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A review on anti-inflammation activity of phenol compound paeonol

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Abstract Paeonol is a bioactive phenol present in *Dioscorea japonica*, *Paeonia suffruticosa* and *Paeonia lactiflora*. It is the main active ingredient in the traditional Chinese medicines Mudanpi and Xu Changqing. Clinical applications of paeonol are mainly focused on anti-inflammatory effects due to its ability to act as an antioxidant, a regulator of inflammatory enzyme activities, a modulator of inflammatory signaling pathways and a regulator of adhesion molecules to modulate inflammation through molecular mechanisms of action. In addition, paeonol also regulates inflammation by regulating the metabolism of gut microbes. In this review, we searched PubMed, Web of Science, ESI and other websites using “paeonol” “inflammation” “oxidative stress” “signaling pathways” and “gut microbiota” as keywords. We mainly referred to the relevant literature in the last decade and systematically summarized the studies on the anti-inflammatory effects of paeonol to provide a reference for new drug development and clinical application of paeonol.

Keywords: paeonol; inflammation; molecular mechanisms; gut microbes

1 Introduction

Inflammation is the body’s natural defense mechanism against injury or infection when the body is injured, infected or irritated [1]. Typical symptoms of inflammation include redness, swelling, pain, fever, and dysfunction, and when inflammation is excessive or persistent, it may lead to disease and tissue damage [2]. Chronic inflammation involves the body’s specific immune response, and is related to rheumatic diseases, colitis, cardiovascular diseases, allergies, cancer, neuroinflammation, etc. [3-9]. Inflammation involves different immune cell types such as mast cells, T cells, B cells, NK cells, neutrophils, and macrophages. Inflammatory factors released by immune cells (such as IL-1β, IL-2, TNF-α, IL-6, IL-8, IFN-γ, etc.) are closely related to the occurrence and development of inflammation [10-15]. Studies have shown that oxidative stress can promote the occurrence and development of inflammation. Under oxidative stress, reactive oxygen species (ROS) and reactive nitrogen species (RNS) can directly or indirectly activate inflammatory signaling pathways and trigger inflammatory reactions [16,17]. In addition, the activities of some regulatory enzymes, such as inducible nitric oxide synthase (iNOS), matrix metalloproteinases (MMPs), lipoxygenase and cyclooxygenase (COX), play an important role in the occurrence and development of inflammation [18-21]. According to research, NF-κB,

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Janus kinase/Signal transduction and transcriptional activator (JAK-STAT), Toll-like receptor (TLR) pathway, mitogen-activated protein kinase (MAPK), PI3K/Akt, Adenylate-activated protein kinase (AMPK) and other pathways have been identified as regulatory signaling pathways for inflammation initiation and abatement [22-27]. Immune cells such as T cells, NK cells and macrophages can release TNF-α to mediate inflammation and injury, and at the same time, TNF-α can also induce the expression of cell adhesion factors such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [28, 29].

At present, steroid and non-steroidal anti-inflammatory drugs are commonly used in the treatment of acute inflammation [30, 31]. However, for chronic inflammation, these existing chemosynthetic anti-inflammatory drugs are not completely effective and have certain adverse reactions [32]. Natural active substances often have the characteristics of novel structure, high activity and few adverse reactions, and are often considered as a new therapeutic strategy for the prevention and treatment of inflammatory diseases. In this regard, people pay more and more attention to the search and development of anti-inflammatory drugs from natural products [33].

Paeonol is a natural active ingredient isolated from the root of Paeonia lactiflora in the buttercup family, and is a biologically active phenol [34]. Paeonol has a chemical structure of 2'-hydroxy-4'-methoxyacetophenone (Fig. 1), a molecular weight of 166.17 g/mol and a melting point of 52.5 °C.

