, NO, pge2, TNF-α, iNOS, COX-2, ROS, MMP-3, MMP-13, ADAMTS ↓ MAPK, NF-κB, TXNIP/NLRP3	123–128
Tetrandrine	Murine and human macrophages Pulmonary inflammation and fibrosis mice TBI mice AS mice	↓ TNF-α, IL-1β, IL-6, MCP-1, TGF-β1, COX-2 ↓ IRE1α/JNK/C/EBP, STING/TBK1/NF-κB, ERK, STAT3	129–134
Peiminine	RAW264.7 and Osteosarcoma cells UC mice Male BALB/c mice COPD rats LPS-induced mastitis mice	↓ IL-1β, IL-6, IL-17, TNF-α, iNOS, COX-2 ↓AKT/NF-κB, ERK1/2, p38 MAPK	135–142

signaling pathway in ulcerative colitis [114] and has demonstrated efficacy in dry eye by inhibiting the PI3K/AKT/NF-κB and MAPK signaling pathways [115].

3.1.2. Matrine

Matrine, an alkaloid that can be isolated from *Sophora flavescens* Aiton roots, plants, and fruits, has been a longstanding component of Chinese medicinal practices for over two millennia. It exhibits diverse pharmacological effects, including anticancer, anti-inflammatory, antibacterial, and detoxification properties [119]. Its anti-inflammatory actions are multifaceted, including: (a) Suppression of cytokine production. Matrine significantly reduces proinflammatory factors like IL-2, IL-6, IL-1β, TNF-α, myeloperoxidase activity, and nitric oxide production while also suppressing the expression of phosphorylated JAK2/JAK2 and phosphorylated STAT3/STAT [116]. (b) Regulation of inflammatory signaling pathways. Matrine attenuates inflammation by downregulating the NF-κB signaling pathway and upregulating the ERK1/2 signaling pathway [117] and by activating the UCP2/SIRT3/PGC1α signaling pathway, reducing iron accumulation and reactive oxygen species generation in acute lung injury [118]. It is also suggested that matrine modulates inflammation through the PI3K/AKT signaling pathway [120] and by regulating the MAPK and JAK/STAT signaling pathways [121]. (c) Modulation of immune cell populations. Matrine normalizes the regulatory T cell to Th17 cell ratio and reduces the levels of IL-6, IL-10, TGF-β, and Rorγt [122].

3.1.3. Leonurine

Leonurine, a unique alkaloid isolated from the leaves of *Leonurus japonicus* Houtt, exhibits a range of pharmacological effects. Beyond its traditional roles in uterine contraction and sedation, leonurine also offers cardiovascular and neuroprotective properties and demonstrates anticancer, anti-inflammatory, and antiplatelet aggregation capabilities [123]. Regarding inflammatory diseases, leonurine's effects include: (a) Inhibition of cytokine production. It significantly suppresses IL-1β-induced generation of IL-6, nitric oxide, PGE_2, TNF-α, and the expression of iNOS, COX-2, reactive oxygen species, MMP-3, MMP-13, and ADAMTS. Furthermore, leonurine effectively inhibits IL-1β-stimulated activation of NF-κB [124, 125]. (b) Regulation of inflammatory signaling pathways. Leonurine inhibits the MAPK and NF-κB signaling pathways [126] and modulates the TXNIP/NLRP3 signaling pathway [127]. It also regulates the Hippo signaling pathway *via* the miR-21/YOD1/YAP axis, thereby alleviating joint inflammation in a CIA rat model [128].

