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Mini Review

Arctigenin: Harnessing Nature's Power as an Anti-Inflammatory Agent

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Abstract

Inflammation is a crucial response to injury and infection, but when it becomes chronic, it can contribute to various diseases such as arthritis, cardiovascular issues, and neurodegenerative disorders. Traditional anti-inflammatory drugs like NSAIDs and corticosteroids effectively alleviate symptoms but often come with significant side effects, including gastrointestinal, cardiovascular, and renal complications. This has sparked growing interest in natural anti-inflammatory agents derived from plants, known for their potential to mitigate these adverse effects. Bioactive compounds found in plants, including flavonoids, terpenoids, and alkaloids, have demonstrated promising anti-inflammatory properties. Arctigenin, a bioactive lignan present in several plants, has attracted attention due to its potent anti-inflammatory effects. Arctigenin works by influencing critical inflammatory pathways, such as inhibiting NF-κB activation, reducing pro-inflammatory cytokines, and counteracting oxidative stress. Its mechanism involves suppressing inflammatory mediators and enzymes like COX-2 and iNOS. Additionally, arctigenin blocks the MAPK and PI3K/Akt signaling pathways, underscoring its potential therapeutic value. In addition, arctigenin shows promise as a candidate for drug development due to its multifaceted anti-inflammatory mechanisms and limited side effects. However, extensive follow-up studies, including clinical trials and pharmacokinetic evaluations, are necessary to fully understand its therapeutic potential, safety profile, and effectiveness in human use.

Keywords: *Arctium lappa L.*; Compositae; Arctigenin; Anti-inflammatory; Pathogenesis

Introduction

Inflammation is a critical and evolutionarily conserved process that activates both immune and non-immune cells to protect the host from bacteria, viruses, toxins, and diseases, thereby facilitating tissue repair and recovery [1]. Acute inflammation involves a series of cellular and molecular events designed to mitigate harm or infection, ultimately restoring tissue homeostasis. However, when acute inflammation is not properly regulated, it can progress into chronic inflammation, leading to various chronic inflammatory diseases [2]. At the tissue level, infection or injury triggers local immune, vascular, and inflammatory cell responses,

resulting in redness, swelling, heat, pain, and tissue loss [3]. Pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and vascular endothelial growth factor (VEGF), play crucial roles in this process. Several biological therapies have been developed to manage inflammation, including those that target specific cytokines or their receptors, inhibit lymphocyte trafficking, prevent monocyte-lymphocyte costimulatory molecule binding, or deplete B lymphocytes [4]. Kinase inhibitors that act downstream of cytokine receptors represent a promising frontier in anti-inflammatory drug development. These orally active small-molecule inhibitors target intracellular signaling pathways. Determining an effective concentration that avoids organ toxicity is critical, given the involvement of many intracellular signaling molecules in normal cellular functions. Statins, commonly used for lowering serum cholesterol, also exhibit anti-inflammatory properties. Nonetheless, a major side effect of biologicals is a reduced host defense against infections, which, if detected early, can be effectively treated with antibiotics [5]. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed medications for inflammation [6]. In elderly patients over 60, approximately 7.3% filled at least one NSAID prescription within a year [7]. The adverse effects of NSAIDs are primarily due to the inhibition of the cyclooxygenase (COX) enzyme, with gastrointestinal complications, renal disturbances, and cardiovascular events being the most significant side effects [8].

Unlike modern allopathic drugs, which typically consist of single active components targeting specific pathways, herbal medicines often rely on a synergistic approach, where multiple plant-derived molecules act on various elements of complex cellular pathways [9]. For instance, garlic (*Allium nigrum*) contains sulfur compounds with significant biological activities useful in managing inflammatory disorders. Similarly, hesperidin is recognized for its anti-inflammatory properties [10]. Curcumin, the primary component of turmeric (*Curcuma longa*), has been used in Ayurvedic medicine for centuries to treat inflammatory disorders [11]. Numerous studies have documented the role of various herbs in inflammation remission, with Curcuma longa showing the most clinical evidence for treating different inflammatory conditions such as rheumatoid arthritis (RA), uveitis, and inflammatory bowel disease (IBD) [12]. *Arctium lappa* L. (Asteraceae), known as "Bardana," is a traditional anti-inflammatory agent in folk medicine. Arctigenin, a bioactive lignin isolated from *A. lappa*, inhibits the production of inducible nitric oxide synthase, interleukin-6, interleukin-2, interferon-gamma, and TNF-α in macrophages [13]. Both arctigenin and its glycoside, arctiin, are key active components of *Arctium lappa* L., with arctigenin showing potent anti-inflammatory effects and various other biological activities, including anti-tumor, anti-leukemic, anti-colitis, anti-viral, and vascular protective effects [14]. This review explores arctigenin's anti-inflammatory properties, elucidates its molecular mechanisms, evaluates its therapeutic applications, and identifies clinical use challenges, consolidating findings from preclinical and clinical studies to understand its potential in medical research and treatment.