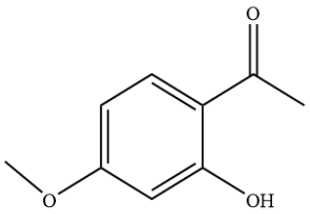

Fig. 1 Chemical structure of paeonol

Paeonol is a white crystalline powder, insoluble in water, and its clinical application is restricted by its poor water solubility and rapid metabolism [35]. For this reason, the development of different formulation of paeonol is a research hotspot in recent years. Paeonol possesses pharmacological actions that include neuroprotection, anti-tumor, anti-inflammatory, and anti-cardiovascular disease with a good potential application value and development prospects [36]. Paeonol has been studied as a typical anti-inflammatory active ingredient since the 1960s [37]. The clinical application of paeonol mainly focuses on its anti-inflammatory activity, which is due to its excellent regulation of inflammatory factors and inflammatory pathways, can regulate inflammation from various molecular mechanisms of action. Fig. 2 systematically summarizes the molecular mechanism of anti-inflammatory action of paeonol. In addition, intestinal microorganisms are closely related to inflammation, and inflammatory responses can be caused by changes in intestinal microbial species or disturbances in intestinal flora. Studies have shown that paeonol acts as a regulator of gut microbes and thus regulates inflammation.

2 Paeonol as an antioxidant

Oxidative stress is caused by the imbalance of cellular oxidants and antioxidants in the body under the action of induction factors, resulting in poor elimination of reactive oxygen species (ROS). Oxidative stress can lead to the destruction of REDOX signaling and control [38]. The imbalance of this protective mechanism can lead to the damage of cellular molecules such as DNA, proteins and lipids [39]. In addition, under hypoxia conditions, the mitochondrial respiratory chain may also produce nitric oxide (NO), thus producing RNS [40]. Long-term overproduction of ROS/RNS will lead to the damage of cell structure and function, which will