3.1.4. Tetrandrine

Tetrandrine, a bisbenzylisoquinoline alkaloid that can be isolated from the roots of *Stephania tetrandra* S. Moore, possesses a wide range of pharmacological activities, including anti-inflammatory, anticancer, antimicrobial, antidiabetic, antioxidant, immunosuppressive, cardiovascular, and calcium channel blocking properties [129]: Specifically, its anti-inflammatory actions include: (a) Reduction of cytokine production: Tetrandrine significantly decreases the levels of inflammatory factors and fibrosis markers such as TNF-α, IL-1β, IL-6, MCP-1, TGF-β1, hydroxyproline, interferon-gamma-γ (IFN-γ), COX-2, and collagen type I [130, 131]. (b) Regulation of inflammatory signaling pathways: Tetrandrine modulates the IRE1α/JNK/C/EBP homologous protein signaling pathway [132], reduces macrophage inflammation, and alleviates atherosclerosis by targeting the STING/TBK1/NF-κB, ERK, and STAT3 signaling pathways[133, 134].

3.1.5. Peiminine

Peiminine, an isosterol alkaloid that can be isolated from *Fritillaria thunbergii*, has diverse effects, including antitussive, asthmatic, anti-inflammatory, antitumor, cough reduction, and antioxidant properties [135-138]. The effects of peiminine on inflammatory diseases include the following: (a) It inhibits cytokine production, significantly reducing inflammatory factors (IL-1β, IL-6, IL-17, and TNF-α) in acute lung injury in mice [139] and reducing iNOS and COX-2 gene expression in inflamed mice [140]. (b) It modulates inflammatory signaling pathways, inhibiting the phosphorylation of the AKT/NF-κB, ERK1/2, and p38 MAPK signaling pathways [141], and regulating the EGFR/PI3K/mTOR/MAPK signaling pathwayway [140, 142].

3.2. Flavonoids

Flavonoids, a class of yellow pigments derived from 2-phenylchromenone, are ubiquitous in plants and are recognized as valuable secondary plant metabolites possessing significant medicinal properties [143]. They demonstrate anti-inflammatory effects, provide liver protection and detoxification, exhibit antifungal properties, and are utilized in the treatment of acute and chronic hepatitis, as well as cirrhosis. Furthermore, flavonoids offer anti-free radicals and antioxidant benefits [144]. Additionally, flavonoids play a crucial role in the inhibition and management of cardiovascular diseases [145] (Table 2).

3.2.1. Glycyrrhizin (GL)

GL, an active natural product isolated from the roots and stems of *Glycyrrhiza glabra*, possesses anti-inflammatory, antiviral, antiallergic, and immunomodulatory effects [146]. Extensive research has been conducted on its molecular mechanisms in inflammatory diseases. GL's primary anti-inflammatory actions include: (a) Inhibition of cytokine production. GL significantly reduces the levels of NO, PGE_2, iNOS, COX-2, TNF-α, IL-1β, IL-6, matrix metalloproteinase-3 (MMP3), matrix metalloproteinase-13 (MMP13), and C-telopeptide of type II collagen, as well as inhibiting a disintegrin and metalloproteinase with thrombospondin-5 production [147, 148]. (b) Inhibition of inflammatory signaling pathways. GL suppresses the release of HMGB1 and the HMGB1-receptor for advanced glycation end-products (RAGE)/TLR4/NF-κB/AKT signaling pathway in inflammatory states [149] and inhibits the PI3K/mTOR and p38MAPK signaling pathways [150, 151].

3.2.2. Curcumin

Curcumin, a key component in *Curcuma longa*, is renowned for its anti-inflammatory, antioxidant, and antibacterial properties. This phytochemical has been extensively utilized in traditional herbal medicine in India and China, demonstrating efficacy in treating inflammatory diseases [152, 153]. Curcumin's anti-inflammatory mechanisms encompass several aspects: (a) Reduction of proinflammatory mediators, whereby curcumin decreases the expression of IL-1β, IL-1, IL-6, IL-8, IL-17, IL-27, TNF-α, iNOS, NO,

