

## Review Article

# Therapeutic potential of *Lonicera japonica* Thunb. in inflammation: mechanistic insights from molecular targets

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## ABSTRACT

Inflammation is a complex biological response essential for tissue repair in acute settings, yet chronic dysregulation contributes to progressive tissue damage and the pathogenesis of numerous diseases. *Lonicera japonica* Thunb. (honeysuckle), a traditional Chinese medicinal herb renowned for its “heat clearing and detoxifying” properties, exhibits multi-target anti-inflammatory activity through synergistic modulation of inflammatory signaling cascades. This review systematically consolidates current knowledge regarding the anti-inflammatory bioactive components of honeysuckle and provides comprehensive insights into their therapeutic mechanisms. We focus on molecular targets, elucidating how honeysuckle constituents regulate key inflammatory pathways, thus offering a foundation for developing *Lonicera japonica*-based therapeutics against inflammation-driven pathologies. Additionally, we critically evaluate the challenges and limitations in translating these findings into clinical applications.

**Keywords:** *Lonicera japonica* Thunb., inflammation, bioactive compounds, therapeutic targets, molecular mechanisms

## 1. INTRODUCTION

Inflammation is a fundamental pathophysiological response to tissue injury induced by diverse stimuli, including mechanical trauma, ischemia, microbial infection, toxic exposure, and physical insults [1-5]. This intricate biological cascade orchestrates cellular adaptations and immune activation, thereby facilitating tissue repair and regenerative proliferation. However, dysregulated inflammation, resulting from persistent triggers or impaired resolution mechanisms, contributes to chronic inflammation, a well-established pathogenic driver underlying cardiovascular disorders, malignancies, diabetes mellitus, neurodegenerative disorders, and autoimmune syndromes [6].

Contemporary anti-inflammatory pharmacotherapy relies predominantly on steroidal anti-inflammatory drugs and non-steroidal anti-inflammatory drugs. However, the clinical application of both classes is markedly constrained by their adverse effect profiles. Long-term administration of steroidal anti-inflammatory drugs is frequently accompanied by severe systemic

complications, such as immunosuppression and metabolic disturbances, whereas non-steroidal anti-inflammatory drugs are prone to inducing gastrointestinal toxicity, including ulcerogenesis and hemorrhage [7]. In contrast to synthetic single-target drugs, which often interfere with physiology through targeted inhibition, traditional Chinese medicine (TCM) uses a holistic therapeutic strategy that restores homeostasis through multi-component, multi-target modulation, thereby offering gradual physiological interventions with minimal disruption to normal functions [8, 9]. Clinically, TCM has demonstrated efficacy across various diseases. For example, *Cortex Mori* extract has shown efficacy in regulating blood glucose levels, alleviating insulin resistance, ameliorating lipid levels, and decreasing liver injury in patients with diabetes [10]. Recent reviews have further substantiated the therapeutic potential of TCM components in regulating metabolic homeostasis and inflammatory responses. Similarly, *Anemarrhena asphodeloides* polysaccharides have been shown to effectively modulate hepatic lipid metabolism

in hyperthyroid models [11]. Additionally, *Gymnema sylvestre* root protein fractions have shown neuroprotective effects by influencing multiple signaling pathways [12]. Furthermore, Banxia Baizhu Tianma decoction has demonstrated effectiveness in ameliorating critical obesity-related hypertension parameters, including body weight, total cholesterol, and blood pressure, in mouse models [13]. Beyond these findings, *Rhizoma Coptidis* polysaccharides exhibit notable anti-diabetic and antioxidant effects [14]. Collectively, these studies underscore the critical roles of TCM in managing diverse diseases. Notably, its therapeutic potential extends to mitigating inflammation, thus highlighting its promise as a valuable strategy in this field [15, 16].

In recent years, *Lonicera japonica* Thunb. (honeysuckle), a traditional Chinese medicine known for its properties of clearing heat and detoxifying, has gained increasing scientific attention for its anti-inflammatory pharmacological properties and bioactive potential [17]. This perennial species in the Caprifoliaceae family is medicinally used in the form of dried flower buds or unopened flowers. First documented in *Shen Nong's Herbal Classic* (*Shennong Bencao Jing*, c. 200 BCE) as a superior-grade medicinal herb, it has been used to treat various inflammatory diseases in China for millennia. Characterized by a sweet taste and cold nature [18], honeysuckle exhibits heat-clearing and detoxifying, as well as antimicrobial and anti-inflammatory effects; it is clinically applied to manage abscesses, pustules, pharyngitis, erysipelas, dysentery, febrile respiratory infections, and pyrexia [19, 20]. Because of these therapeutic properties, honeysuckle is classified as an herbal antibiotic in traditional pharmacopeias. Consequently, the anti-inflammatory active ingredients of honeysuckle have attracted extensive attention in recent years [21–26].

In contrast to other heat-clearing and anti-inflammatory TCMs, *Taraxacum mongolicum*, primarily through taraxasterol, inhibits the TLR4/MyD88/NF- $\kappa$ B pathway to suppress inflammation and oxidative stress [27]. *Forsythia suspensa*, acting primarily via phillyrin, can inhibit LPS-induced pro-inflammatory reaction and LX2 cell activation through TLR4/MyD88/NF- $\kappa$ B signaling pathway, thereby inhibiting liver fibrosis [28]. Meanwhile, *Scutellaria baicalensis*, through its active component baicalin, regulates JAK2/STAT3 signaling by inhibiting JAK2 and STAT3 phosphorylation in BV2 microglia induced by  $\beta$ -amyloid peptide [29]. Honeysuckle contains multi-component groups (including phenolic acids and flavonoids), which synchronously regulate multiple targets (TLR2/4, NF- $\kappa$ B, and NOD-like receptor family pyrin domain-containing 3 [NLRP3]) in acute and chronic inflammation. The synergy of its components enhances its efficacy, thus highlighting its unique “multi-component-multi-target” advantage. However, this complex, multi-component, multi-target nature, despite contributing to its well-established empirical efficacy, poses a major challenge to comprehensive and systematic elucidation of its precise molecular mechanisms, which currently remain to be fully determined. Honeysuckle

research has evolved from studying crude extracts to elucidating the specific molecular mechanisms of its diverse compounds. Early work has demonstrated general anti-inflammatory effects in animal models (e.g., edema) and frequently implicated the NF- $\kappa$ B pathway [30, 31]. More recent efforts have identified more than 500 compounds, including phenolic acids, flavonoids, iridoids, and polysaccharides [32], and have begun to describe their immune modulation. For example, phenolic acids (e.g., isochlorogenic acids) inhibit NF- $\kappa$ B and antagonize TRPV3, thus decreasing pro-inflammatory cytokines [33, 34]. Flavonoids (e.g., luteolin and quercetin) regulate the PI3K/Akt/NF- $\kappa$ B and JAK-STAT pathways, which are crucial for cytokine storm control [35, 36]. Iridoids and polysaccharides inhibit the NLRP3 inflammasome, a key driver of chronic inflammation [37, 38].

Although major advancements have been made in understanding the anti-inflammatory properties of honeysuckle, its intricate multi-component, multi-target nature requires an integrated perspective. Extensive research has characterized single components and single targets, thus providing foundational insights into specific molecular interactions. However, systematic integration of these findings is required to comprehensively elucidate the holistic pharmacological mechanisms underlying the synergistic effects of honeysuckle. Similarly, establishing a more systematic and quantitative correlation of the TCM theory of heat clearing and detoxification with modern molecular mechanisms, and effectively bridging basic research findings to clinical application, are key areas for comprehensive review.

To enable deeper understanding, this review presents a comprehensive overview based on an integrative approach. First, it constructs a hierarchical multi-component-multi-target-multi-pathway synergistic regulatory network to systematically elucidate the complementary and cooperative relationships among key bioactive compound classes and core inflammatory signaling axes. Second, it establishes a quantitative, mechanism-based connection between TCM theory and modern pharmacology. By correlating heat clearing with measurable biological events, and correlating detoxification with the restoration of immune homeostasis and suppression of pathological pathway overactivation, it seeks to provide rigorous scientific evidence of TCM's holistic therapeutic rational. Third, it integrates cross-disciplinary technologies, leveraging network pharmacology, multi-omics, structural biology, and chemical proteomics, to summarize core synergistic component combinations. This approach is aimed at transforming TCM's empirical synergy into predictable, verifiable, optimizable, and precise synergy.

This review, consolidating molecular targets and mechanisms from a synergistic perspective, is aimed at bridging the gap between traditional use and modern pharmacological understanding. Specifically, this review provides a target-centric overview of the anti-inflammatory actions of *Lonicera japonica* Thunb. and its bioactive constituents. In addition, the direct molecular

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interactions between the components of honeysuckle and specific targets (e.g., TLRs, NF- $\kappa$ B, NLRP3, JAK-STAT, and TRPV3) are cataloged; the implications for novel anti-inflammatory drug development are discussed (Figure 1); and the current research landscape and future directions in this field are critically evaluated.

### 2. OVERVIEW OF THE ACTIVE ANTI-INFLAMMATORY INGREDIENTS IN HONEYSUCKLE

The prominent anti-inflammatory activity of honeysuckle is attributable to its diverse array of bioactive phytochemicals, which modulate multiple inflammatory pathways via distinct pharmacological mechanisms. This section provides a systematic review of the anti-inflammatory constituents of this plant organized into two principal categories: (1) bioactive extracts with demonstrated anti-inflammatory effects (Section 2.1) and (2) characterized chemical compounds exhibiting specific anti-inflammatory properties (Section 2.2).

#### 2.1 Anti-Inflammatory active components in extract of honeysuckle

The anti-inflammatory properties of honeysuckle extracts have been well documented in pharmacological research. Studies have demonstrated the therapeutic efficacy of

these extracts in both acute and chronic inflammatory models. In acute inflammation, honeysuckle extract markedly alleviates xylene-induced edema and exhibits rapid anti-inflammatory effects [39]. Furthermore, its efficacy is comparable to that of dexamethasone in suppressing carrageenan-induced hind paw edema in rats [40]. For chronic inflammation, oral administration of honeysuckle granule tablets exerts measurable inhibition on cotton pellet-induced granulomas [41]. Notably, the route of administration also affects the anti-inflammatory efficacy. Loganin and sweroside showed stronger anti-inflammatory and analgesic activity when parenterally administered, indicating that stronger activities can be anticipated via the intravenous route than the oral [42]. Parenteral administration similarly demonstrates potent inhibition of paw edema induced by protein exudation or carrageenan, thus confirming its broad-spectrum anti-inflammatory potential [43].

**2.1.1 Anti-inflammatory mechanisms of honeysuckle aqueous extract.** The aqueous extract of honeysuckle (HWE) exhibits multi-target anti-inflammatory activity. Experimental evidence from Lei et al. has revealed that HWE effectively suppresses xylene-induced mouse ear edema and decreases acetic acid-triggered peritoneal capillary hyperpermeability, thus confirming its acute

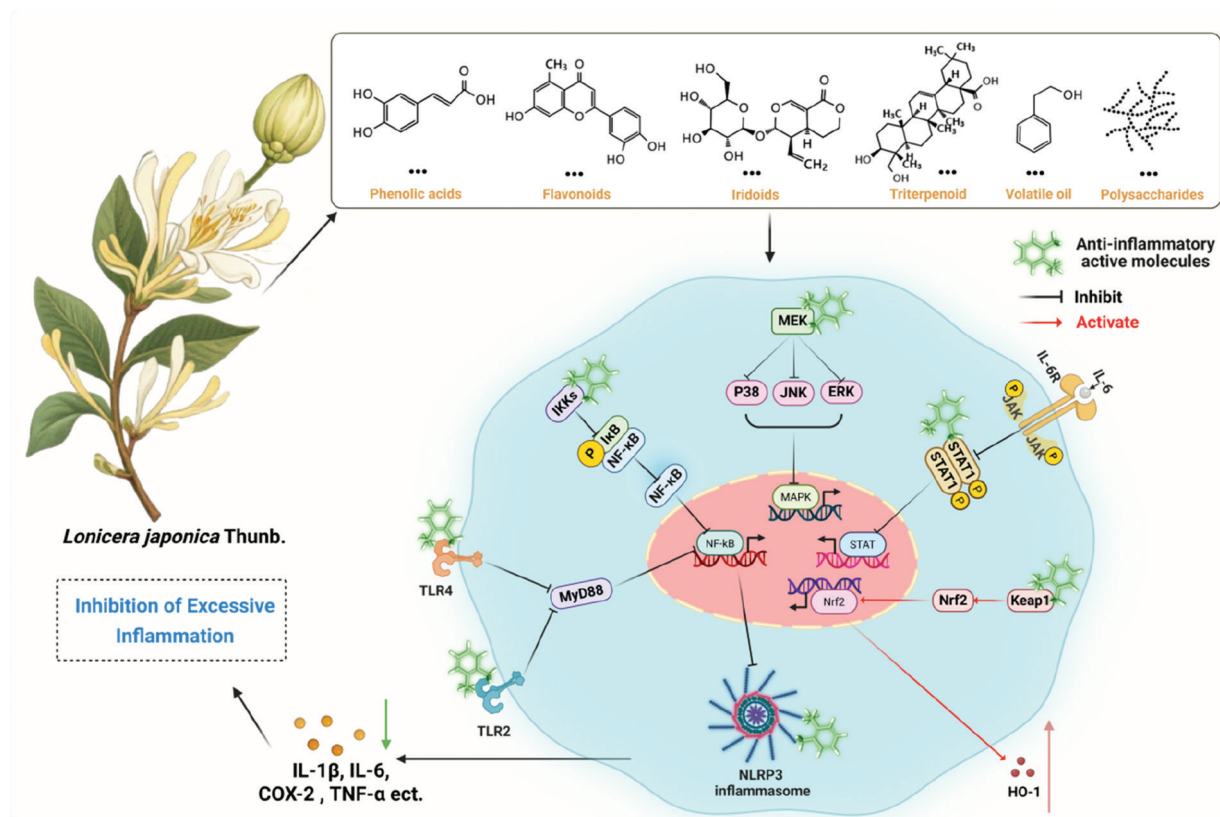


Figure 1 | Multi-target anti-inflammatory mechanisms of bioactive compounds from *Lonicera japonica* Thunb. (honeysuckle). This figure was created with BioRender.com.