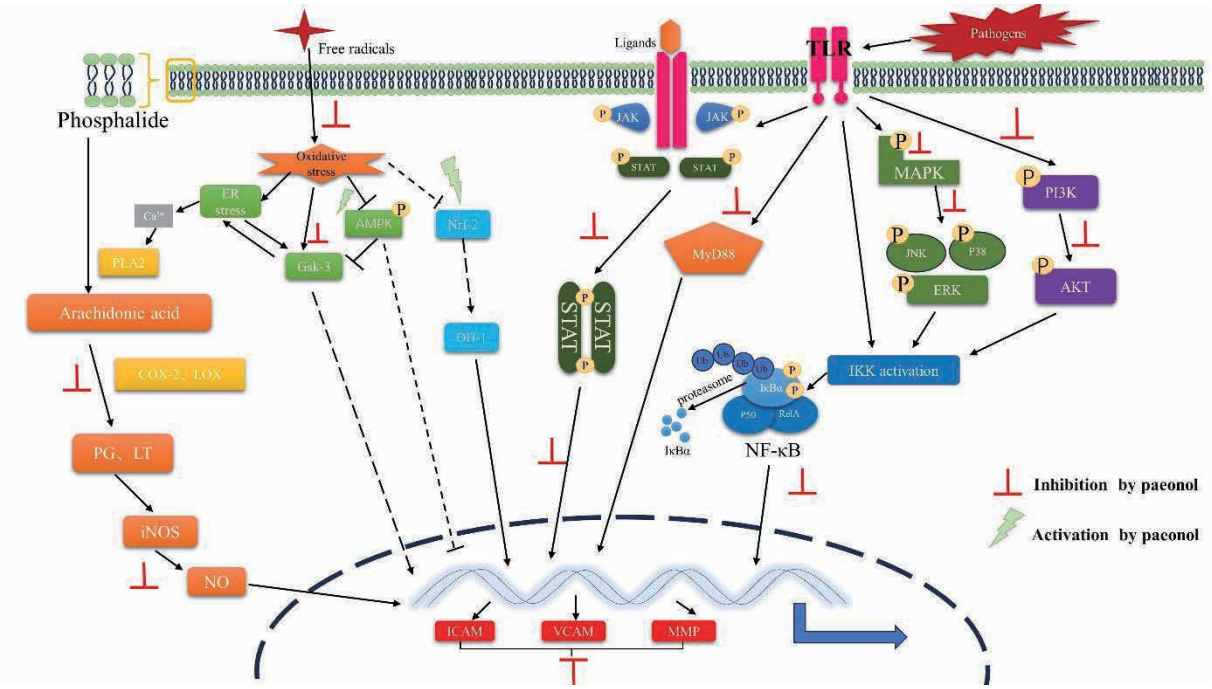

Fig. 2 Molecular mechanism of anti-inflammatory action of paeonol

cause irreversible damage, leading to cell necrosis and apoptosis [41]. Studies have shown that excess ROS/RNS produced in the process of oxidative metabolism can lead to the secretion and synthesis of inflammatory factors, thus initiating the inflammatory response [42]. For example, oxidative stress increases levels of TNF-α and IL-6 [43]. Paeonol has been reported to have excellent antioxidant activity, with hydroxyl radical scavenging activity and 1, 1-diphenyl-2-trinitrophenylhydrazine (DPPH) free radical scavenging activity, and has a significant inhibitory effect on LPS-induced NO production [44]. When the cell is exposed to toxic chemicals or the function of the cell is impaired, inhibition of nuclear factor E2-related factor 2 (Nrf-2) can lead to overexpression of ROS [45]. The activation of Nrf-2 will further stimulate the activation of heme oxygenase-1 (HO-1), and the activated expression of Nrf-2/HO-1 will reduce the oxidative stress of cells [46]. Guo, et al. [47] used hydrogen peroxide melanocytes to model oxidative stress and verified that paeonol can protect melanocytes from oxidative stress by activating Nrf-2. Studies have found that paeonol can inhibit liver oxidative stress by activating Nrf-2/HO-1, reduce inflammation, further prevent liver cell apoptosis, and improve liver ischemia/reperfusion (HIR) [48]. Inflammatory factors released by activated microglia have been implicated in the pathogenesis of neurodegenerative diseases，administration of paeonol to lipopolysaccharide (LPS)-induced-treated microglia inhibited microglial migratory activity and ROS production [49]. Similarly, paeonol can prevent cognitive dysfunction in streptozotocin (STZ)-induced rat Alzheimer's disease (AD) models, improve oxidative stress and neuroinflammation, and effectively inhibit nerve cell apoptosis [50]. Chae, et al. [51] discovered that paeonol inhibited the LPS-induced release of NO, PGE2, and IL-6 from RAW264.7 cells. Furthermore, paeonol blocked the activation of inducible nitric oxide synthase induced by LPS. Overall, many inflammatory responses are associated with oxidative stress, and paeonol, as an antioxidant with excellent free radical scavenging ability, plays an important role in the treatment of inflammation.

3 Paeonol as a modulator of inflammatory enzyme activities

The synthesis of prostaglandins (PGs) includes the conversion of arachidonic acid (AA) to prostaglandin

H2 (PGH2) catalyzed by cyclooxygenases (COX-2). Subsequently, prostaglandin synthase converts PGH2 to PGs [52]. The production of PGs is related to the existence of a large amount of NO in the body, which is due to the "cross-talk" effect between iNOS and COX-2. iNOS can up-regulate the expression of COX-2, and COX-2 also promotes the expression of iNOS, both of which jointly participate in inflammation [53]. In addition, lipoxygenase (LOX) is involved in the synthesis of PGs and has a regulatory effect on AA [54].

Studies have shown that paeonol can inhibit the expression of COX-2 in cells and reduce the level of PGE2 in a concentration-dependent manner and time-dependent manner [55, 56]. He, et al. [57] found that paeonol has a therapeutic effect on neuroinflammation, which is related to its ability to inhibit the expression of COX-2 and iNOS protein induced by LPS. In addition to this paeonol inhibited oxidized low-density lipoprotein (ox-LDL)-mediated increase in LOX-1 protein expression in a concentration-dependent manner [58]. LOX plays a major role in leukotriene derivatization in the AA pathway, which has been implicated in a variety of inflammatory diseases, including asthma, rheumatoid arthritis, and inflammatory bowel disease [59].