Table 2 Construction and anti-inflammatory mechanisms of flavonoids

Flavonoids	Models	Mechanisms of action	Ref.
Glycyrrhizin	OA mice TMJOA rat ALI mice I/R-induced renal injury in mice	↓ NO, PGE_2, iNOS, COX-2, TNF-α, IL-1β, IL-6, MMP3 and MMP13 ↓ HMGB1-RAGE/TLR4-NF-κB/AKT	146–151
Curcumin	Neonatal neurons cells RAW264.7 cells Male C57BL/6 mice T1DM and T2DM mice	↓ IL-1β, IL-1, IL-6, IL-8, IL-17, IL-27, TNF-α, iNOS, NO and COX-2 ↓ JAK/STAT, NF-κB, Wnt/JNK1 and PI3K/AKT	152–158
Baicalin	H9 cells Fibroblasts ALI mice Pulmonary fibrosis rats SD rat I/R	↓ IL-6, IL-1β, TNF-α, TGF-β, TLR4, MCP-1 and MyD88 ↓ JAK/STAT, Nrf2, MAPK, TLR4/NF-κB, NLRP3 and PI3K/AKT	159–166
Quercetin	Senescent cell in small and large intestine in mice THP-1 macrophage pyroptosis Old mice Asthmatic mice	↓ IL-6, IL-1β, TNF-α, MCP-1, CXCL1, CXCL2 and CXCL10 ↓ ROS/AMPK and TLR2/Myd88/NF-κB	167–172

and COX-2 [154, 155]. (b) Inhibition of signaling pathways, including the NLRP3 inflammasomes and the JAK/STAT, NF-κB, Wnt/JNK1, and PI3K/AKT pathways [156-158]. (c) Regulation of immune cells, wherein curcumin inhibits Th17 differentiation and promotes Treg/Th17 rebalancing, thereby reducing inflammation [154].

3.2.3. Baicalin

Baicalin, a flavonoid compound isolated from *Scutellaria baicalensis*, is commonly used in traditional Chinese medicine (TCM) and exhibits antibacterial, diuretic, anti-inflammatory, antimetabolic, antispasmodic, and anticancer properties [159]. The effects of baicalin on inflammatory diseases include the following: (a) Reducing proinflammatory mediators. It significantly inhibits the infiltration of inflammatory cells, such as T-cells, T helper cells, neutrophils, and macrophages, and decreases the mRNA levels of cytokines, including IL-6, IL-1β, TNF-α, TGF-β, TLR4, MCP-1, and MyD88 [160, 161]. (b) Inhibiting inflammatory signaling pathways. Baicalin targets the JAK/STAT, Nrf2, MAPK, TLR4/NF-κB, NLRP3, and PI3K/AKT signaling pathways to reduce inflammation [162-166].

3.2.4. Quercetin

Quercetin, a flavonol compound commonly found in the stem bark, leaves, flowers, seeds, buds, and fruits of many plants, predominantly as glycosides, exhibits diverse biological activities. Its pharmacological properties include anti-inflammatory, antiallergic, cardioprotective, analgesic, anticancer, and hypotensive effects [167]. Quercetin's anti-inflammatory action is substantial, and its mechanisms involve: (a) Reducing proinflammatory mediators. It inhibits the expression of IL-6, IL-1β, TNF-α, MCP-1, CXCL1, CXCL2 and CXCL10 in macrophages, which can consequently downregulate Th-2-derived IL-4 [168-170]. (b) Inhibiting inflammatory signaling pathways. Quercetin suppresses the LPS/ATP-induced elevation in TLR2/Myd88 and p-AMPK, thereby inhibiting the ROS/AMPK and TLR2/Myd88/NF-κB signaling pathways to mitigate inflammation [171]. Additionally, it hinders the tumor growth factor-β1/Smad signaling pathway, contributing to its anti-inflammatory role [172].

3.3. Terpenoids

Terpenoids, organic compounds derived from mevalonate with the isoprene unit as their fundamental structural element, represent a significant class of naturally occurring substances crucial in Chinese medicine. They exhibit a diverse array of physiological effects, including expectorant, cough suppressant, anti-inflammatory, antibacterial, and analgesic properties, as detailed in Table 3.