anti-inflammatory properties [44]. Independent investigations have corroborated these findings: HWE not only attenuates xylene-induced inflammatory response, but also enhances splenic immune function and decreases serum levels of the pro-inflammatory cytokines interleukin (IL)-6 and tumor necrosis factor (TNF- $\alpha$ ) [45]. In mouse models, topical application of HWE, when administered prophylactically, effectively inhibits paw edema mediated by protease-activated receptor 2 (PAR2), and concurrently suppresses myeloperoxidase activity and TNF- $\alpha$  expression in affected tissues [46].

Mechanistic studies have elucidated the molecular targets of HWE. Xu et al. have demonstrated dual inhibitory effects on both cyclooxygenase (COX) isoforms in A549 cells, including dose-dependent suppression of COX-2 mRNA transcription and protein synthesis [47]. Further research has identified HWE's modulation of inflammatory signaling pathways: specifically, it inhibits the signal transducer and activator of transcription (STAT)/nuclear factor kappa B (NF- $\kappa$ B) axis while upregulating heme oxygenase-1 (HO-1) in virus-infected macrophages, supporting its broad-spectrum immunoregulatory potential [30].

**2.1.2 Anti-inflammatory mechanisms of honeysuckle ethanol extract.** The ethanol extract of honeysuckle (HWE-EtOH) demonstrates broad-spectrum anti-inflammatory efficacy across diverse models. Lee et al. have systematically evaluated the n-butanol fraction of HWE-EtOH and revealed its inhibitory effects on acute, granulomatous, and chronic inflammatory responses in rodent systems [48]. Further evidence from Tzeng et al. has highlighted HWE-EtOH's hepatoprotective properties: it attenuates hepatic inflammation and fibrogenesis via the modulation of key inflammatory mediators [49]. A mechanistic breakthrough by Kao et al. has elucidated HWE-EtOH's multi-pathway regulation in lipopolysaccharide (LPS)-induced acute lung injury: dose-dependent suppression of inhibitor of nuclear factor kappa B (I $\kappa$ B) phosphorylation was found to effectively inhibit NF- $\kappa$ B activation, while modulating mitogen-activated protein kinase (MAPK)/STAT signaling cascades. Concurrent enhancement of extracellular signal-regulated kinase (ERK)/specificity protein 1 (Sp1) axis activity and inhibition of c-Jun N-terminal kinase (JNK)/p38 mitogen-activated protein kinase (p38) pathways have been found to collectively contribute to resolving pulmonary inflammation in BALB/c models [31].

## 2.2 Examples of honeysuckle with anti-inflammatory properties

To date, 507 compounds have been isolated and identified from honeysuckle, including volatile oils, organic acids, flavonoids, iridoids, triterpenes, and triterpenoid saponins [32]. This section provides a comprehensive overview of research on honeysuckle with anti-inflammatory properties, according to chemical classification (Figure 2).

**2.2.1 Anti-inflammatory phenolic acids from honeysuckle.** The phenolic acid components in honeysuckle have favorable anti-inflammatory effects. Song et al. have identified eight bioactive phenolic acids (neochlorogenic acid, cryptochlorogenic acid, 3,5-dicaffeoylquinic acid, 3,4-dicaffeoylquinic acid, 4,5-dicaffeoylquinic acid, chlorogenic acid, caffeic acid, and methyl caffeate) that effectively alleviate LPS-induced inflammation in RAW264.7 macrophages, among which caffeic acid and its ester derivatives exhibit superior anti-inflammatory activity [53]. Mechanistic investigations have revealed that phenolic acid compounds modulate critical inflammatory pathways. Zhang et al. have reported ferulic acid's suppression of pro-inflammatory cytokines (IL-6, IL-8, IL-1 $\beta$ , and TNF- $\alpha$ ) at the transcriptional level [54]. Liu et al. have further demonstrated NF- $\kappa$ B inhibition by six phenolic acids in honeysuckle oral formulations: neochlorogenic acid, chlorogenic acid, cryptochlorogenic acid, and heterochlorogenic acids A, B, and C [33]. In metabolic inflammation, caffeic acid normalizes cardiac TNF- $\alpha$ , IL-1 $\beta$ , MCP-1, and IL-6 expression in diabetic mice [55, 56]. Notably, isochlorogenic acid derivatives have shown marked therapeutic potential. Chen et al. have additionally validated isochlorogenic acid A's protective effects against LPS-induced acute lung injury via TNF- $\alpha$ /IL-6 downregulation [57]. Structural-activity analysis by Yu et al. has confirmed distinct anti-inflammatory efficacy among isochlorogenic acid isomers (A, B, C) [58].

**2.2.2 Anti-inflammatory flavonoids from honeysuckle.** Honeysuckle-derived flavonoids exhibit multi-target anti-inflammatory activities by modulating key signaling pathways. Experimental studies have demonstrated their efficacy in attenuating NF- $\kappa$ B-mediated inflammatory responses, notably by ameliorating ulcerative colitis in rodent models [59]. Han et al. have further elucidated their mechanism, by revealing their suppression of TNF- $\alpha$  and IL-1 $\beta$  via inhibition of the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/NF- $\kappa$ B pathway; these findings highlight their therapeutic potential for inflammatory disorders [35]. Notably, structural diversity underpins the bioactivity of these honeysuckle-derived flavonoids. Monomeric constituents such as luteolin and apigenin demonstrate marked anti-inflammatory effects by regulating pro-inflammatory cytokines [60, 61]. Pharmacological analyses have identified glycosylated derivatives, including luteolin 7-glucoside, luteolin 7-galactoside, and hyperoside—compounds recognized [62]. Expanded studies have validated that luteolin [63], quercetin [64], biflavonoids [65], and luteoloside [66] dose-dependently suppress pro-inflammatory mediators. Contemporary research has further confirmed their broader immunomodulatory properties, and demonstrated that cardiac glycosides in honeysuckle exhibit synergistic anti-inflammatory, antimicrobial, and immunostimulatory activities [67].

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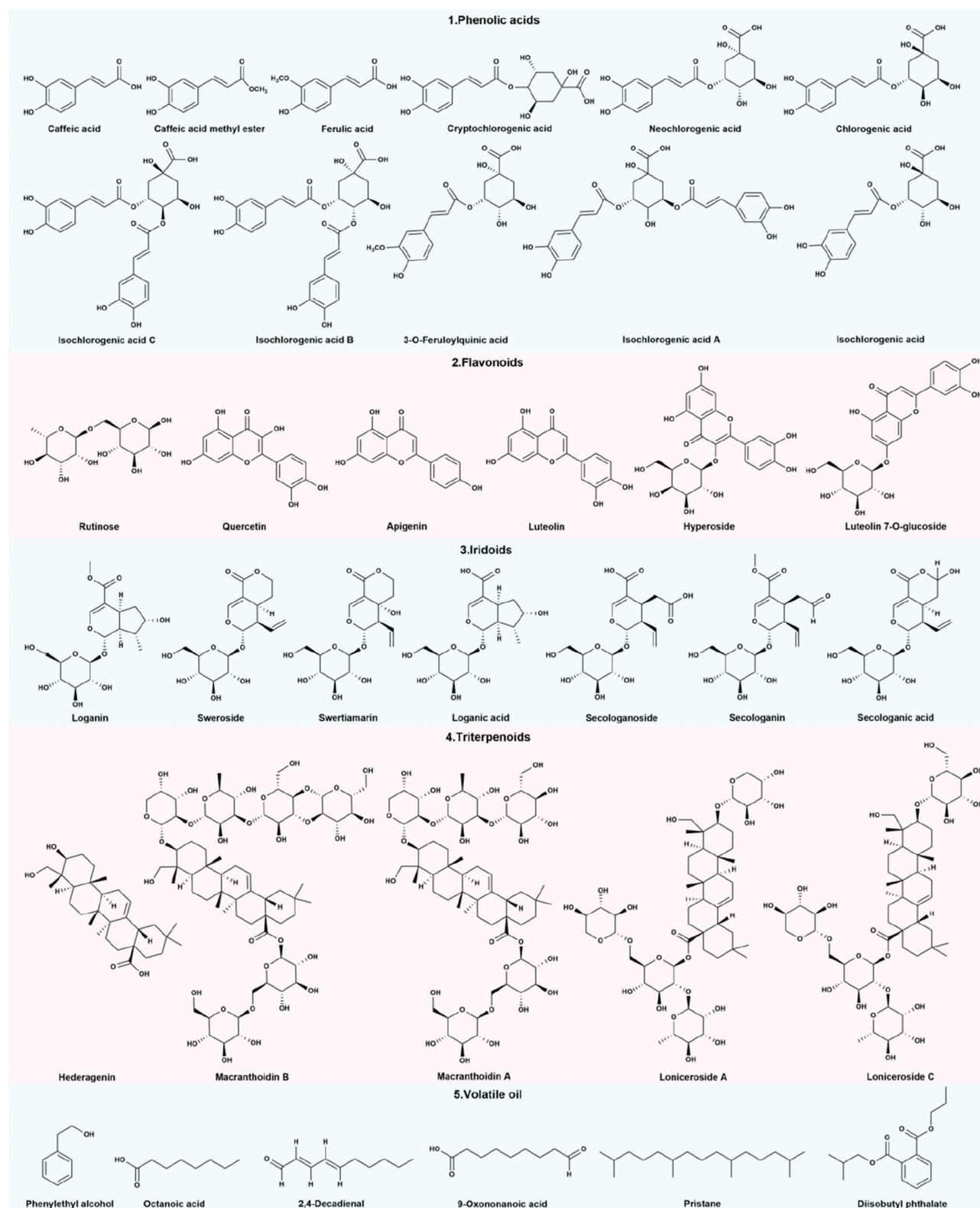


Figure 2 | Anti-inflammatory honeysuckle compounds encompassing diverse chemical and structural categories [50-52].

**2.2.3 Anti-inflammatory iridoids from honeysuckle.** Iridoid compounds in honeysuckle demonstrate targeted anti-inflammatory properties through pathway modulation. Studies have reported that iridoid compounds in honeysuckle, such as loganin and sweroside, possess anti-inflammatory activity [68]. Liu et al. have identified six NF- $\kappa$ B-inhibiting iridoids (loganic acid, secologanoside, secologanic acid, sweroside, secoxyloganin, and secologanin) in honeysuckle oral formulations and confirmed their transcriptional regulation of pro-inflammatory mediators [33]. Mechanistic studies have further validated that iridoid compounds, such as loganin and sweroside, extracted from honeysuckle, have notable inhibitory effects on edema induced by fresh egg white and carrageenan in rats [42]. Moreover, Wang et al. have found that loganin in honeysuckle exhibits anti-inflammatory activity [69].

**2.2.4 Anti-inflammatory triterpenoid saponins from honeysuckle.** Triterpenoid saponins in honeysuckle exhibit potent anti-inflammatory activity through two mechanisms: suppressing inflammatory mediators and modulating endocrine function. Structural analysis has identified hederagenin and oleanolic acid as the primary saponin aglycones, and hederagenin as predominant in bioactive fractions [69]. Triterpenoid saponins inhibit inflammatory cascades by blocking the synthesis of pro-inflammatory mediators while stimulating adrenocortical hormone production. Triterpenoid saponins [70]. Notably, saponin derivatives of honeysuckle exhibit considerable therapeutic efficacy. Oleanolic acid has shown marked anti-inflammatory properties in experimental models [71], whereas honeysuckle-derived saponins A and C exhibit efficacy comparable to that of aspirin for suppressing inflammation [72]. This multi-target activity establishes triterpenoid saponins as key contributors to honeysuckle's broad-spectrum anti-inflammatory profile.