Arctigenin: Multifaceted Bioactive Molecule

The chemical structure of arctigenin is characterized by a dibenzylbutyrolactone skeleton, which plays a crucial role in its bioactivity. This structure allows arctigenin to interact with various molecular targets, facilitating its diverse pharmacological effects. The unique configuration of arctigenin's chemical structure underpins its multifaceted biological activities, which include significant anti-inflammatory and antioxidant effects. As research progresses, the therapeutic potential of arctigenin continues to expand, highlighting its role in the development of treatments for a variety of inflammatory and oxidative stress-related conditions.

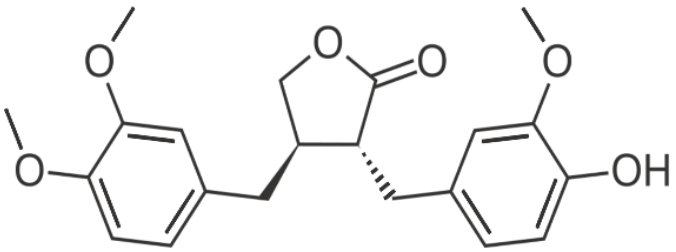

Figure 1: Chemical structure of arctigenin.

In traditional Chinese medicine, *A. lappa* has been employed to treat a range of ailments, including sore throats, infections, and inflammatory conditions, underscoring the ethnomedical significance of arctigenin. The ethnopharmacological applications of arctigenin are extensive due to its diverse and potent biological activities. It has garnered significant attention for its anti-inflammatory, anti-oxidant, anti-viral, and anti-cancer properties, making it a promising candidate for the development of novel therapeutic agents. Arctigenin's anti-inflammatory effects are particularly noteworthy. Research indicates that arctigenin can effectively inhibit the production of pro-inflammatory cytokines and mediators such as nitric oxide (NO) and prostaglandin E2 (PGE2). This inhibition is primarily achieved through the suppression of nuclear factor-kappa B (NF-κB) activation, a critical regulator in the inflammatory response [15]. Moreover, arctigenin has been shown to modulate oxidative stress pathways, contributing further to its anti-inflammatory properties. It reduces the levels of reactive oxygen species (ROS) and enhances the activity of antioxidant enzymes, thereby mitigating oxidative damage and inflammation [16]. These dual actions of reducing inflammation and oxidative stress position arctigenin as a valuable agent in treating chronic inflammatory diseases.