3.3.1. Triptolide

Triptolide, a diterpene epoxide lactone isolated from *Tripterygium Wilfordii*, exhibits a broad spectrum of biological functions. It demonstrates anti-inflammatory, antioxidant, anti-rheumatoid, anti-Alzheimer's, anticancer, and immunosuppressive effects [173]. Triptolide's anti-inflammatory mechanisms include: (a) Downregulating proinflammatory mediators. It reduces LPS-induced production of inflammatory mediators such as COX-2, IL-1β, NF-κB, NLRP3 inflammasome, TNF-α, and TGF-β [174, 175]. (b) Inhibiting inflammatory signaling pathways. Triptolide modulates inflammation by targeting the CARD9/p38 MAPK, Nrf2, NF-κB, AK/STAT, and AKT/mTOR signaling pathways [176-179].

3.3.2. Taraxasterol

Taraxasterol, a bioactive triterpenoid that can be isolated from the *Taraxacum* L. of the Compositae family, offers a range of pharmacological effects, including anti-infective, antiviral, antitumor, and immune system protection [180]. Its anti-inflammatory effects are characterized by: (a) Reducing proinflammatory cytokines. Taraxasterol significantly inhibits LPS-induced cytokines like IL-1β, IL-6, IL-8, TNF-α, prostaglandin E_2 (PGE_2), OPG, RANKL, IFN-γ, NO, MMP-1, and MMP-3. It also blocks NF-κB activation and suppresses NLRP3 inflammasomes by modulating i-κB, IKK, and TAK1 [181-183]. (b) Inhibiting inflammatory signaling pathways. Taraxasterol downregulates TLR2, TLR4, and NF-κB p65, targeting the TLRs/NF-κB signaling pathway and hinders the PI3K/AKT/mTOR signaling pathways [184-186].

3.3.3. Andrographolide

Andrographolide, a diterpenoid lactone compound that can be isolated from the herb *Andrographis paniculata*, exhibits a broad spectrum of therapeutic applications, including expectorant, detoxifying, anti-inflammatory, analgesic, antibacterial, anti-infective, and antidysentery effects, and is recognized as a natural antibiotic drug [187]. The anti-inflammatory actions of andrographolide are characterized by: (a) Reducing proinflammatory mediators. It inhibits the production of cytokines such as IL-6, IL-1β, Nrf2, MCP-1, ROS, and TNF-α and decreases the levels of p-AKT, p-PI3K, and phosphorylated endothelial nitric oxide synthase [188, 189]. (b) Regulating inflammatory signaling pathways. Andrographolide modulates the JAK/PI3K/AKT, NF-κB, MAPK, Nrf2/HO-1, ROS-JNK, and JAK/STAT signaling pathways, leading to anti-inflammatory and antiapoptotic effects [190-192].

Table 3 Construction and anti-inflammatory mechanisms of terpenoids

Terpenoids	Models	Mechanisms of action	Ref.
Triptolide	cSCC cells CIA rat Obese db/db mice TP-treated IgAN mice DHCA rat Colorectal cancer mice	↓ COX-2, IL-1β, NF-κB, NLRP3, TNF-α, and TGF-β ↓CARD9/p38 MAPK, Nrf2, NF-κB, JAK/STAT and AKT/mTOR	173–179
Taraxasterol	PCa cells Macrophages CIA mice FCA- induced-rat Endotoxic shock mice Con A-induced acute hepatic injury in mice	↓ IL-1β, IL-6, IL-8, TNF-α, PGE_2, OPG, RANKL, IFN-γ, NO, MMP-1 and MMP-3 ↓ IKK, TAK1, TLR2 and TLR4 ↓ TLRs/NF-κB, PI3K/AKT and mTOR	180–186
Andrographolide	Alveolar type II epithelial cells LAD ligation mice Litopenaeus vannamei	↓ IL-6, IL-1β, Nrf2, MCP-1, ROS and TNF-α ↓ p-AKT and p-PI3K ↓ JAK/PI3K/AKT, NF-κB, MAPK, Nrf2/HO-1, ROS-JNK and JAK/STAT	187–192
Artemisinin	Female C57BL/6 mice HFD-fed ApoE mice PF rat RA rat	↓ TGF-β, IL-4, IL-1β, IL-6, IL-10, TNF-α, TLR2, CCL2, CCL20, CXCL2 and CXCL10 ↓ JAK2-STAT3 and PI3K/AKT/mTOR	193–198