**2.2.5 Anti-inflammatory volatile oil from honeysuckle.** Honeysuckle volatile oil has shown potent anti-inflammatory efficacy through multiple administration routes. Pharmacological evaluations by Su et al. have revealed that its anti-inflammatory activity at concentrations of 1 mg/mL (in vitro) or 0.8 mg/kg (in vivo) is comparable to that of hydrocortisone used at 2.5-fold higher concentration. Notably, CO<sub>2</sub> supercritical extracts of this volatile oil exhibit superior anti-inflammatory performance including robust therapeutic effects with both topical and systemic administration [73]. This efficacy via two distinct routes highlights potential as a multi-route anti-inflammatory agent.

**2.2.6 Anti-inflammatory polysaccharides from honeysuckle.** Honeysuckle polysaccharides (HPs) exhibit broad-spectrum anti-inflammatory activity through multi-level regulatory mechanisms. In macrophage models, HPs suppress inflammatory mediator release,

pro-inflammatory cytokine secretion (e.g., TNF- $\alpha$ , IL-1 $\beta$ , and IL-6), and inflammatory protein expression via NF- $\kappa$ B/MAPK pathway inhibition. Zebrafish studies have further demonstrated their ability to attenuate macrophage migration/aggregation and downregulate transcription factor-associated pro-inflammatory gene expression [74]. Allergic contact dermatitis is an immune-mediated inflammatory reaction triggered by skin contact with specific allergens. Tian et al. have found that HPs decrease ear edema in mice in a dose-dependent manner, as well as serum IgE levels. HPs also decrease levels of the proinflammatory cytokine TNF- $\alpha$  in mouse ear tissues; therefore, HPs have inhibitory effects on allergic contact dermatitis, although the mechanism of action is not yet clear [75]. Atopic dermatitis, also referred to as atopic eczema, is a prevalent, pruritic, inflammatory, and allergic dermatological condition manifesting predominantly in skin folds [76]. HPs have been found to regulate related genes and consequently restore epithelial barrier function and alleviate atopic dermatitis in mice. Bai et al. have found that HPs (WLJP-025p) markedly alleviate skin hyperplasia and pathological abnormalities in mice with atopic dermatitis, and additionally inhibit the upregulation of Beclin1, p-VPS34, LC3 A/B, and VLK1 induced by 2,4-dinitrochlorobenzene. WLJP-025p drives the degradation of NLRP3 inflammasomes by upregulating p62 phosphorylation. Moreover, WLJP-025p effectively increases the expression of nuclear factor erythroid 2-related factor 2 (Nrf2, a key factor in alleviating oxidative stress-mediated damage) and HO-1. Moreover, WLJP-025p markedly increases the phosphorylation of p62 Ser403 and the expression of ubiquitin in mouse skin tissue [38]. Zhang et al. have discovered that WLJP-025p in inflammation treatment binds nuclear factor NF- $\kappa$ B activator 1 (Act1), thereby regulating the MAPK/NF- $\kappa$ B/activator protein 1 (AP-1) axis, promoting the recovery of epithelial barrier function, and alleviating atopic dermatitis in mice [77].

Gouty arthritis is an inflammatory response, either acute or chronic, caused by the deposition of urate crystals in joints and surrounding tissues, because abnormal uric acid metabolism or excretion in the body leads to elevated levels of uric acid in the blood (hyperuricemia). Yang et al. have found that HPs decrease the inflammatory index, dysfunction index, and the levels of IL-1 $\beta$ , TNF- $\alpha$ , and COX-2 related inflammatory factors in mice, and therefore might serve as a potential therapeutic agent for gouty arthritis [78]. Rheumatoid arthritis is a common chronic inflammatory disease that can lead to severe skeletal deformities and affect cardiac function. Bi et al. have isolated a new polysaccharide (LJCP-2b) from honeysuckle, which has been demonstrated in vitro to affect the function of TNF- $\alpha$ -induced rheumatoid arthritis fibroblast-like synoviocytes [79]. The preventive or therapeutic effects in rheumatoid arthritis are achieved through decreasing cell viability, increasing the apoptosis rate, and

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decreasing migration and adhesion ability, as well as levels of IL-6 and IL-1 $\beta$ . Allergic rhinitis, a common chronic non-infectious inflammatory disease affecting the nasal mucosa, is caused primarily by allergen inhalation. HPs decrease the number of eosinophils, inhibit the secretion of inflammatory factors, and down-regulate the mRNA expression of T cell-associated cytokines in the nasal mucosa in mice in a dose-dependent manner, thereby exerting an anti-allergic rhinitis effect [80]. Furthermore, Wang et al. have used network pharmacology to substantiate the protective effects of HPs against learning and memory impairments [81]. In conclusion, HPs have considerable promise for the development of anti-inflammatory pharmaceuticals.

### 3. OVERVIEW OF THE DIRECT TARGETS OF THE ANTI-INFLAMMATORY ACTIVE COMPONENTS FROM HONEYSUCKLE

The identification of drug targets provides an essential biological foundation for understanding the therapeutic effects of drugs. Research on drug targets not only enhances understanding of the functional properties of natural products but also promotes the discovery of novel active lead compounds. Recent advances in cell biology, molecular biology, chemical biology, structural biology, and bioinformatics have revealed the targets and pharmacological mechanisms through which honeysuckle effectively treats inflammatory diseases. The primary aim of this section is to provide a comprehensive summary of the specific target proteins and molecular mechanisms involved in the anti-inflammatory effects of honeysuckle (Table 1), thereby offering valuable insights into its application and development in the treatment of inflammatory diseases.

#### 3.1 Receptor-targeting anti-inflammatory active components

**3.1.1 Toll-like receptor 2 (TLR2).** Because abnormal activation of TLR2 signaling has been implicated in inflammatory pathologies, this pathway has been established as a critical therapeutic target for anti-inflammatory drug development. Chlorogenic acid elicits TLR2-mediated anti-inflammatory effects through multiple mechanisms: it suppresses TLR2 gene expression in heat-stressed mice [82] and significantly downregulates IL-1 $\beta$ , IL-6, IL-8, and TLR2 mRNA levels in *Staphylococcus aureus*-infected models ( $P < 0.01$ ), without affecting expression of TNF- $\alpha$  or myeloid differentiation primary response 88 (MyD88) [83]. Luteolin exerts anti-inflammatory activity by inhibiting TLR2 surface protein expression, thereby attenuating NF- $\kappa$ B/MAPK signaling cascades; blocking nuclear translocation of the p65 transcription factor; and decreasing IL-1 $\beta$ , IL-6, and TNF- $\alpha$  cytokine secretion [84]. Quercetin similarly modulates inflammation through TLR2 inhibitory regulation [85]. Ferulic acid exhibits multimodal anti-inflammatory action by decreasing inflammatory cell counts in mouse

blood; decreasing serum IL-1 $\beta$ /IL-6 levels; and downregulating aortic expression of TLR2, TLR4, MyD88, and NF- $\kappa$ B p65; therefore, TLR pathway inhibition might have protective effects against PM2.5-induced vascular inflammation [86] (Figure 3).

**3.1.2 Toll-like receptor 4 (TLR4).** The TLR4 signaling pathway shares substantial mechanistic overlap with TLR2, both of which are transmembrane receptors. Notably, TLR4 activation selectively activates the interferon regulatory factor 3 (IRF-3) pathway in addition to inflammatory signaling. Similarly to TLR2, TLR4 activation initiates downstream pro-inflammatory signaling cascades. TLR4 is therefore a critical focus in inflammatory disease research. Experimental evidence has indicated that potassium oxonate induces renal TLR4 and NLRP3 overexpression. Luteolin, luteolin derivatives, and apigenin have shown therapeutic efficacy in hyperuricemic mice by suppressing TLR4/MyD88/NLRP3/IL-1 $\beta$  axis activation and serum pro-inflammatory cytokine levels, thereby effectively countering hyperuricemia-induced inflammation. Emerging evidence confirms luteolin's ability to downregulate the TLR4/MyD88 pathway in uric acid-induced gouty arthritis models [87]. These findings collectively characterize honeysuckle-derived TLR4-targeting components with therapeutic potential against inflammatory pathologies through multimodal pathway modulation (Figure 3).

**3.1.3 Toll-like receptor 9 (TLR9).** TLR9, in contrast to surface-expressed TLR2 and TLR4, exhibits distinct subcellular localization and is located primarily in intracellular compartments such as endosomes and lysosomes. This receptor recognizes pathogen-associated DNA, including bacterial and viral genetic material, as well as self-DNA in autoimmune pathologies. After ligand binding, TLR9 recruits adaptor proteins and subsequently activates downstream MAPK and NF- $\kappa$ B signaling cascades, thereby driving inflammatory responses. This mechanism positions TLR9 as a promising therapeutic target for inflammatory disorders. Oleanolic acid has shown anti-inflammatory efficacy in experimental pulpitis by modulating the TLR9/MyD88/NF- $\kappa$ B p65 signaling pathway [71]. Mechanistic studies have revealed that oleanolic acid suppresses TLR9 and MyD88 protein expression, blocks NF- $\kappa$ B p65 nuclear translocation, and decreases pro-inflammatory mediator release, thereby attenuating pulp tissue inflammation and oxidative stress. Although these findings suggest TLR9 pathway inhibition as a potential therapeutic strategy for acute/chronic pulpitis, current evidence remains preliminary, and rigorous validation is necessary through controlled experimental paradigms. Existing research has focused predominantly on mapping signaling cascades and quantifying inflammatory protein expression, whereas investigation of direct TLR9 receptor engagement has been limited. Further studies are required to establish causal relationships between TLR9 activation and

Table 1 | Anti-inflammation targets of honeysuckle.

| Type | Target | Natural products               | Mechanisms of action                                                                                                                                                                                                                | Experimental model                                                                                 | Reference |
|------|--------|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|-----------|
|      |        | Honeysuckle extract            | Inhibits NO secretion; downregulates release of IL-1 $\beta$ , IL-6, and TNF- $\alpha$ cytokines; decreases levels of iNOS, COX-2, and NF- $\kappa$ B p65 proteins                                                                  | Xylene-induced ear edema in mouse models; LPS-induced RAW 264.7 macrophages                        | [39]      |
|      |        |                                | Demonstrates comparable therapeutic efficacy to dexamethasone in treating acute inflammation                                                                                                                                        | Carrageenan-induced hind paw edema in rats                                                         | [40]      |
|      |        |                                | Suppresses both inflammatory exudation and proliferative responses                                                                                                                                                                  | Croton oil-induced granuloma pouch in rats                                                         | [43]      |
|      |        | Honeysuckle granule tablets    | Has chronic anti-inflammatory properties                                                                                                                                                                                            | Cotton pellet-induced granuloma formation in rats                                                  | [41]      |
|      |        | Aqueous extract of honeysuckle | Has acute anti-inflammatory properties                                                                                                                                                                                              | Xylene-induced ear edema and acetic acid-induced peritoneal capillary permeability in mouse models | [44]      |
|      |        |                                | Improves the spleen index in mice; decreases IL-6 and TNF- $\alpha$ in serum                                                                                                                                                        | Xylene-induced ear edema in mice                                                                   | [45]      |
|      |        |                                | Improves paw edema and vascular permeability; inhibits myeloperoxidase activity and decreases TNF- $\alpha$ expression in paws                                                                                                      | PAR2-induced paw edema in mice                                                                     | [46]      |
|      |        |                                | Inhibits activity of COX-1 and COX-2; downregulates COX-2 mRNA and protein expression                                                                                                                                               | A549 cell line                                                                                     | [47]      |
|      |        |                                | Modulates by the STAT/NF- $\kappa$ B signaling pathway and HO-1 expression                                                                                                                                                          | Virus-infected RAW264.7 cells                                                                      | [30]      |
|      |        | Ethanol extract of honeysuckle | Inhibits inflammatory molecules                                                                                                                                                                                                     |                                                                                                    | [49]      |
|      |        |                                | Inhibits phosphorylation of I $\kappa$ B in a dose-dependent manner, thereby downregulating NF- $\kappa$ B activity, enhancing ERK phosphorylation, upregulating Sp1 activity, and inhibiting phosphorylation of JNK, p38, and STAT | LPS-induced acute lung injury in BALB/c mice                                                       | [31]      |
|      |        | Ferulic acid                   | Suppresses the pro-inflammatory cytokines IL-6, IL-8, IL-1 $\beta$ , and TNF- $\alpha$ at the transcriptional level                                                                                                                 | LPS-induced bovine endometrial epithelial cells                                                    | [54]      |
|      |        | Caffeic acid                   | Suppresses TNF- $\alpha$ , IL-1 $\beta$ , MCP-1, and IL-6 at the transcriptional level                                                                                                                                              | Diabetic mice                                                                                      | [55, 56]  |
|      |        | Heterochlorogenic acid A       | Decreases expression of the inflammatory cytokines TNF- $\alpha$ and IL-6                                                                                                                                                           | LPS-induced acute lung injury                                                                      | [57]      |
|      |        | Flavonoids in Honeysuckle      | Attenuates the NF- $\kappa$ B signaling pathway                                                                                                                                                                                     | Experimental ulcerative colitis rat models                                                         | [59]      |
|      |        | Flavonoids in Honeysuckle      | Suppresses TNF- $\alpha$ and IL-1 $\beta$ via PI3K/Akt/NF- $\kappa$ B pathway inhibition                                                                                                                                            | LPS-induced microglia                                                                              | [35]      |
|      |        | Luteolin                       | Inhibits TNF- $\alpha$ -induced IL-8 expression                                                                                                                                                                                     | Intestinal epithelial cells                                                                        | [63]      |