Mechanistic Aspect of Arctigenin

Arctigenin exhibits significant anti-inflammatory properties by targeting multiple inflammatory pathways. It inhibits nuclear factor kappa B (NF-kB) activation in lipopolysaccharide (LPS)- or peptidoglycan (PGN)-stimulated peritoneal macrophages, decreasing the expression of pro-inflammatory cytokines as Interleukin-1-beta (IL-1β), Interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [17-19], while increasing Interleukin 10 (IL-10) and CD204 levels [20]. Additionally, arctigenin inhibits LPS-induced phosphorylation of phosphoinositide 3-kinase (PI3K), Ak strain transforming (AKt), and IKK-β, but not interleukin-1 receptor-associated kinase 1 (IRAK-1) phosphorylation [21]. It also suppresses the nuclear translocation of NF-kB p65 and the binding of PI3K antibody in LPS-stimulated macrophages. In systemic inflammation models, arctigenin reduces blood levels of IL-1β and TNF-α and mitigates symptoms in trinitrobenzene sulfonic acid (TNBS)-induced colitic mice by regulating various cytokines and signaling pathways [22]. Arctigenin blocks LPS-inducible nitric oxide synthase (iNOS) expression by inhibiting I-kBa phosphorylation and the nuclear translocation of p65, contributing to its anti-inflammatory effects [23]. It also inhibits activator protein 1 (AP-1) binding and TNF-α production in LPS-exposed cells [24], significantly reducing NF-kB DNA binding and phosphorylation of IkB and IKK [25]. Arctigenin modulates immune responses by regulating TNF-α and nitric oxide production and lymphocyte proliferation [26]. In LPS-stimulated RAW264.7 cells, arctigenin reduces the phosphorylation of the signal transducer and activator of transcription 1 (STAT1), signal transducer and activator of transcription 3 (STAT3), and Janus kinase 2 (JAK2) [27]. It decreases iNOS phosphorylation by inhibiting extracellular signal-regulated kinase (ERK) and Src activation, thereby suppressing iNOS enzyme activity [28]. Inactivated human T lymphocytes, arctigenin inhibits proliferation, interleukin-2 (IL-2), and interferon-gamma (IFN-γ) production and decreases NF-AT-mediated reporter gene expression [29]. Additionally, it impacts AKT and protein kinase C (PKC) expression, affecting downstream genes like NF-κB and Mitogen-activated protein (MAP) kinases [30]. Arctigenin also alleviates LPS-induced acute lung injury by downregulating NF-κB p65 and promoting the phosphorylation of IκBα and adenosine monophosphate-activated protein kinase (AMPKα) activation [31]. It enhances heme oxygenase-1 expression and decreases MAPK phosphorylation [32]. In colonic tissues, it reduces inflammatory cell infiltration and downregulates multiple inflammatory markers [33]. In TNBS-induced colitis, arctigenin lowers levels of TNF-α and IL-6, while increasing IL-10 levels, promoting neuronal survival [34]. It inhibits the differentiation of T helper 17 (Th17) and Th1 cells and suppresses the mammalian target of the rapamycin complex 1 (mTORC1) pathway in T cells using Electrophoretic mobility shift assay (EMSA) and Western blotting, respectively [35]. Furthermore, arctigenin inhibits NF-κB signaling in porcine circovirus 2 (PCV2) infection, reducing inflammatory cell infiltration and cytokine expression [36,37]. It protects against liver necroinflammation and enhances IL-10 production, thereby improving hepatic function [38]. Arctigenin also safeguards tubular epithelial cells from transforming growth factor-beta (TGF-β1)-induced changes by inhibiting the ROS/ERK1/2/NF-κB pathway [39]. Lastly, it ameliorates psoriatic manifestations in an imiquimod-induced murine model by reducing inflammatory cell adhesion and chemotaxis [40].

Doses/Concentration (Mode of Administration)	Models	Findings	Data sources
62.6 µg/ml (Intraperitoneal)	PCV2-induced infection in pro-inflammatory cytokine production (Transfection, luciferase reporter)	Suppresses NF-κB activation	[14]
100, 30, & 10 µM (Topical)	LPS-activated human peripheral blood mononuclear cells and RAW264.7 cells (PDEs enzyme)	Suppresses the TNF-α production with IC50=35.18 µM.	[40]
5,10 & 20 µg/g (Intraperitoneal)	Thioglycollate-induced acute peritonitis (Mice)	↓ inflammation cells and inhibits cytokine expression	[37]
5 & 10 µg/g (Intraperitoneal)	ConA-induced acute hepatitis (Mice)	↑ liver function and reduces inflammation markers.	[41]
50 µmol/l	TNF-α stimulated BEAS-2B cells (NF-κB-luciferase)	Inhibits PI3K/AKT and Ras/MAPK pathways.	[30]