3.3.4. Artemisinin

Artemisinin, a sesquiterpene lactone isolated from *Artemisia annua*, is well-known for its antimalarial properties and possesses various pharmacological effects, including anti-inflammatory, antitumor, pulmonary hypertension, antidiabetic, embryotoxic, antifungal, immunomodulatory, antiviral, anti-pulmonary fibrosis, antibacterial, and cardiovascular benefits [193]. Artemisinin's anti-inflammatory mechanisms include: (a) Regulating proinflammatory mediators, such as modulating the expression of TGF-β, IL-4, IL-1β, IL-6, IL-10, TNF-α, TLR2, CCL2, CCL20, CXCL2, and CXCL10 [194, 195]. (b) Inhibiting inflammatory signaling pathways, including downregulating the NF-κB/NLRP3 signaling pathway by blocking the activation of the NLRP3 inflammasome and NF-κB in renal epithelial cells, thereby offering anti-inflammatory effects [196]. Additionally, it suppresses the JAK2-STAT3 and PI3K/AKT/mTOR signaling pathways [197, 198].

3.4. Lignans

Lignans, natural compounds derived from phenylpropanoid monomers in plants, constitute a class of phytoestrogens renowned for their anti-inflammatory, anticancer, and antioxidant properties (Table 4).

3.4.1. Arctigenin (ATG)

ATG, a lignan-like compound isolated from *Arctium lappa*, demonstrates a broad spectrum of pharmacological properties, including antioxidant, immunomodulatory, antitumor, and anti-leukemic effects, with particularly notable anti-inflammatory actions [30]. The effects of ATG in inflammatory diseases include the following: (a) Reduces proinflammatory mediators by decreasing inflammatory cytokines such as IL-6, IL-1β, IL-8, PGE_2, MCP-1, TNF-α, and TGF-β [199, 200]. (b) Inhibition of inflammatory signaling pathways. ATG blocks LPS-induced phosphorylation of PI3K, AKT, and IKKβ, as well as p-PI3K antibody binding and NF-κB p65 nuclear translocation in macrophages, thereby preventing the PI3K/AKT signaling pathway [31]. ATG also counteracts Toxoplasma gondii-induced HMGB1/TLR4/NF-κB signaling pathway activation [201] and modulates the AMPK, PPAR-γ/ROR-γt, MAPK, HO-1, and iNOS signaling pathways [33, 202].

3.4.2. Magnolol

Magnolol, an active compound extracted from *Magnolia officinalis* Cortex, exhibits specific and prolonged muscle relaxant properties as well as potent antimicrobial effects, including the inhibition of platelet aggregation. Additionally, it possesses various pharmacological attributes, such as anti-inflammatory, antibacterial, antipathogenic, antiulcer, antioxidant, and antitumor activities, and can inhibit morphine withdrawal response [203]. Magnolol's impact on inflammatory diseases includes: (a) Reducing proinflammatory mediators. Magnolol upregulates Nrf2 and HO-1, while downregulating NLRP3, caspase-1 p20, IL-1β, IL-4, IL-6, IL-10, iNOS, TNF-α, and COX-2 in mouse skin. Topical application of Magnolol effectively blocks the transcriptional activation of iNOS and COX-2 [204, 205]. (b) Regulating inflammatory signaling pathways. Magnolol downregulates p-JNK and p-P38, inhibits the expression of p-κBα and p-P65 in the NF-κB signaling pathway, and modulates the MAPK and NF-κB signaling pathways for immune regulation [206]. Furthermore, Magnolol inhibits the JAK2/STAT3 and TLR2 signaling pathways [207, 208].