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**Table 1** | Continued

| Type      | Target    | Natural products            | Mechanisms of action                                                                                                                                                                                                                              | Experimental model                                                                                                   | Reference |
|-----------|-----------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|-----------|
| Receptors | TLR2      | Biflavonoids                | Inhibits expression of pro-inflammatory factors such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IFN- $\gamma$ in mice                                                                                                                            | LPS-induced RAW 264.7 macrophages; DSS-induced SPF male C57BL/6J mouse models; LPS-induced SPF male ICR mouse models | [65]      |
|           |           | loganin and sweroside       | Positively regulates the ERK-Sp1-IL-10 axis; negatively regulates the I $\kappa$ B/NF- $\kappa$ B-p38/JNK-proinflammatory cytokine axis                                                                                                           | LPS-induced acute lung injury                                                                                        | [68]      |
|           |           | Honeysuckle polysaccharides | Downregulates secretion of key inflammatory factors and expression of inflammatory proteins in the NF- $\kappa$ B signaling pathway; inhibits secretion of multiple inflammatory factors; blocks NF- $\kappa$ B/MAPK signaling pathway activation | LPS-induced RAW 264.7 macrophages; CuSO <sub>4</sub> -induced zebrafish inflammation models                          | [74]      |
|           |           | Honeysuckle polysaccharides | Decreases serum IgE and histamine; decreases TNF- $\alpha$ in local tissues                                                                                                                                                                       | Picryl chloride-induced allergic contact dermatitis mouse models                                                     | [75]      |
|           |           | WLJP-025p                   | Upregulates expression of Nrf2 and HO-1; modulates the Bedin1/PS34/LC3 pathway; increases phosphorylation of p62 at Ser403, thus promoting ubiquitin-dependent degradation of the NLRP3 inflammasome and suppressing inflammatory responses       | 2,4-Dinitrochlorobenzene-induced atopic dermatitis mouse models                                                      | [38]      |
|           |           | WLJP-025p                   | Inhibits the MAPK/NF- $\kappa$ B/AP-1 signaling pathway                                                                                                                                                                                           | 2,4-Dinitrochlorobenzene-induced atopic dermatitis mouse models                                                      | [77]      |
|           |           | Honeysuckle polysaccharides | Decreases both the inflammation index and dysfunction index, while decreasing levels of the inflammatory factors IL-1 $\beta$ , TNF- $\alpha$ , and COX-2                                                                                         | Gouty arthritis mouse models                                                                                         | [78]      |
|           |           | LJCP-2b                     | Decreases IL-6 and IL-1 $\beta$                                                                                                                                                                                                                   | TNF- $\alpha$ -induced rheumatoid arthritis fibroblast-like synoviocytes                                             | [79]      |
|           |           | Honeysuckle polysaccharides | Decreases eosinophil number; inhibits secretion of inflammatory factors and mRNA expression of T cell-associated cytokines in mouse nasal mucosa                                                                                                  | T cells; allergic rhinitis mouse models                                                                              | [80]      |
|           |           | Chlorogenic acid            | Downregulates TLR-2 and NF- $\kappa$ B expression                                                                                                                                                                                                 | Heat-stressed mice                                                                                                   | [82]      |
|           |           | Chlorogenic acid            | Downregulates IL-1 $\beta$ , IL-6, IL-8, and TLR2 mRNA levels                                                                                                                                                                                     | <i>Staphylococcus aureus</i> -infected models                                                                        | [83]      |
|           |           | Luteolin                    | Inhibits the TLR2/NF- $\kappa$ B/MAPK pathway; targets p65 via Twist1, thus suppressing macrophage migration; decreases M1 polarization; promotes M2 polarization                                                                                 | <i>Staphylococcus aureus</i> -infected mammary epithelial cells; macrophage models; bovine/mouse mastitis models     | [84]      |
|           |           | Quercetin                   | Inhibits TLR-2/4 signaling pathways; downregulates pro-inflammatory cytokines (TNF- $\alpha$ /IL-1 $\beta$ /HMGB1)                                                                                                                                | Human corneal epithelial cells; mouse keratitis models                                                               | [85]      |
|           | TLR2/TLR4 | Ferulic acid                | Inhibits TLR2/TLR4 expression; blocks the MyD88/NF- $\kappa$ B pathway                                                                                                                                                                            | PM2.5 intratracheal instillation-induced mouse aortic inflammation models                                            | [86]      |

Table 1 | Continued

| Type    | Target   | Natural products                             | Mechanisms of action                                                                                                                                                                                                                         | Experimental model                                                                                                                                            | Reference |
|---------|----------|----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Enzymes | TLR4     | Luteolin, luteolin derivatives, and apigenin | Decreases TLR4/MyD88/NLRP3/IL-1 $\beta$ and serum pro-inflammatory cytokine levels                                                                                                                                                           | Potassium oxoide induced-hyperuricemic mice                                                                                                                   | [87]      |
|         |          | Luteolin,                                    | Downregulates the TLR4/MyD88 pathway                                                                                                                                                                                                         | Uric acid-induced gouty arthritis in rats                                                                                                                     | [87]      |
|         | TLR9     | Oleanolic acid                               | Targets the TLR9/MyD88/NF- $\kappa$ B p65 pathway; decreases IFN- $\gamma$ /IL-6 release                                                                                                                                                     | Pulpitis rat models                                                                                                                                           | [71]      |
|         | TRPV3    | Isochlorogenic acid A, isochlorogenic acid B | Selectively inhibits TRPV3 via T636/F666 binding; decreases channel activity, and pro-inflammatory mediators                                                                                                                                 | Topical irritant-induced mouse ear edema models; chemically induced chronic pruritus mouse models TRPV3 hyperactivation-induced keratinocyte apoptosis models | [34]      |
|         | AGE-RAGE | Chlorogenic acid, caffeic acid               | Blocks AGE-RAGE interaction; inhibits expression of inflammatory signaling components (ROS/p38 MAPK/NF- $\kappa$ B-associated kinases)                                                                                                       | HUVECs                                                                                                                                                        | [88]      |
|         | TREM2    | Chlorogenic acid                             | Performs TREM2-dependent NF- $\kappa$ B regulation; decreases inflammatory cytokine release                                                                                                                                                  | LPS-induced RAW 264.7 macrophages                                                                                                                             | [89]      |
|         | AMPK     | Quercetin                                    | Directly activates the AMPK/SIRT1 pathway, thus suppressing MG-induced NF- $\kappa$ B inflammatory responses                                                                                                                                 | MG-infected layer hen models; primary chicken embryo fibroblast models                                                                                        | [90, 91]  |
|         | JAK      | Caffeic acid                                 | Downregulates expression of the IL-6 receptor complex component gp130; inhibits JAK1 phosphorylation, thus decreasing STAT3 activation                                                                                                       | Fibroblast-like synoviocyte cell line                                                                                                                         | [92]      |
|         |          | Caffeic acid                                 | Inhibits UVB-induced IL-10/JAK1 upstream signaling; decreases p-STAT3; downregulates STAT3 transcriptional activity                                                                                                                          | Chronic UVB irradiation-induced mouse skin carcinogenesis models                                                                                              | [93]      |
|         | PI3K     | Chlorogenic acid                             | Blocks the PI3K/AKT pathway; decreases ROS production; inhibits NF- $\kappa$ B activation                                                                                                                                                    | LPS-induced sepsis cell models                                                                                                                                | [94]      |
|         | MAPK     | Chlorogenic acid                             | Targets MAPK3; modulates the MAPK signaling pathway, thus downregulating expression of the pro-inflammatory cytokines IL-1 and IL-6                                                                                                          |                                                                                                                                                               | [95]      |
|         |          | Neochlorogenic acid                          | Decreases phosphorylation levels of p38 and JNK proteins in the MAPK signaling pathway without affecting phosphorylation of the ERK subfamily                                                                                                | Mammary epithelial cells                                                                                                                                      | [83]      |
|         |          | Caffeic acid                                 | Inhibits phosphorylation of p38, JNK, and ERK proteins in the MAPK signaling pathway, thus decreasing the expression of associated inflammatory cytokines                                                                                    | LPS-induced mouse mastitis models                                                                                                                             | [96]      |
|         |          | Caffeic acid                                 | Blocks AKT/IKK phosphorylation; inhibits I $\kappa$ B $\alpha$ degradation; decreases NF- $\kappa$ B p65 nuclear translocation; suppresses p38 and ERK phosphorylation levels, thereby interrupting MAPK-mediated inflammatory amplification | LPS-induced mouse mastitis models; LPS-stimulated mammary epithelial cell inflammation models                                                                 | [97]      |
|         |          | Luteolin                                     | Decreases phosphorylation levels of p38, JNK, and ERK                                                                                                                                                                                        | IL-1 $\beta$ -stimulated SW982 cells                                                                                                                          | [98]      |

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Table 1 | Continued

| Type                  | Target         | Natural products      | Mechanisms of action                                                                                                                                                                                                                                                                                                                                                 | Experimental model                                                                                                        | Reference |
|-----------------------|----------------|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|-----------|
| Transcription factors | NF- $\kappa$ B | Oleanolic acid        | Decreases phosphorylation levels of p-JNK, p-ERK, and p-p38, thus blocking pro-inflammatory signaling; inhibits NLRP3 inflammasome activation; suppresses I $\kappa$ B $\alpha$ degradation and NF- $\kappa$ B p65 nuclear translocation                                                                                                                             | High-fat diet-induced obese mouse models; LPS/IFN- $\gamma$ -induced macrophage models                                    | [99]      |
|                       |                | Chlorogenic acid      | Activates the Nrf2/Sirt1 antioxidant pathway; inhibits NF- $\kappa$ B and TLR-2 gene expression                                                                                                                                                                                                                                                                      | Heat stress-induced testicular injury mouse models                                                                        | [82]      |
|                       |                | Isochlorogenic acid C | Decreases I $\kappa$ B degradation; prevents release of the NF- $\kappa$ B (p65/p50 complex); decreases phosphorylated p65 levels; attenuates NF- $\kappa$ B nuclear translocation, thereby suppressing downstream pro-inflammatory gene transcription                                                                                                               | LPS-stimulated bovine mammary epithelial cells; LPS-induced mouse mastitis models                                         | [100]     |
|                       | Luteolin       | Luteolin              | Inhibits I $\kappa$ B $\alpha$ phosphorylation; blocks NF- $\kappa$ B p65 nuclear translocation; decreases pro-inflammatory gene transcription                                                                                                                                                                                                                       | LPS-induced RAW 264.7 macrophages                                                                                         | [98]      |
|                       |                | Luteolin              | Inhibits the STAT1/3-NF- $\kappa$ B inflammatory axis; activates the Nrf2/HO-1 antioxidant pathway                                                                                                                                                                                                                                                                   | Pseudorabies virus-induced inflammatory response in RAW264.7 cells                                                        | [101]     |
|                       |                | Rutin                 | Downregulates NF- $\kappa$ B and MAPK14 (p38 $\alpha$ ) signaling pathways, thus attenuating inflammatory responses; inhibits the release of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , and IL-33)                                                                                                                                                   | HgCl <sub>2</sub> -induced renal injury rat models                                                                        | [102]     |
|                       | Lonicerin      | Lonicerin             | Blocks NF- $\kappa$ B activation, thus decreasing transcription of downstream pro-inflammatory cytokines (TNF- $\alpha$ , IL-6, etc.); inhibits M1 polarization; promotes M2 polarization                                                                                                                                                                            | Collagen-induced arthritis mouse models; RAW264.7 macrophages                                                             | [103]     |
|                       |                | Sweroside             | Targets the NF- $\kappa$ B pathway by downregulating IKK $\alpha$ and p-NF- $\kappa$ B while upregulating I $\kappa$ B, thereby decreasing inflammatory cytokines; activates the PI3K/AKT/ $\beta$ -catenin pathway; upregulates p-AKT and p-GSK-3 $\beta$ ; enhances $\beta$ -catenin signaling; inhibits osteoclast marker proteins (NFAT2, CTSK, and MMP-9)       | Complete Freund's adjuvant-induced arthritis models; osteoclast differentiation models; osteoblast differentiation models | [104]     |
|                       | Oleanolic acid | Oleanolic acid        | Decreases MafK expression, thereby inhibiting p65 acetylation and ultimately attenuating NF- $\kappa$ B transcriptional activity; suppresses expression of NF- $\kappa$ B downstream target genes (e.g., TNF- $\alpha$ , cIAP2, and I $\kappa$ B $\alpha$ ), thus decreasing the production of inflammatory mediators, while activating the Nrf2 antioxidant pathway | LPS-induced RAW 264.7 macrophages                                                                                         | [105]     |
|                       |                | Sweroside             | Inhibits IL-1 $\beta$ -induced NF- $\kappa$ B p65 phosphorylation and I $\kappa$ B $\alpha$ degradation, thereby blocking NF- $\kappa$ B nuclear translocation and transcriptional activity; decreases phosphorylation of mTORC1 downstream effectors S6K1 and S6, thus suppressing protein synthesis and cellular metabolism                                        | Primary rat articular chondrocytes                                                                                        | [106]     |