20, 40, & 80 mg/kg (Intragastrical)	Convection-enhanced drug delivery-induced brain injury (Mice)	↓ brain hematoma and inflammation markers.	[34]
50 mg/kg (Intraperitoneal)	LPS-induced acute lung injury (Mice)	↓ NO production and lung inflammation.	[32]
0.5 & 1 μM	TGF-β1-induced epithelial-mesenchymal transition (EMT)-like changes (Renal tubular epithelial & HK-2 cells)	Inhibits MCP-1 activation, and ROS/MAPK/NF-κB pathways.	[39]
30 & 100 mg/kg (Intravenous)	LPS-induced acute lung injury (Male Sprague-Dawley rats)	↓ TNF-α, IL-1, & IL-6 levels, NF-κB & p65 expressions, and ↑ AMPK	[31]
10 to 20 μmol/l (Intraperitoneal)	LPS-induced inflammation in peritoneal macrophage (Male mice)	Inhibits NF-κB activation & p65 nuclear translocation, suppresses PI3K & AKT phosphorylation, increases IL-10 & CD204 levels; decreases IL-1, IL-6, and TNF-α levels.	[22]
5 mg/kg (Intraperitoneal)	LPS-induced colitis (mice)	↓ IL-1β, TNF-α, NF-κB activation; MPO, IL-6, PI3K, AKT, IKK phosphorylation; ↑ IL-10 and CD204 express ion	
25 & 50 mg/kg; intravenous, oral, intraperitoneal	Dextran sulfate sodium-induced colitis in mice (Electrophoretic mobility shift assay (EMSA) and Western blotting)	↓ cytokines expressions. Blocking Th1/Th17 responses, activating NF-κB, suppressing MAPK, and inhibiting mTORC1 all reduce Th1/Th17 levels and related inflammation.	[33] [35]
50 μM	LPS-induced inflammation in RAW 264.7	↓ iNOS enzyme activity and iNOS phosphorylation via preventing ERK and Src activation.	[28]
10 to 50 μM		↓ phosphorylation and nucleus translocation of JAK, STAT1 and STAT3, as well as suppression of iNOS, IL-1, and IL-6 gene expression.	[27]
3 to 100 μM		(IC50=8.4 μM) significantly suppressed LPS-induced production of NO. Inhibited the release of TNF-α in LPS-activated RAW 264.7 and THP-1 cells (IC_{50}=19.6 & 25.0 μM). Suppressed the release of IL-6 with IC50=29.2μ M in RAW 264.7 cells.	[21]
0.1 to 10 μM		Inhibiting NF-κB, reducing iNOS and COX-2, and suppressing phosphorylation of IκB, IKK, and MAPKs dampens inflammatory signalling.	[25]

8.25 to 25 μM	Anti-CD3/CD28 Ab-stimulated cell proliferation and cytokine gene expression in primary human T lymphocyte.	IC_{50} of 15.7 μM activated T lymphocyte proliferation. ↓ NF-AT-mediated reporter gene expression; suppression of IL-2 and IFN- gene expression; inhibited T lymphocyte proliferation.	[29]
0.1-10 μM	Silica-induced inflammation in RAW264.7	Inhibited the intracellular ROS production.	[20]
0.01 to 1 μM	LPS-induced inflammation in RAW264.7 (*in vitro*)	↓ TNF-α generation and mRNA levels, reduction of AP-1-consensus oligonucleotide binding, and inhibition of MAPK phosphorylation and activation. Arctigenin potently inhibited the activity of MKK1 (IC_{50}=1 μM).	[24]
0.01 to 1 μM		NO production and iNOS expression are suppressed by inhibiting IκBα phosphorylation and p65 nuclear translocation, with strong iNOS inhibition by LPS (IC50 < 0.01 μM)	[23]
1 to 16 μM	LPS-stimulated murine macrophage RAW2647 and human macrophage U937	Inhibited strongly TNF-α production by lipopolysaccharide-stimulated RAW2647 and differentiated U937 (IC_{50}=5.0 & 3.9 μM); attenuated T & B cell proliferation stimulated by concanavalin A (IC_{50}=2.9 & 14.6 μM) by LPS.	[26]

Table 1: Summary of preclinical studies on arctigenin's anti-inflammatory effects and its impact on inflammatory markers.

Conclusion and Future Perspectives

Arctigenin is emerging as a promising natural compound with potent anti-inflammatory properties, offering a novel approach to managing inflammation by targeting key pathways such as the inhibition of NF-κB activation and suppression of pro-inflammatory cytokines like TNF-α and IL-6. Its regulation of enzymes like COX-2 and iNOS further enhances its potential as a safer alternative to traditional anti-inflammatory drugs, which often have significant side effects. With its multifaceted mechanisms and favorable safety profile, arctigenin holds great promise for developing new therapeutic strategies for chronic inflammatory conditions, including arthritis, neuroinflammation, and possibly certain cancers. However, to fully realize its potential, future research should focus on clinical trials, pharmacokinetics, and dosage optimization in humans. As these studies progress, arctigenin could play a key role in advancing safer, more holistic treatments for inflammatory diseases, marking a significant step toward integrating nature's resources into modern medicine.

Declaration of competing interest: The authors declared that they have no conflicts of interest.

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