3.4.3. Schisandrin B

Schisandrin B, a primary biphenyl cyclooctene lignan that can be isolated from *Schisandra chinensis*, exhibits anticancer and anti-inflammatory properties [209, 210]. Its anti-inflammatory actions include: (a) Reducing proinflammatory mediators. Schisandrin B mitigates the upregulation of IL-6, MMP3, MMP13, iNOS, and the downregulation of type II collagen, aggrecan, and SRY-box transcription factor 9 (SOX9) induced by IL-1β. Furthermore, it markedly diminishes the phosphorylation of the p65 subunit, its nuclear translocation, and the activation of MAPKs in chondrocytes from rats, triggered by IL-1β [211]. Additionally, it reduces inflammatory markers such as IL-1β, TNF-α, and ROS [212]. (b) Regulating inflammatory signaling pathways. Schisandrin B inhibits the NLRP3 inflammasomes *in vivo* and *in vitro* in colitis models and suppresses the phosphorylation of JNK (p-JNK) and p38 (p-P38) in the NF-κB signaling pathway, ultimately reducing inflammation [213]. It also targets the NLRP3 signaling pathway [214].

3.5. Others

Additional natural products utilized in TCM are summarized in Table 5.

3.5.1. FSA

Forsythia suspensa, a plant species, contains a phenylethanol glycoside compound known as FSA, which demonstrates antibacterial, antiviral, antioxidant, anti-infective, and antipyretic (fever-reducing) properties [215]. FSA's role in inflammatory diseases involves the following mechanisms: (a) Reducing proinflammatory mediators: FSA attenuates the levels of IL-6, IL-1β, and TNF-α in mouse kidney cells, and decreases the expression of COX-2 and iNOS. It also inactivates phosphorylated ERKs (p-ERKs), phosphorylated p38MAPK (p-p38MAPK), and phosphorylated JNK (p-JNK) while regulating the expression of monocyte chemoattractant protein-1 (MCP-1) and IL-10 [216, 217]. (b) Regulating inflammatory signaling pathways: FSA mitigates the LPS-induced inhibition of mammary alveolar cell proliferation, reduces the expression of

Table 4 Construction and anti-inflammatory mechanisms of lignans

Lignans	Models	Mechanisms of action	Ref.
Arctigenin	Murine liver cell line NCTC-1469 cells Arctigenin-treated mice	↓ IL-6, IL-1β, IL-8, PGE_2, MCP-1, TNF-α and TGF-β ↓ PI3K, AKT, IKKβ and p-PI3K AMPK, PPAR-γ/ROR-γt, MAPK, HO-1 and iNOS ↓ PI3K/AKT and HMGB1/TLR4/NF-κB	199–202
Magnolol	CUMS microglia U937 cells RAW264.7 cells Salt-sensitive hypertension mice C57BL/6 mice TPA-induced-mice	↓ Nrf2, HO-1, NLRP3, IL-1β, IL-4, IL-6, IL-10, iNOS, TNF-α and COX-2 ↓ JAK2/STAT3 and TLR2	203–208
Schisandrin B	Sch B- induced-rat Type 1 and type 2 diabetic mice UC mice Sprague-Dawley rats	↓ IL-6, MMP3, MMP13, iNOS, IL-1β, TNF-α and ROS ↓ p-JNK and p-P38 ↓NF-κB and NLRP3	209–214