Table 1 | Continued

| Type         | Target | Natural products   | Mechanisms of action                                                                                                                                                                                                                               | Experimental model                                                                                                                                                                                                                                                                                                         | Reference             |
|--------------|--------|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
|              | Nrf2   | Chlorogenic acid   | Activates the PI3K/Akt-Nrf2/HO-1 pathway, thus indirectly inhibiting NF-κB activation; decreases phosphorylation of IκBα and NF-κB, thereby blocking NF-κB signaling                                                                               | Weaned piglets; porcine jejunal epithelial cells                                                                                                                                                                                                                                                                           | [107]                 |
|              |        | Caffeic acid       | Inhibits Keap1, thereby blocking Keap1-mediated Nrf2 degradation                                                                                                                                                                                   | High-fat diet-induced metabolic dysfunction-associated steatotic liver disease mouse models; primary hepatocytes                                                                                                                                                                                                           | [108]                 |
|              | STAT   | Quercetin          | Binds Keap1, thus blocking Keap1-mediated degradation of Nrf2; promotes AKT1 phosphorylation, thus inhibiting FoxO1 nuclear translocation and decreasing the production of inflammatory mediators                                                  | LPS-stimulated RAW264.7 cells; LPS-induced systemic inflammatory response mouse models                                                                                                                                                                                                                                     | [109]                 |
|              |        | Quercetin          | Activates the Nrf2/HO-1 pathway via p38/ERK-MAPKs; inhibits NF-κB/NO (partially independently of HO-1)                                                                                                                                             | LPS-induced BV-2 microglial cells                                                                                                                                                                                                                                                                                          | [110]                 |
| Inflammasome | NLRP3  | Luteolin           | Rapidly decreases Tyr705-STAT3 phosphorylation and promotes its ubiquitination-mediated degradation; gradually decreases Ser727-STAT3 phosphorylation through inhibition of CDK5 activity                                                          | Human hepatocellular carcinoma cell line HLF; HAK-1B HCC cells xenotransplanted into nude mice to establish xenograft tumor models                                                                                                                                                                                         | [111]                 |
|              |        | Luteolin           | Blocks IL-6-induced phosphorylation of JAK2 and STAT3 (Tyr705), thus inhibiting STAT3 nuclear translocation                                                                                                                                        | Maternal immune activation models                                                                                                                                                                                                                                                                                          | [36]                  |
|              |        | Luteolin, Apigenin | Inhibits the IFN-γ/STAT1/CD40 pathway, thus decreasing microglial activation and pro-inflammatory cytokine release                                                                                                                                 | N9 microglial cell line; primary microglia                                                                                                                                                                                                                                                                                 | [112]                 |
|              |        | Luteolin           | Decreases p-STAT3 (Tyr705) expression, thus directly inhibiting STAT3 transcriptional activity; decreases IFN-γ-induced p-STAT1 (Tyr701), thereby decreasing TNF-α release from macrophages; suppresses COX-2, thus mitigating inflammatory damage | C57BL/6 mouse experimental autoimmune thyroiditis models; IFN-γ-stimulated RAW264.7 macrophages                                                                                                                                                                                                                            | [113]                 |
|              |        |                    | Chlorogenic acid                                                                                                                                                                                                                                   | Downregulates NLRP3 and Caspase-1 protein expression, thus inhibiting IL-1β maturation and secretion; decreases p-IκBα and NF-κB p65 levels, thus blocking NF-κB activation and decreasing downstream inflammatory cytokine release; lowers pro-inflammatory factors while increasing the anti-inflammatory cytokine IL-10 | LPS-induced BV2 cells |
|              | NLRP3  | Lonicerin          | Directly binds EZH2 (key residues: His129/Arg685); enhances EZH2 activity; promotes autophagic degradation of NLRP3                                                                                                                                | Human monocytic cell line; mouse bone marrow-derived macrophages; dextran sulfate sodium-induced ulcerative colitis mouse models                                                                                                                                                                                           | [23, 115]             |
|              |        | Lonicerin          | Inhibits the NLRP3 inflammasome and suppresses NF-κB, thus decreasing M1 polarization                                                                                                                                                              | Collagen-induced arthritis DBA/1 mouse models; RAW264.7 cells                                                                                                                                                                                                                                                              | [23, 115]             |

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Table 1 | Continued

| Type   | Target | Natural products            | Mechanisms of action                                                                                                                                                                                                    | Experimental model                                                                                                                                        | Reference |
|--------|--------|-----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Others |        | Sweroside                   | Inhibits assembly of the NLRP3-ASC-pro-caspase-1 complex                                                                                                                                                                | LPS-stimulated mouse bone marrow-derived macrophages; methionine-choline deficient diet-induced non-alcoholic steatohepatitis mouse models                | [37]      |
|        |        | Ferulic acid                | Downregulates expression of NLRP3, caspase-1, and IL-1 $\beta$ /IL-18; blocks formation of the NLRP3-ASC-pro-caspase-1 complex, thereby inhibiting inflammasome activation                                              | 18 Gy $\gamma$ -radiation-induced cell damage in human keratinocytes female Wistar rats (190–210 g) exposed to 40 Gy $^{60}\text{Co}$ $\gamma$ -radiation | [116]     |
|        |        | Luteolin                    | Inhibits NLRP3 inflammasome activation; decreases IL-1 $\beta$ secretion                                                                                                                                                | LPS-induced RAW 264.7 macrophages; LPS-induced mouse acute lung injury models; complete Freund's adjuvant-induced rat arthritis models                    | [87]      |
|        | HMGB1  | Rutin                       | Targets the HMGB1/TLR4/MyD88/NF- $\kappa$ B signaling pathway                                                                                                                                                           | Acetic acid-induced ulcerative colitis rat models                                                                                                         | [117]     |
|        | AKT1   | Chlorogenic acid, sweroside | Inhibits the PI3K/AKT pathway, thus decreasing the production of pro-inflammatory cytokines; suppresses MAPK3 (ERK1/2), thus blocking MAPK phosphorylation and downregulating the transcription of inflammatory factors | LPS-induced rat fever models; LPS-stimulated macrophages                                                                                                  | [118]     |
|        | EGR1   | Caffeic acid                | Alleviates psoriasis-associated inflammation by inhibiting the EGR1-CHAC1 signaling axis, thereby decreasing keratinocyte ferroptosis and pro-inflammatory factors                                                      | Primary human epidermal keratinocytes                                                                                                                     | [119]     |
|        | SIRT1  | Sweroside                   | Activates SIRT1, thereby inhibiting the NF- $\kappa$ B pathway and exerting anti-inflammatory effects                                                                                                                   | LPS-induced RAW 264.7 macrophages; rheumatoid arthritis fibroblast-like synoviocytes                                                                      | [120]     |
|        | SHP2   | Oleanolic acid              | Activates SHP2, thereby inhibiting STAT3 phosphorylation without affecting STAT1, and ultimately locking Th17 cell differentiation                                                                                      | 2,4,6-Trinitrobenzenesulfonic acid-induced colitis mouse models; CD4+ T cells; T cell-specific SHP2 knockout mice                                         | [121]     |

disease-specific inflammatory responses, and to elucidate the structural basis of ligand-receptor interactions (Figure 3).

**3.1.4 Transient receptor potential vanilloid 3 (TRPV3).** TRPV3, a member of the transient receptor potential (TRP) channel family, participates in diverse physiological processes, particularly temperature sensing and nociceptive signaling. Under inflammatory conditions, upregulated TRPV3 expression and activity contribute to pathological hyperalgesia and chronic pain; consequently, this channel is a therapeutic target for pain management. Pharmacological modulation of TRPV3 signaling has potential for alleviating neuropathic and inflammatory pain disorders. Qi et al. have identified novel pharmacological actions of isochlorogenic acid A (Iaa) and B (Isb) as TRPV3 gating modifiers. Molecular docking and site-directed mutagenesis have shown that the binding residues (T636 and F666) are critical for the interaction between isoforms and TRPV3, and that Isb forms a clamp-like interaction that enhances the potency of TRPV3 inhibition [34]. These findings position Iaa/Isb as dual-purpose agents, not only as therapeutic candidates for keratinization disorders, dermatitis, and chronic itch, but also as valuable pharmacological probes for elucidating TRPV3-related pathomechanisms. These compounds selectively inhibit

temperature-sensitive TRPV3 currents by decreasing channel opening probability, and they effectively attenuate TRPV3 hyperactivity-induced keratinocyte apoptosis, ear edema, and chronic pruritus (Figure 3).

**3.1.5 Advanced glycation end products (AGEs).** AGEs, compounds formed during glycation, react with proteins, lipids, or nucleic acids, and consequently affect cells' structure and function. The harmful effects of AGEs on human health have attracted increasing attention, particularly the chronic inflammatory response induced by the interaction between AGEs and their receptor, RAGE [88]. AGE-RAGE activation can lead to downstream activation of various intracellular signaling pathways, such as the NF- $\kappa$ B and MAPK pathways. Chlorogenic acid and caffeic acid potently suppress the AGE-BSA-induced inflammatory response in human umbilical vein endothelial cells (HUVECs) via reactive oxygen species (ROS)/p38 MAPK/NF- $\kappa$ B pathway inhibition [88]. Both caffeic acid and chlorogenic acid demonstrate inhibitory effects on AGE-BSA-induced mRNA expression of ICAM-1, VCAM-1, and MCP-1 in HUVECs, and simultaneously suppress the elevated protein levels of TNF- $\alpha$  and IL-1 $\beta$ . Notably, caffeic acid exhibits more potent inhibitory effects than chlorogenic acid. Furthermore, both compounds effectively disrupt the AGE-RAGE positive feedback regulatory loop. The underlying mechanism

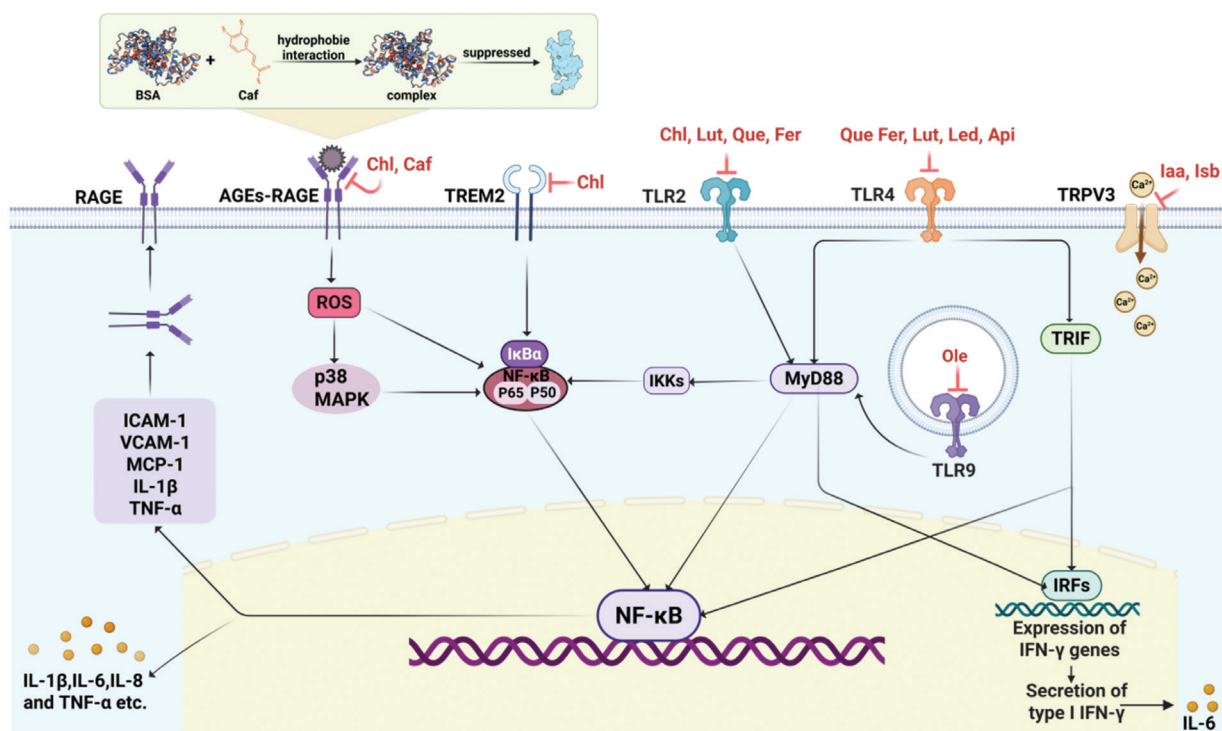


**Figure 3 | Honeysuckle exerts anti-inflammatory effects through modulating the TLR2/4/9, RAGE, TREM2, and TRPV3 pathways.**