NO is a biological signaling molecule involved in various physiological reactions in the body, which is catalyzed by iNOS. Past studies have shown that NO can participate in a variety of *in vivo* biochemical reactions such as cardiovascular regulation neurotransmission, immunomodulation, and oxidative stress, and is beneficial in most cases, however, excess NO may be associated with inflammatory diseases [60]. Excessive NO reacts with oxygen (or superoxide) to generate nitrogen oxides, which subsequently interact with biomolecules, playing a pivotal role in the initiation of acute inflammation [61]. Nitric oxide can react with the superoxide anion to produce peroxynitrite, a potent oxidizing agent responsible for DNA damage *in vivo*, oxidation of low-density lipoproteins, and inhibition of mitochondrial respiration. These actions can lead to apoptosis and cell death [60, 62]. The impact of paeonol on R848-induced iNOS mRNA expression in macrophages was investigated through protein blotting. The results indicated a concentration-dependent inhibition of the relative expression level of iNOS mRNA by paeonol [63].

MMPs comprise a series of tightly regulated proteases that degrade numerous extracellular matrix (ECM) and basement membrane protein components, and tissue inhibitors of metalloproteinases (TIMPs) act as endogenous protease inhibitors to maintain dynamic homeostasis by directly or indirectly inhibiting MMPs activity [64, 65]. The imbalance between MMPs and TIMP is associated with inflammation, and inflammatory factors such as IL-1β, TNF-α, and IFN-γ can stimulate MMPs expression through NF-κB activation [66]. Expression of MMPs can be involved in inflammation, fibrotic diseases, cancer and other related pathological processes [65]. Wang, et al. [67] demonstrated that IL-1β induced abnormal MMP expression in mouse chondroprogenitor cells (ATDC5), while paeonol administration effectively reduced MMP expression levels, offering a potential treatment for osteoarthritis (OA). Abdominal aortic aneurysm (AAA) represents a chronic inflammatory condition distinguished by restrictive dilation, Chen, et al. [68] demonstrated that paeonol suppressed the expression of MMPs, inhibited the activation of the NF-κB pathway, and effectively treated AAA. These results indicate that paeonol can be used as a regulator of enzyme activity that produces inflammation.

4 Paeonol as a modulator of inflammatory signaling pathways

NF-κB, JAK-STAT, TLR pathway, MAPK, PI3K/Akt, and AMPK have been recognized as crucial regulatory signaling pathways involved in the initiation and abatement of inflammation [69, 70]. Paeonol serves as a modulator of inflammatory signaling pathways, effectively suppressing the expression levels of inflammatory mediators.

NF-κB is a transcription factor that has been implicated in apoptosis, inflammation, and various autoimmune diseases, and activation of NF-κB is thought to be part of the stress response, which

can be activated by stimuli such as bacterial and viral infections (e.g. Toll-like receptors recognize pathogens), inflammatory factors, and antigen receptors [71]. Upon activation of the NF-κB pathway, degradation of the IKK complex induces NF-κB activation and release into the nucleus, where NF-κB-mediated transcriptional activation occurs, engaging the relevant genes in inflammatory and immune cascade responses [72]. The ultimate outcome of this signaling cascade is the generation of inflammatory cytokines (such as TNF, IL-1β, and IL-6) that stimulate an inflammatory reaction [73]. Zhang, et al. [74] used L-arginine to induce acute pancreatitis (AP) in mice in their experiments. They observed the effect of paeonol on the NF-κB signaling pathway in mice by intraperitoneal injection and found that paeonol could play an anti-inflammatory role in pancreatitis by modulating this signaling pathway, thus significantly improving the symptoms of L-arginine-induced AP. Moreover, Li, et al. [75] found that paeonol could alleviate periodontitis in rats by modulating the Nrf-2/NF-κB pathway, and attenuate the inflammatory response and oxidative stress in gingival tissues.