Table 5 Construction and anti-inflammatory mechanisms of others

Compounds	Models	Mechanisms of action	Ref.
Forsythoside A	MPC-5 podocytes RAW 264.7 cells LPS-induced- MAC-T cells	↓ IL-6, IL-1β, IL-10, TNF-α, iNOS, COX-2, p-ERK, p-p38, p-JNK and MCP-1 ↓ NF-κB, MAPK, JAK/STAT, Nrf2, RLR, TRAF, TLR7, and PPAR-γ/RXR-α	215–220
Osthole	ES2 and OV90 ovarian cancer cells Intestinal Caco-2 cell Collagen-induced arthritis rat acetic acid and formalin-induced-mice carotid artery balloon injury rat Prg-IgAN mice KOA rat	↓ COX-2, IL-1β, IL-6, IL-8, iNOS, MMP-1, MMP-3, MMP-13 and TNF-α ↓ NLRP3, HMGB1, NF-κB, AMPK/ULK1 and TGF-β1/Smad2	221-230

inflammatory factor mRNAs, and inhibits the AMPK/mTOR/UNC-51-like kinase 1 (ULK1) signaling pathway, thereby exerting anti-inflammatory and protective effects [218]. Additionally, FSA targets various signaling pathways, including NF-κB, MAPKs, JAK/STAT, Nrf2, retinoic acid-inducible gene-I (RLR), tumor necrosis factor receptor-associated factors (TRAFs), TLR7, and peroxisome proliferator-activated receptor-gamma/retinoid X receptor-alpha (PPAR-γ/RXR-α) [219, 220].

3.5.2. Osthole

Osthole, a coumarin compound derived from *Cnidium monnieri*, possesses anti-inflammatory, hypotensive, broad-spectrum antimicrobial, and anticancer properties [221-223]. The anti-inflammatory actions of osthole include: (a) Reducing proinflammatory mediators, as it diminishes the secretion of cytokines such as COX-2, IL-1β, IL-6, IL-8, iNOS, MMP-1, MMP-3, MMP-13, and TNF-α during inflammation [224-226]. (b) Regulating inflammatory signaling pathways, effectively downregulating proinflammatory factors like TNF-α, IL-1β, NF-κB (p65), and inhibiting the NLRP3, HMGB1, NF-κB, AMPK/ULK1, and TGF-β1/Smad2 signaling pathways [227-230].

4. Medicinal Plants as Anti-inflammatory Agents Based on Effects on Periodontitis

Inflammation represents a vital immune response catalyzed by cells and inflammatory mediators. This response aids in the healing of damaged tissues and preserves tissue homeostasis under pathological conditions. However, as inflammation progresses and inflammatory factors, as well as the JAK/STAT pathway, become dysregulated, the inflammatory response shifts from a defensive mechanism to one that can lead to self-harm.

Periodontitis, a leading cause of tooth loss, poses a significant health challenge globally. Oral bacteria initiate the immune process of periodontitis, but host susceptibility significantly influences the disease's development and severity [231]. The initiation of the immune response to oral bacteria is a key factor in the development of periodontitis, but host susceptibility also substantially influences the disease's progression and severity. Periodontitis arises from localized bacterial accumulation and their byproducts, with the host's immune response playing a central role in the destruction of periodontal tissues, exceeding the impact of plaque alone [4, 232]. Consequently, managing inflammation, in addition to removing irritants, is essential in the treatment of periodontitis.

Current anti-inflammatory treatments for periodontitis predominantly include antibiotics such as metronidazole gel, spiramycin, chlorhexidine film, doxycycline hydrochloride gel, and tinidazole. Although effective, these drugs can lead to side effects like drug resistance and flora imbalances [50, 233, 234]. Given the increasing misuse of antibiotics, there is an urgent need to explore nonantibiotic antimicrobial and anti-inflammatory alternatives for clinical use. Various natural products in Chinese medicine have been utilized effectively, either alone or as adjuncts, in treating periodontitis [235, 236]. A study demonstrated that incorporating the Chinese medicine compound Pudilan into standard periodontitis treatment significantly enhances clinical outcomes, as indicated by improvements in gingival index, plaque index, and probing depth [237]. Baicalin exhibits potent anti-inflammatory activity. Studies suggest baicalin can alleviate the inflammatory response and significantly decrease alveolar bone loss in rats suffering from periodontitis by blocking the TLR2 and TLR4/MyD88/p38 MAPK/NF-κB signaling pathways, making it a promising candidate for periodontitis treatment [238]. Additionally, BBR has been shown to effectively reduce alveolar bone loss and inflammation in rats with periodontitis, likely by suppressing the G protein-coupled estrogen receptor-mediated P38MAPK/NF-κB signaling pathway [239]. Furthermore, sweeteners from Glycyrrhiza glabra significantly inhibited the TNF-α-induced upregulation of HMGB1, IL-6, and IL-1β in human periodontal ligament stem cells, and lowered HMGB1, IL-6, IL-1β, and TNF-α levels in the gingival sulcus fluid of rats with periodontitis. This suggests GL as an effective agent in the treatment of chronic periodontitis [240]. Quercetin has also been observed to reduce alveolar bone loss in mice with periodontitis by activating the NRF2 signaling pathway, improving the antioxidant capabilities of periodontal ligament cells, and mitigating oxidative stress [241].