This figure was created with [BioRender.com](https://www.biorender.com). Chl, Chlorogenic Acid; Lut, Luteolin; Que, Quercetin; Fer, Ferulic Acid; Lut, Luteolin Derivatives; Api, Apigenin; Ole, Oleanolic Acid; Caf, Caffeic Acid; Neo, Neochlorogenic Acid; Isc, Isochlorogenic Acid C; Rut, Rutin; Lon, Lonicerin; Swe, Sweroside; Isa, Isochlorogenic Acid; Iaa, Isochlorogenic Acid A; Isb, Isochlorogenic Acid B; Wlj, WLJP-025p.

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involves RAGE activation through AGE binding, which in turn initiates intracellular ROS generation and subsequent activation of key signaling pathways. This cascade leads to upregulated expression of critical kinases including MAPK and NF- $\kappa$ B, and ultimately promotes cellular inflammatory responses. NF- $\kappa$ B activation particularly enhances the expression of inflammatory mediators such as TNF- $\alpha$ , IL-1 $\beta$ , MCP-1, ICAM-1, and VCAM-1, thereby exacerbating inflammatory reactions and impairing wound healing ability. Importantly, the AGE-RAGE interaction establishes a self-amplifying cycle through positive feedback regulation, and consequently results in increased RAGE expression and membrane oligomerization processes (Figure 3).

**3.1.6 Triggering receptor expressed on myeloid cells-2 (TREM2).** TREM2, a transmembrane glycoprotein receptor expressed on macrophages, plays a critical regulatory role in modulating macrophage activation and suppressing inflammatory responses [122]. Chlorogenic acid has been demonstrated to ameliorate inflammatory responses in LPS-stimulated macrophages through downregulation of iNOS and NF- $\kappa$ B p65 protein expression while upregulating TREM2 expression [89]. To investigate the role of TREM2 in chlorogenic acid-mediated suppression of macrophage activation, researchers have knocked down TREM2 expression with TREM2-specific small interfering RNA (TREM2-siRNA). Comparative analysis revealed that the TREM2-siRNA + chlorogenic acid + LPS co-treatment group exhibited significantly greater iNOS and NF- $\kappa$ B p65 protein levels ( $P < 0.05$ ) and markedly lower TREM2 expression than observed in the chlorogenic acid + LPS treatment group. Notably, TREM2-siRNA effectively reversed the anti-inflammatory effects of chlorogenic acid, whereas the scrambled siRNA control group showed no interference with chlorogenic acid's activity. These findings suggest that the anti-inflammatory properties of chlorogenic acid in LPS-activated macrophages are likely to be mediated through TREM2-dependent mechanisms (Figure 3).

### 3.2 Enzyme-targeting anti-inflammatory active components

**3.2.1 The AMP-activated protein kinase (AMPK).** The AMPK signaling pathway is an evolutionarily conserved energy sensor that coordinates cellular responses to metabolic stress. AMPK activation exerts inhibitory effects on the NF- $\kappa$ B signaling pathway, a central regulator of inflammatory responses, through suppression of inflammatory gene transcription. Notably, in pathological conditions such as type 2 diabetes mellitus, diminished AMPK activity is associated with exacerbated inflammatory states and insulin resistance. This regulatory ability positions AMPK as a promising therapeutic target for various inflammation-related disorders, including metabolic syndrome, cardiovascular diseases, and neurodegenerative conditions. Recent investigations have revealed that quercetin ameliorates Mycoplasma

gallisepticum (MG)-induced inflammation through modulation of the AMPK/silent information regulator 2 homolog 1 (SIRT1)/NF- $\kappa$ B signaling axis [90, 91]. Mechanistically, bioinformatic analyses have demonstrated that quercetin shares structural similarities with established AMPK activators and exhibits comparable binding site affinities. Specifically, quercetin has been predicted to bind the AMPK $\gamma$ 1 subunit in chickens, and this computational prediction has been substantiated through a comprehensive multi-level investigation combining bioinformatic analysis with experimental validation across in vivo models, cellular systems, and molecular assays. Quercetin-mediated activation of AMPK enhances SIRT1 expression while suppressing NF- $\kappa$ B nuclear translocation, thereby attenuating MG-induced inflammatory damage. This suppression is particularly evident in the downregulation of pro-inflammatory cytokine production and mitigation of oxidative stress markers. These findings position quercetin as a novel AMPK $\gamma$ 1-targeted therapeutic candidate against MG infection, with broader implications for treating pathogen-driven inflammatory disorders (Figure 4).

**3.2.2 Janus kinase (JAK).** The JAK signaling pathway is a critical intracellular signaling cascade that orchestrates inflammatory responses through sequential phosphorylation events. After JAK dimerization and autophosphorylation, this pathway activates downstream effectors including STAT proteins and MAPKs, and ultimately drives inflammatory processes. Emerging evidence highlights chlorogenic acid as a multi-target anti-inflammatory agent with dual therapeutic effects comprising cytokine suppression (notably TNF- $\alpha$  and IL-6 downregulation [65]) and targeted modulation of key signaling pathways. Experimental evidence has demonstrated its ability to inhibit inflammatory cell proliferation via coordinated suppression of the JAK/STAT and NF- $\kappa$ B signaling axis, thereby attenuating the expression of pro-inflammatory mediators [92]. Mechanistic investigations in collagen-induced arthritis models have further elucidated the anti-inflammatory properties of chlorogenic acid, a principal bioactive constituent of honeysuckle. Through integrated pharmacological and molecular approaches, researchers have established that chlorogenic acid effectively inhibits IL-6-induced inflammatory proliferation in fibroblast-like synoviocytes. This therapeutic action correlates with the following specific pathway modulation effects: (1) dose-dependent attenuation of STAT3 phosphorylation (p-STAT3) and JAK1 expression in the JAK/STAT cascade, and (2) a marked decrease in NF- $\kappa$ B subunit p50 (p50) nuclear translocation and I $\kappa$ B kinase (IKK) phosphorylation in the NF- $\kappa$ B pathway [123]. These coordinated effects substantially impair the activation of both signaling networks. Furthermore, caffeic acids has shown remarkable chemopreventive potential in cutaneous biology. Long-term ultraviolet B (UVB, 280–315 nm) exposure in mouse models has indicated this caffeic acid ability to suppress

epidermal hyperplasia through selective inhibition of JAK-STAT3 signaling transduction. Given STAT3's critical role in mediating inflammation, cellular proliferation, and oncogenic transformation, pharmacological targeting of this pathway has emerged as a novel preventive strategy against UVB-induced skin carcinogenesis [93]. This mechanistic understanding positions both chlorogenic acid and caffeic acid as promising candidates for inflammation-associated disorder management through precision modulation of JAK-STAT signaling networks (Figure 4).

**3.2.3 Phosphoinositol 3-kinase (PI3K).** The PI3K/AKT signaling pathway is a crucial regulatory axis in cellular signal transduction and inflammatory modulation. Li et al. have conducted a comprehensive investigation of the anti-inflammatory mechanisms of chlorogenic acid and demonstrated its therapeutic potential in sepsis management via PI3K/AKT pathway regulation [94]. In vivo, chlorogenic acid administration significantly attenuates sepsis-induced hepatic damage, as evidenced by lower serum alanine aminotransferase and serum aspartate aminotransferase levels ( $P < 0.05$ ) and pro-inflammatory cytokine concentrations ( $P < 0.05$ ) than observed in septic model controls. Histopathological analysis via H&E staining confirmed improved hepatic architecture with diminished structural disorganization, vascular congestion, and inflammatory cell infiltration. Mechanistically, chlorogenic acid treatment substantially suppressed NF- $\kappa$ B p65 nuclear translocation while downregulating

PI3K/AKT pathway activation, as evidenced by decreased PI3K and p-AKT protein expression ( $P < 0.05$ ). To validate these findings, the researchers used an LPS-stimulated RAW264.7 macrophage model of sepsis. chlorogenic acid intervention effectively mitigated p65 nuclear translocation, inflammatory mediator production, and ROS generation through PI3K/AKT pathway modulation. Complementary pharmacological inhibition experiments with LY294002 (a specific PI3K inhibitor) demonstrated comparable effects to moderate-dose chlorogenic acid treatment, by significantly decreasing ROS levels, inflammatory factors, and p65 nuclear translocation while suppressing p65 expression. Both experimental approaches consistently revealed PI3K/AKT pathway downregulation after therapeutic intervention. These findings collectively suggest that chlorogenic acid exerts its anti-sepsis effects through strategic modulation of the PI3K/AKT signaling axis. The concordant results from in vivo and in vitro models, coupled with pharmacological pathway inhibition data, strongly implicate PI3K as a critical molecular target for chlorogenic acids anti-inflammatory action in sepsis pathophysiology (Figure 4).

**3.2.4 Mitogen-activated protein kinase (MAPK).** The MAPK signaling pathway, comprising evolutionarily conserved serine/threonine kinases, is a central regulator of cellular responses to extracellular stimuli. Given its critical involvement in inflammatory pathogenesis and

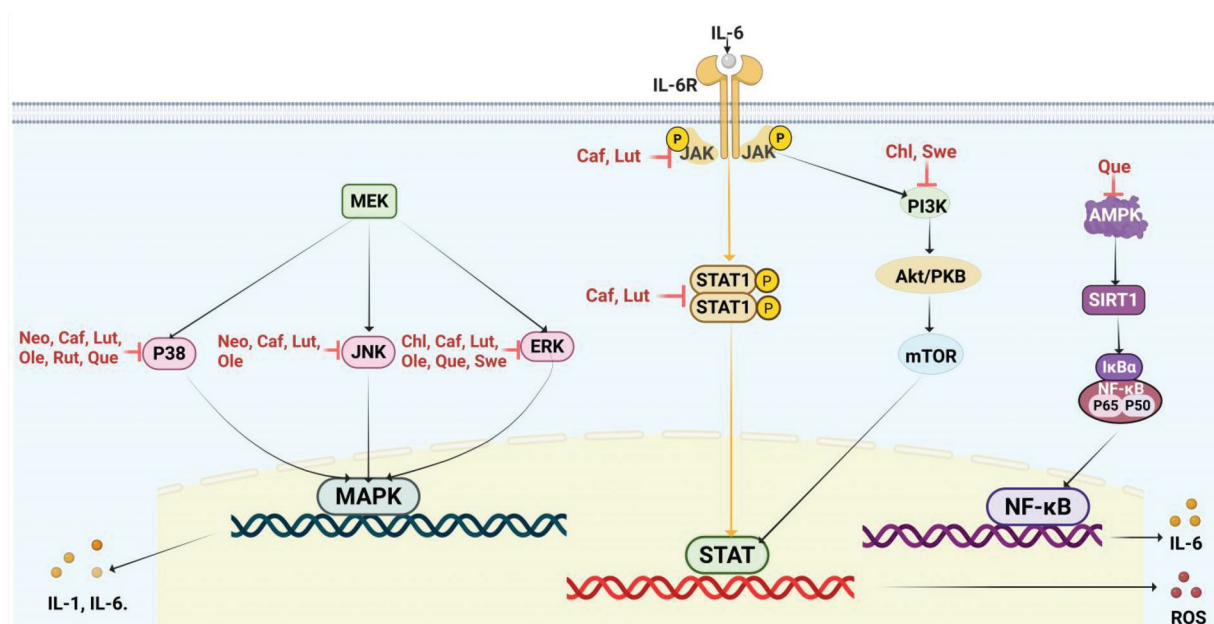


**Figure 4 | Honeysuckle exerts its anti-inflammatory effects through modulating the AMPK, PI3K, JAK, and MAPK pathways.**

This figure was created with [BioRender.com](https://www.biorender.com). Chl, Chlorogenic Acid; Lut, Luteolin; Que, Quercetin; Fer, Ferulic Acid; Lud, Luteolin Derivatives; Api, Apigenin; Ole, Oleanolic Acid; Caf, Caffeic Acid; Neo, Neochlorogenic Acid; Isc, Isochlorogenic Acid C; Rut, Rutin; Lon, Lonicerin; Swe, Sweroside; Isa, Isochlorogenic Acid; Iaa, Isochlorogenic Acid A; Isb, Isochlorogenic Acid B; Wlj, WLJP-025p.