When the cytokine binds to the receptor outside the cell membrane, the cytokine receptor is activated and transmits the signal to JAK kinase, which undergoes phosphorylation and further phosphorylates the downstream molecule STAT; the phosphorylated STAT can enter the nucleus of the cell, and the activated STAT dimer binds to the conserved genome regulatory sequences on the DNA in order to induce the expression of many genes [76]. Previous studies have shown that activation of Janus kinase (JAK) and STAT signaling pathways further leads to the activation of genes encoding inflammatory mediators, which propagate and amplify inflammatory factors such as IL-6 and TNF-α [77]. Paeonol inhibits STAT3 phosphorylation in a concentration-dependent manner, blocks IL-6-induced STAT3 activation, and reduces inflammatory promotion in the tumor microenvironment [78]. In addition, paeonol reduced trinitrobenzene sulfonic acid (TNBS)-induced colitis in mice by interfering with the transcriptional activity of STAT1 [79].

TLR are an important class of protein molecules involved in non-specific immunity (natural immunity), whereby innate immune cells of dendritic cells recognize invading pathogens and respond appropriately to resolve the infection. Inflammatory DCs in psoriasis are an important source of inflammatory factors that mediate inflammation in keratin-forming cells, thereby amplifying inflammation [80]. Meng [81] investigated the effect of paeonol on inflammation in a mouse model of imiquimod induced psoriasis, and found that paeonol dose-dependently treated psoriasis by decreasing MyD88, a key TLR junction protein molecule in the Toll-like receptor signaling pathway, and blocking the TLR7/8-mediated signaling pathway in DC, demonstrating that paeonol can alleviate psoriasis by inhibiting inflammatory factor production to alleviate IMQ-induced psoriasis in mice.

MAPK is a family of serine/threonine kinases, and four distinct groups of MAPKs exist in mammals, ERK1/2, ERK5, JNK1/2/3, and p38, which are activated by specific MAPK kinases (MAPKK) [82]. Among these MAPK family members, mitogens and growth factors predominantly stimulate the ERK1/2 pathway, while oxidative stress and inflammation serve as primary triggers for the JNK and p38 pathways [83]. Preliminary animal study data suggest anti-inflammatory activity of targeted ERK, JNK, p38 inhibitors [84]. Tang, et al. [85] induced inflammation in RAW 264.7 cells (mouse monocyte macrophage leukemia cells) with LPS and found that paeonol reduced intracellular levels of P38 and ERK1/2 phosphorylation in a dose-dependent manner, which in turn ameliorated airway inflammation in mice. In addition, paeonol and its metabolites inhibited dextrose sodium sulfate-induced colitis by blocking the phosphorylation of MAPK/ERK 1/2 and p38 [44]. Inflammation is not mediated by a single signaling pathway, and it has been shown that paeonol significantly attenuates allergen-induced airway lung eosinophilic inflammation by modulating the NF-κB /Toll-like receptor 4 /MAPK signaling pathway [85, 86]. Similarly, paeonol blocked LPS-stimulated inflammatory responses in BV-2 and

RAW264.7 cells by modulating MAPK and NF-κB signaling pathways [87].

The transcriptional activity of NF-κB is regulated by intracellular cascade reactions, including MAPK and PI3K/Akt pathways. Among them, MAPK is known as the upstream activator of NF-κB, which regulates the transcriptional activation of the NF-κB pathway [88]. In the PI3K/Akt pathway, activated Akt increases IKKα phosphorylation and activates the NF-κB pathway [89]. Previous research has demonstrated that PI3K/Akt can mitigate the production of inflammatory factors, such as TNF-α, IL-1β, and IL-6, exerting an anti-inflammatory role [90]. Studies indicate that paeonol substantially inhibits IL-1β and TNF-α induced phosphorylation of PI3K/AKT [67, 91], exhibiting promising therapeutic effects on arthritis diseases.

AMPK is an enzyme complex that plays an important role in both macrophage polarization and inflammation development [92]. AMPK is involved in the regulation of the inflammatory response, which is due to the fact that AMPK can inhibit the activation of the NF-κB pathway indirectly through downstream proteins and suppress inflammatory factor expression [93]. Glycogen synthase kinase-3 beta (GSK-3β) is a redox-sensitive signaling molecule and a key regulator of the balance between inflammatory and anti-inflammatory factors, and endoplasmic reticulum (ER) stress can induce an inflammatory response through GSK-3-related signaling pathways, in which the AMPK / GSK-3 pathway is associated with inflammatory responses [94-96]. Studies have shown that paeonol promotes AMPK activation and decreases GSK-3β activation in the rat kidney, reduces Pd-induced inflammation and ER stress, and has a protective effect on the kidney [97].