In summary, the management of inflammation is a critical component in the treatment of periodontitis. The substantial potential of Chinese Medicine for clinical application and further development in the treatment of periodontitis is evident. The collective findings affirm the viability of Chinese medicine in the management of periodontitis.

5. Conclusion and Prospects

Inflammation represents a pivotal factor in the pathogenesis of numerous diseases, necessitating the identification of novel therapeutic targets for drug development. This is equally applicable in the context of periodontitis. Periodontitis, a leading cause of tooth loss, significantly impacts patients' daily diet and facial aesthetics, posing a persistent challenge in healthcare. Currently, treatments for periodontitis largely rely on the use of antibiotics such as metronidazole and chlorhexidine, which often lead to undesirable side effects, including bacterial imbalances and antibiotic resistance.

The conclusions of this paper are: (a) Most herbs reviewed exhibit properties of "clearing heat and removing toxins, reducing inflammation, and relieving pain". (b) The same natural products in Chinese medicine can regulate multiple signaling pathways in periodontitis and inflammatory diseases. (c) Different natural products in Chinese medicine may affect the same signaling pathway.

This paper systematically reviews seven key signaling pathways associated with periodontitis and inflammatory diseases, alongside the therapeutic effects and mechanisms of eighteen

representative natural products in Chinese medicine. The findings demonstrate the significant clinical potential of Chinese medicine for the treatment of periodontitis. This paper draws the following conclusions: (a) The majority of the reviewed herbs possess properties that "clear heat and remove toxins, reduce inflammation, and alleviate pain". (b) The same natural products utilized in Chinese medicine can regulate multiple signaling pathways implicated in periodontitis and inflammatory disorders. (c) Diverse natural products in Chinese medicine may target the same signaling pathway. Natural products derived from Chinese medicine have been extensively utilized in the treatment of inflammatory diseases, though their use is often limited to adjunctive therapy rather than primary treatment compared to conventional chemically synthesized drugs. This limitation can be attributed to several factors: (a) The precise mechanisms underlying the anti-inflammatory effects of natural products in Chinese medicine remain incompletely understood. (b) The majority of research on natural products in Chinese medicine has been confined to the preclinical stage, with a paucity of clinical trial data. (c) Patient acceptance poses a significant challenge to the clinical research of anti-inflammatory natural products in Chinese medicine. To enhance patient acceptance and recognition of Chinese medicine preparations, increased promotion and gathering of robust clinical trial data are necessary.

In conclusion, while some limitations exist in the research of natural products in Chinese medicine, their clinical application and potential in managing conditions such as periodontitis and other inflammatory diseases have been demonstrated. Natural products in Chinese medicine exhibit satisfactory clinical efficacy and safety when compared to conventional chemically synthesized drugs. Herbal remedies are increasingly being viewed as viable alternatives to traditional pharmaceuticals for the treatment of periodontitis and are garnering attention for their potential in managing this and other inflammatory disorders.

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Declaration of competing interest

These authors have no conflict of interest to declare.

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