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oncogenesis, MAPK cascades have emerged as prime therapeutic targets for anti-inflammatory and anti-neoplastic drug discovery. chlorogenic acid exhibits selective MAPK modulation through preferential targeting of MAPK3 (ERK1), coupled with significant downregulation of IL-1 $\beta$  and IL-6 expression, thereby conferring anti-inflammatory efficacy [95]. Mechanistic investigations with *Staphylococcus aureus*-challenged bovine mammary epithelial cells have demonstrated that chlorogenic acid specifically attenuates phosphorylation of p38 and JNK isoforms while preserving ERK activation status, thus indicating subfamily specific regulatory ability [83]. Caffeic acid demonstrates broader-spectrum MAPK inhibition. As reported by Zhang et al. [96], this phenolic compound concurrently suppresses phosphorylation of p38, JNK, and ERK subfamilies, and effectively blocks MAPK pathway activation and subsequent pro-inflammatory cytokine production. These findings align with those from Kan et al. [97], who have identified dual inhibition of NF- $\kappa$ B and MAPK signaling as the molecular basis underlying caffeic acid's mammary gland protective effects in inflammatory models. Extended pharmacological implications are as follows. The flavonoid luteolin exhibits multi-target regulation across MAPK cascades in diverse cellular contexts, although precise mechanistic characterization requires further investigation [98]. The triterpenoid oleanolic acid ameliorates chronic adipose tissue inflammation in high-fat diet-induced mouse models through MAPK pathway suppression, thus suggesting its therapeutic potential for metabolic-inflammatory disorders [99] (Figure 4).

### 3.3 Transcription factors targeting anti-inflammatory active components

**3.3.1 Nuclear factor kappa B (NF- $\kappa$ B).** The NF- $\kappa$ B signaling pathway is activated through a conserved mechanism involving extracellular stimulus detection, IKK-mediated phosphorylation of I $\kappa$ B regulatory subunits, and subsequent proteasomal degradation of I $\kappa$ B. This process liberates NF- $\kappa$ B dimers for translocation to the nucleus, where they initiate transcription of pro-inflammatory mediators through  $\kappa$ B element binding. Pharmacological modulation of this pathway has been extensively investigated, and multiple natural compounds have demonstrated therapeutic potential through distinct inhibitory mechanisms. Chlorogenic acid suppresses heat stress-induced inflammation in mouse models via coordinated downregulation of NF- $\kappa$ B and TLR2 expression [82]. Structural analogs including isochlorogenic acids A/B exhibit broad anti-inflammatory activity through NF- $\kappa$ B pathway inhibition, decreased oxidative stress, and suppression of pulmonary edema/apoptosis [34], whereas isochlorogenic acid C specifically targets NF- $\kappa$ B activation in both bovine mammary epithelial cells and mouse mammary inflammation models [100]. Flavonoid derivatives demonstrate multimodal regulation: luteolin from honeysuckle blocks NF- $\kappa$ B nuclear translocation in HMC-1 mast cells by stabilizing I $\kappa$ B $\alpha$ , modulating AKT/histone

deacetylase/histone acetyltransferase activity [98, 124], and concurrently suppressing STAT1/3-dependent NF- $\kappa$ B activation while inducing HO-1 expression in viral inflammation models [101]. Rutin exerts anti-inflammatory effects through downregulation of TNF- $\alpha$ /IL-1 $\beta$ /IL-33 and inhibition of NF- $\kappa$ B/MAPK crosstalk [102]. Terpenoid compounds exhibit distinct mechanistic profiles. Sweroside decreases NF- $\kappa$ B fluorescence intensity, upregulates I $\kappa$ B protein expression, and downregulates the protein levels of IKK $\alpha$  and p-NF- $\kappa$ B in osteoclasts; it also reduces the expression of the inflammatory factors TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, thereby alleviating osteoclast inflammation [104]. Oleanolic acid modulates epigenetic-inflammatory interactions in macrophages by suppressing v-maf musculoaponeurotic fibrosarcoma oncogene homolog K (MafK) expression and p65 acetylation, thereby inhibiting NF- $\kappa$ B-mediated NO/prostaglandin E2/IL synthesis [105]. Sweroside protects chondrocytes against IL-1 $\beta$ -induced inflammation through dual NF- $\kappa$ B/mechanistic target of rapamycin complex 1 (mTORC1) pathway blockade [106]. Additionally, Ionicerin alleviates experimental rheumatoid arthritis progression via NF- $\kappa$ B-dependent regulation of M1 macrophage polarization [103] (Figure 5).

### 3.3.2 Nuclear factor erythroid 2-related factor 2 (Nrf2).

Nrf2, a primary regulator of cellular redox homeostasis, orchestrates antioxidant responses through dynamic interactions with the cytosolic Kelch-like ECH-associated protein 1 (Keap1)/Nrf2 complex. Under oxidative challenge, Nrf2 dissociates from Keap1, undergoes nuclear translocation, and activates antioxidant response element-driven transcription of cytoprotective genes. Beyond its canonical antioxidant function, Nrf2 modulates inflammatory cascades by cross-regulating pro-inflammatory mediator expression. Emerging evidence indicates that natural compounds exert anti-inflammatory effects through Nrf2-mediated pathway modulation. Chlorogenic acid demonstrates dual-phase regulatory ability, by enhancing Nrf2 activation and consequently upregulating HO-1 expression while concurrently suppressing NF- $\kappa$ B signaling through inhibition of I $\kappa$ B $\alpha$  phosphorylation and NF- $\kappa$ B nuclear accumulation, thus ultimately attenuating pro-inflammatory cytokine production [107]. Caffeic acid exerts hepatoprotective effects in metabolic dysfunction-associated fatty liver disease models by directly targeting Keap1; this interaction stabilizes Nrf2, thereby counteracting oxidative damage and lipid accumulation in hepatocytes [108]. Quercetin modulates macrophage responses through coordinated regulation of two interconnected pathways, via AKT1-Forkhead box protein O1 (FOXO1) axis modulation and Keap1-Nrf2 system activation, thus effectively mitigating LPS-induced cytokine storms [109]. This bifunctional mechanism is further evidenced by quercetin's ability to suppress NF- $\kappa$ B-mediated inflammation while potentiating Nrf2 antioxidant responses in LPS-challenged systems [110] (Figure 5).

**3.3.3 Signal transducers and activators of transcription (STATs).** The STAT family comprises critical intracellular mediators that transduce extracellular signals into transcriptional responses. Given their central involvement in oncogenesis and inflammatory pathology, STAT proteins, particularly STAT1 and STAT3, have emerged as promising therapeutic targets for anti-neoplastic and anti-inflammatory drug development. Pharmacological investigations have revealed distinct STAT modulation patterns: luteolin demonstrates dual inhibitory effects on STAT3 phosphorylation at Tyr705 [36, 111] and STAT1 activation [112], thereby suggesting broad-spectrum JAK-STAT pathway suppression. Parallel studies have identified luteolin as a potent STAT pathway modulator. Mechanistic analyses have indicated significant inhibition of IFN- $\gamma$ -induced COX-2 expression, STAT1/STAT3 phosphorylation (Tyr701/705), and TNF- $\alpha$  secretion in inflammatory models [113]. This multi-target suppression underlies luteolin's therapeutic efficacy in experimental autoimmune thyroiditis, in which it attenuates thyroid inflammatory infiltration and autoantibody production. Luteolin might therefore serve as a novel therapeutic candidate for early-stage Hashimoto's thyroiditis intervention (Figure 5).

### 3.4 NLRP3 inflammasome-targeting anti-inflammatory active components

The NLRP3 inflammasome, a cytosolic pattern recognition complex, initiates inflammatory responses through coordinated interactions with adaptor proteins (e.g., MyD88, TIR domain-containing adaptor protein), thus

activating downstream NF- $\kappa$ B and MAPK signaling cascades. Emerging pharmacological strategies targeting NLRP3 regulation demonstrate therapeutic potential across inflammatory pathologies. Chlorogenic acid suppresses inflammasome assembly via dual inhibition of NLRP3 oligomerization and NF- $\kappa$ B phosphorylation, and consequently attenuates pro-inflammatory cytokine release [114]. Lonicerin exhibits multi-modal anti-inflammatory action through epigenetic regulation (Enhancer of Zeste Homolog 2 (EZH2) targeting) and autophagy-mediated NLRP3 inactivation, and has shown efficacy in both ulcerative colitis models and M1 macrophage polarization assays [23, 115]. Sweroside exerts systemic anti-nonalcoholic steatohepatitis effects through NLRP3 inflammasome blockade by (1) inhibiting caspase-1 cleavage and Apoptosis-associated speck-like protein containing a CARD (ASC) speck formation in ATP/Nigericin/monosodium urate-stimulated systems; (2) decreasing mitochondrial DNA synthesis in hepatocytes; and (3) ameliorating hepatic steatosis and fibrosis in methionine-choline deficient diet mouse models, as evidenced by decreased serum aspartate aminotransferase/alanine aminotransferase levels and inflammatory infiltration [37]. Novel biomaterial applications include ferulic acid-loaded carbopol hydrogels, which accelerate radiation-induced skin wound healing via NLRP3/caspase-1/IL-1 $\beta$  axis suppression. Transcriptomic profiling has revealed ferulic acid-mediated regulation of immune responses, angiogenesis, and extracellular matrix remodeling [116]. Given that complementary *in vitro* studies have identified luteoloside and apigenin

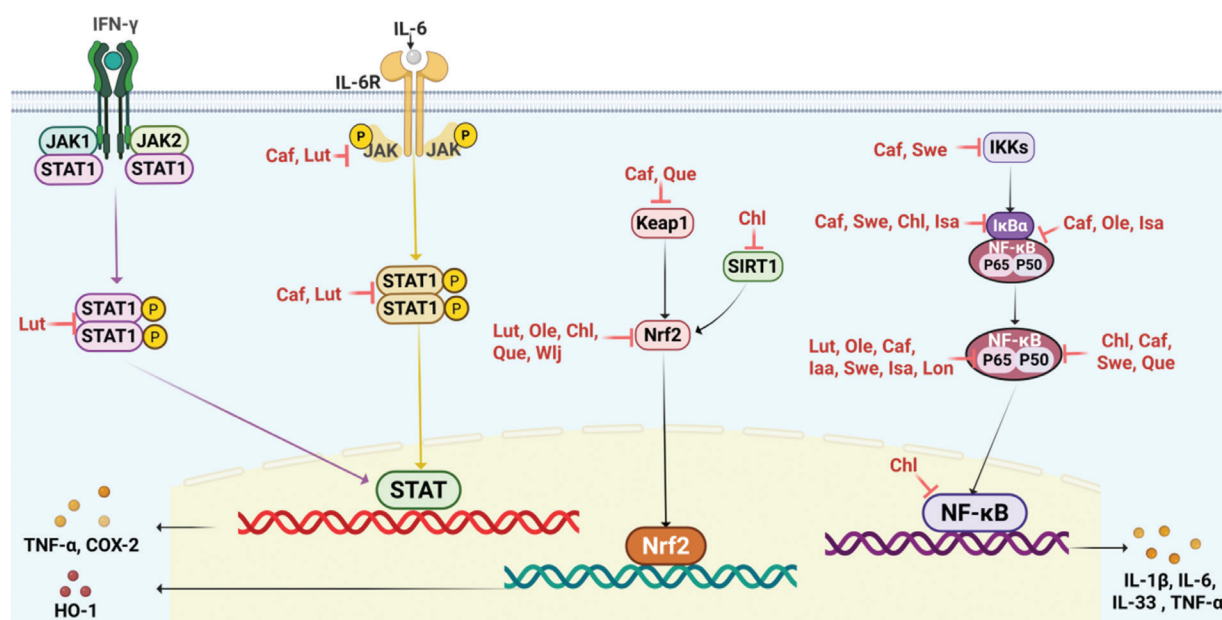


**Figure 5 | Honeysuckle exerts its anti-inflammatory effects through modulating the NF- $\kappa$ B, STATs, and Nrf2 pathways.**

This figure was created with [BioRender.com](https://www.biorender.com). Chl, Chlorogenic Acid; Lut, Luteolin; Que, Quercetin; Fer, Ferulic Acid; Lut, Luteolin Derivatives; Api, Apigenin; Ole, Oleanolic Acid; Caf, Caffeic Acid; Neo, Neochlorogenic Acid; Isc, Isochlorogenic Acid C; Rut, Rutin; Lon, Lonicerin; Swe, Sweroside; Isa, Isochlorogenic Acid; Iaa, Isochlorogenic Acid A; Isb, Isochlorogenic Acid B; Wlj, WLJP-025p.