5 Paeonol as a modulator of of adhesion molecules

ICAM-1 and VCAM-1 mainly regulate the adhesion of leukocytes to endothelial cells in a variety of acute or chronic inflammatory diseases, and promote leukocyte recruitment, migration and activation [98]. ICAM-1 plays an important role in promoting adhesion at sites of inflammation and regulating the body's immune response. ICAM-1 on endothelial cells mediates cell-to-cell or cell-to-matrix contact and binding, thus participating in immune response, inflammatory response, and other physiopathological processes [99]. VCAM-1 is able to transfer white blood cells into tissues by binding to specific molecules on the surface of white blood cells. In addition, it can be secreted into the bloodstream, thereby causing a wider inflammatory response [100]. ICAM-1 and VCAM-1 have been reported to be associated with many inflammatory diseases, including atherosclerosis and arthritis [101]. Song, et al. [102] found that paeonol reduced plaque size in apolipoprotein E-deficient (ApoE-/-) mice by down-regulating the expression of VCAM-1 and matrix metalloproteinase-9 (MMP-9), and inhibited inflammation and oxidative stress during atherosclerosis development. Pan [103] revealed that paeonol concentration-dependently suppressed TNF-α-induced VCAM-1 expression, exhibiting anti-inflammatory, antioxidant, and cardiovascular protective effects attributed to paeonol's inhibition of p38 and ERK1/2 activities. Increased expression of ICAM-1 and VCAM-1 has been shown to correlate with the development of osteoarthritis. Wang, et al. [67] exposed chondrocytes to IL-1β damage and protein blotting analysis of paeonol attenuated the expression of ICAM-1 and VCAM-1. This could suggest that paeonol can act as a regulator of adhesion molecules and thus modulate the inflammatory response.

6 Paeonol as a modulator of gut microbes

The gut is a complex microecosystem, and the interactions between the microbiome and host determine key physiological processes of human metabolism, including inflammatory response, metabolic function, and disease susceptibility and pathogenesis [104]. Studies have shown that inflammation alters gut microbes and their metabolites, and that the affected gut and gut microbes trigger immune responses and metabolic activity, leading to chronic inflammation and ultimately

chronic disease [105]. A large amount of evidence shows that the imbalance of intestinal microbiome can lead to the occurrence of atherosclerosis (AS), and the intestinal microbiome has become a new target for AS treatment [106]. Liu, et al. [107] studied the intestinal flora composition of AS mice by 16S rDNA sequencing, and found that paeonol significantly improved AS by regulating the intestinal flora composition and harmful metabolites of the microflora in AS mice. In addition, paeonol ameliorates hepatic inflammatory damage associated with acute alcoholic liver disease by regulating the gut microbiota [108]. Clostridium butyricum is the key bacteria in the treatment of ulcerative colitis mice by paeonol through the intestinal barrier repair effect. Zhao, et al. [109] studied that paeonol can alleviate ulcerative colitis in mice by increasing short-chain fatty acids from Clostridium butyricum. Another study also showed that paeonol can increase the abundance of intestinal microbiota, partially reverse the disorder of intestinal biota composition, and regulate metabolite levels, which has a significant therapeutic effect on inflammatory diseases [110].

7 Conclusion

Paeonol is a potentially bioactive polyphenol from plant sources with excellent anti-inflammatory activity. In this paper, the anti-inflammatory effects of paeonol were investigated from five aspects: as an antioxidant, as a modulator of inflammatory enzyme activities, as a modulator of inflammatory signaling pathway, as a modulator of adhesion molecules, and as a modulator of gut microbes, indicating that paeonol has valuable therapeutic potential. At present, there are many reports on the anti-inflammatory effects of paeonol, but extensive safety and efficacy data are still needed. Pharmacokinetics and toxicity analysis are also important areas for research of paeonol. In addition, the development of more efficacious and bioavailable and affordable delivery systems for paeonol still needs to be investigated due to its low water solubility and low bioavailability drawbacks.

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