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as potent NLRP3 inhibitors, flavonoid derivatives might potentially attenuate inflammation through TLR4-NLRP3 crosstalk modulation [87] (Figure 6).

### 3.5 Others

Emerging evidence highlights natural compounds as multi-target therapeutic agents against inflammatory pathologies through strategic pathway modulation. Rutin demonstrates colonic protective efficacy in acetic acid-induced ulcerative colitis models via selective inhibition of the high mobility group box 1 (HMGB1)/TLR4/MyD88/NF- $\kappa$ B signaling axis, and therefore might have potential as a gut-targeted anti-inflammatory agent [117]. Sweroside exhibits IL-6 suppression through PI3K/AKT pathway regulation, and molecular docking analyses have identified AKT1 as its primary binding target [118]. Luteolin mitigates oxidative-inflammatory crosstalk by scavenging ROS/reactive nitrogen species, thereby disrupting redox-sensitive signaling cascades [98]. Caffeic acid has shown novel anti-psoriatic mechanisms through dual suppression of early growth response protein 1 (EGR1)-mediated glutathione-specific gamma-glutamylcyclotransferase 1 (CHAC1) activation and ferroptosis inhibition, thus providing both novel chemical entities and mechanistic targets for psoriasis management [119]. Sweroside activates SIRT1, thereby inhibiting the NF- $\kappa$ B pathway and exerting anti-inflammatory effects [120]. Oleanolic acid modulates immune polarization in colitis models via allosteric activation of Src homology 2 domain-containing protein tyrosine phosphatase 2 (SHP2) phosphatase, which subsequently inhibits STAT3-driven Th17 cell differentiation and IL-17 production [121].

## 4. DISCUSSION

The core advantage of *Lonicera japonica* Thunb. (honeysuckle) anti-inflammatory activity is its multi-component synergy mediating multi-target and multi-pathway regulation, a characteristic that not only distinguishes it from synthetic single-target drugs but also fundamentally differentiates it from most natural products examined in research focusing on individual components. Specifically, the bioactive constituents in honeysuckle function not only as distinct agents but also through an intricate molecular synergy. By collectively regulating diverse targets, including receptors, enzymes, and transcription factors, they establish an interconnected network of signaling pathways. This integrated action enhances anti-inflammatory potency and restores immune homeostasis, in alignment with the TCM theory of clearing heat and detoxifying. Honeysuckle therefore provides a unique advantage of treating both symptoms and root causes.

This synergistic mechanism is supported by multiple lines of evidence. For example, chlorogenic acid and luteolin synergistically inhibit IL-1 $\beta$ -induced fibroblast-like synoviocyte proliferation by co-regulating

the NF- $\kappa$ B and JAK/STAT pathways [125]. Furthermore, these compounds dose-dependently enhance LPS-induced secretion of the anti-inflammatory cytokine IL-6, thereby balancing the pro-/anti-inflammatory cytokine network [126]. Beyond pairwise interactions, network pharmacology and experimental validation have demonstrated that the multi-component system of honeysuckle synergistically targets the TLR4/MyD88 axis [27]. These findings collectively confirm that molecular synergy among diverse bioactive components is a key underpinning of honeysuckle superior anti-inflammatory efficacy.

In contrast to single-target therapeutics that primarily modulate isolated nodes of the inflammatory cascade, honeysuckle has a network-based mode of action that involves complex pathway crosstalk. Because of its holistic nature, fully elucidating its efficacy would require transcending the study of isolated components by conducting a systemic exploration of synergistic targeting. Synthesizing these insights, Figure 7 maps the interaction network between the bioactive components and their molecular targets. By intuitively visualizing the shared regulatory nodes, this diagram not only summarizes the core findings of this review but also provides a foundational roadmap for future investigations into the multi-component, multi-target, and multi-signaling pathway mechanisms of honeysuckle.

However, current research still faces several pressing scientific challenges. In the NF- $\kappa$ B signaling pathway, the specific molecular mechanisms through which luteolin inhibits I $\kappa$ B degradation remain unclear; therefore, investigation through molecular docking and structural biology approaches is necessary to elucidate its direct interactions with I $\kappa$ B proteins. Similarly, the precise molecular targets of geniposide in regulating IKK $\alpha$  and p-NF- $\kappa$ B expression require further clarification. At the TLR2 receptor level, the inhibitory mechanisms of luteolin warrant in-depth analysis from the perspectives of receptor conformational changes and signal transduction. Regarding the MAPK pathway, further exploration is necessary to determine the specific binding patterns of caffeic acid, the most potent phenolic acid component, with p38, JNK, and ERK kinases, as well as potential upstream regulatory proteins.

Notably, the pharmacological effects of honeysuckle are not limited to intracellular signal regulation but also involve interventions in the extracellular microenvironment. Caffeic acid and chlorogenic acid have been demonstrated to alleviate inflammatory responses by inhibiting the AGE-RAGE/ROS/MAPK/NF- $\kappa$ B signaling cascade intracellularly. Additionally, these phenolic acids alter the surface charge characteristics of AGE-BSA through mechanisms such as hydrophobic interactions, oxidative conversion, and carboxymethyl lysine chelation, thereby disrupting their RAGE binding [88]. These findings provide a new perspective for understanding the comprehensive anti-inflammatory effects of honeysuckle.

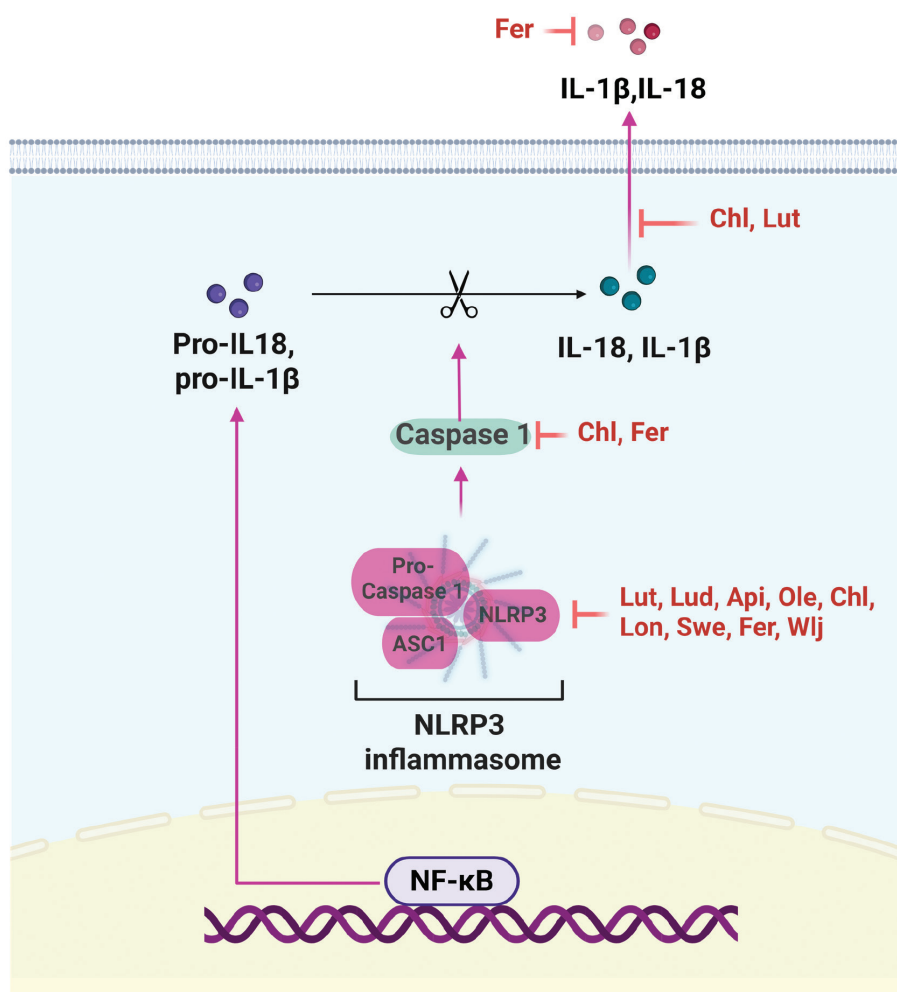


**Figure 6 | Honeysuckle exerts its anti-inflammatory effects through modulating the NLRP3 inflammasome.**

This figure was created with [BioRender.com](https://www.biorender.com). Chl, Chlorogenic Acid; Lut, Luteolin; Que, Quercetin; Fer, Ferulic Acid; Lud, Luteolin Derivatives; Api, Apigenin; Ole, Oleanolic Acid; Caf, Caffeic Acid; Neo, Neochlorogenic Acid; Isc, Isochlorogenic Acid C; Rut, Rutin; Lon, Lonicerin; Swe, Sweroside; Isa, Isochlorogenic Acid; Iaa, Isochlorogenic Acid A; Isb, Isochlorogenic Acid B; Wlj, WLJP-025p.

However, current research still faces substantial limitations. First, preclinical models have critical flaws. LPS-induced RAW264.7 macrophages mimic only acute, single-stimulus inflammation, but they cannot replicate multi-factorial human chronic conditions, and they lack human immune cell heterogeneity. Therefore, existing evidence is primarily preclinical, and extrapolation to humans would pose high risk. Second, although the synergistic hypothesis has received partial experimental support, more systematic quantitative validation through methods such as the Chou-Talalay joint index remains necessary. In translational medicine, the bioavailability of active components remains the primary obstacle to clinical application. Many bioactive compounds in honeysuckle (e.g., flavonoids and chlorogenic acid) exhibit low bioavailability that limits their clinical efficacy [127]. Because luteolin demonstrates poor oral bioavailability [128], novel drug delivery systems, such as PLGA-PEG nanoparticles, have been examined to

enhance bioavailability. Clinically, a phase II honeysuckle oral liquid trial indicated alleviation of acute pharyngitis, in agreement with preclinical data, whereas chlorogenic acid monotherapy failed in ulcerative colitis, thus confirming single-component inadequacy.

In conclusion, this review systematically elucidated the anti-inflammatory mechanisms of honeysuckle and, more importantly, established a research paradigm for deciphering multi-component synergistic interactions in TCM. The development of this framework should not only advance modern research on honeysuckle but also provide valuable insights for analyzing mechanisms in other herbal compound formulations. Future research should focus on precise validation of molecular targets, quantitative analysis of synergistic effects, and the development of novel drug delivery systems, to accelerate the transformation of honeysuckle from a traditional medicinal herb to a modern pharmaceutical product.



enabling simultaneous symptom-root treatment for inflammation-related diseases.

Future research should focus on the following directions: 1) leveraging artificial intelligence and multi-omics (genomics, transcriptomics, and metabolomics) technologies to decipher the dynamic component-target-pathway-disease interaction network of honeysuckle, and to identify core synergistic component combinations and their precise regulatory mechanisms in specific inflammatory conditions, thus laying a foundation for targeted drug development; 2) using structural biology and chemical proteomics to achieve high precision in target validation, thereby clarifying the key binding modes between active components and their molecular targets to guide the optimization of component structures or synergistic ratios for enhanced efficacy and specificity; 3) advancing from traditional cell lines and animal models to more physiologically relevant platforms such as disease-specific organoids and organ-on-a-chip systems, which enable human-relevant physiological evaluation of drug efficacy, toxicity, and pharmacokinetics, thereby decreasing the risk of clinical trial failure; 4) developing novel delivery systems (e.g., lipid nanoparticles, polymer micelles, and targeted ligand-modified nano-carriers) to overcome the poor water solubility, low bioavailability, and non-specific tissue distribution of honeysuckle's active components, thus achieving targeted delivery to inflamed sites and improving the therapeutic index; and 5) promoting high-quality clinical evidence-based research complying with international standards, including randomized controlled trials to evaluate the efficacy, safety, and optimal dosage of synergistic component combinations in specific patient populations, and real-world studies to clarify their clinical positioning. We anticipate that, through the integration of traditional knowledge with modern technology, honeysuckle research can provide a new paradigm for anti-inflammatory drug development that shifts from single-target inhibitors to multi-dimensional regulatory natural product design, and ultimately offers safer and more effective options for the precision treatment of inflammatory diseases.

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#### CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported herein.

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