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Review article

A review for the anti-inflammatory effects of paeoniflorin in inflammatory disorders

Qiqi Xin[a], Rong Yuan[a], Weili Shi[a], Zhengchuan Zhu[a,b], Yan Wang[c], Weihong Cong[a,*]

[a] Laboratory of Cardiovascular Diseases, Xiyuan Hospital of China Academy of Chinese Medical Sciences, Haidian, 100091, Beijing, China
[b] Peking University Traditional Chinese Medicine Clinical Medical School (Xiyuan), Haidian, 100091, Beijing, China
[c] National Integrated Traditional and Western Medicine Center for Cardiovascular Disease, China-Japan Friendship Hospital, Chaoyang, 100029, Beijing, China

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ABSTRACT

Inflammatory disorders result from abnormal immune response and their incidence has increased recently. Thus, there is an urgent need to discover new treatments for inflammatory disorders. In recent years, the natural products contained in Chinese herbs have attracted much attention worldwide owing to their anti-inflammatory effects. Paeoniflorin (PF) is a bioactive compound purified from the Chinese herb *Paeonia lactiflora* and reports have recently emerged suggesting the great potential of *P. lactiflora* as an agent to counter inflammatory disorders. The anti-inflammatory effects of PF have been revealed by *in vitro* studies and *in vivo* animal experiments of different inflammatory disorders, including rheumatoid arthritis, inflammatory bowel disease, psoriasis, and asthma. This review systematically describes the recent progress of studies on the mechanism of PF and its therapeutic potential in inflammatory disorders.

1. Introduction

The immune system is a complex network of inflammatory organs, cells and molecules. Inflammatory disorders are characterized by the imbalance of inflammatory mediators and cells [1,2]. Inflammatory disorders are common, and their prevalence is increasing, particularly in developed countries.

Natural products are considered an important resource in the treatment of inflammatory disorders. *Paeonia lactiflora* is a representative Chinese herb for the treatment of various immunological disorders such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), psoriasis [3,4]. Paeoniflorin (PF), the main bioactive compound extracted from *P. lactiflora* [5], is a monoterpene glycoside with a cage-like pinnae skeleton (Fig. 1).

Many *in vitro* studies and *in vivo* animal experiments have demonstrated the anti-inflammatory and immunosuppressive effects of PF. Subsequently, PF has emerged as a global topic of interest. In this review, we have focused on the mechanism of action and the development of the therapeutic properties of PF in inflammatory disorders.

2. Potential effects of PF on inflammatory disorders

The therapeutic effects of PF have been demonstrated in various inflammatory disorder models, including RA, IBD, psoriasis, and asthma. We will discuss the therapeutic properties of PF on inflammatory disorders (Table 1).

2.1. Rheumatoid arthritis

RA is a long-term autoimmune disease that results in joint pain, swelling, stiffness, and decreased movement in the joints [6]. The principal target of RA is the synovium, which is responsible for the majority of the clinical features of joints. The infiltration of inflammatory cells, including fibroblast-like synoviocytes (FLS), neutrophils, and macrophages, are likely to have important roles in the pathogenesis of RA. They release a variety of cytokines up on stimulation, including TNF-α, IL-1β, and IL-6. Furthermore, increased levels of inflammatory cytokines are powerful activators of FLS, neutrophils, and macrophages, which form a vicious circle.

Previous studies have demonstrated that PF ameliorated RA [7–10]. The scoring of arthritis and the rate of incidence were markedly reduced after the administration of PF. PF clearly decreased the severe swelling and redness of the entire paw. The X-ray images of joints showed that the tissue swelling, and bone destruction were reduced in the PF-treated group. Histopathological evaluation showed that PF distinctly decreased cell infiltration, cartilage impairment, pannus

* Corresponding author. 305 research building, Xiyuan hospital, Haidian District, 100091, Beijing, China.
E-mail addresses: xinqiqiyuan@126.com (Q. Xin), yuanrong427@163.com (R. Yuan), shiweilidoctor@163.com (W. Shi), zhuzhengchuan999@pku.edu.cn (Z. Zhu), wangyanhs@126.com (Y. Wang), congcao@188.com (W. Cong).

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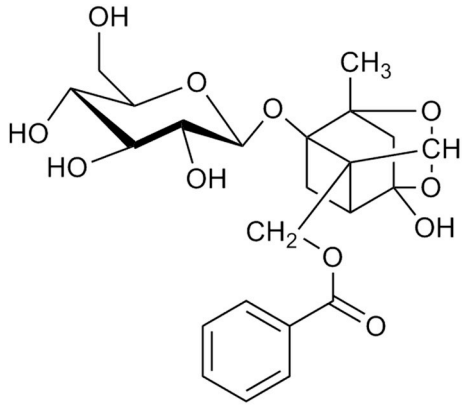

Fig. 1. Chemical structure of paeoniflorin.

formation, synovium hyperplasia, and bone damage. The levels of serum anti-collagen type II antibodies and IgA, IgM, and IgG were significantly lower in the treatment group. Pro-inflammatory mediators, including TNFα, IL-1β, IL-6, cyclooxygenase-2, PGE-2, and granulocyte-macrophage colony stimulating factor, were inhibited after PF administration. The antioxidant effects of PF were indicated by reductions in MDA concentration, and the increased activity of superoxide dismutase, catalase, and glutathione peroxidase. Fei et al. [11], for the first time, suggested that PF accumulates in the intestine and primarily modulates Th1 and Th17 responses in the mesenteric lymph nodes and Peyer's patches, rather than in the spleen, to exert anti-arthritis effects. In addition, PF could also ameliorate RA by inhibiting mTOR, Rho kinase, and NF-κB signaling pathway and decreasing LIFR and ASPN protein [12–15].

The researchers also investigated the cellular mechanisms of PF in the treatment of RA. PF decreased FLS proliferation and inhibited cytokine secretion. Zheng et al. [16] and Chen JY et al. [17] found that PF decreased FLS proliferation in rats with adjuvant arthritis (AA). The effect may be related to the regulation of G protein-coupled signaling in FLS. The increased levels of G protein-coupled receptor kinase 2 and the Gi protein were correlated with the severity of inflammation in RA. PF inhibited the expression of G protein-coupled receptor kinase 2 and Gi protein, and restored protein kinase A activity and cyclic adenosine monophosphate level in FLS [17–19]. Furthermore, Chang et al. [18] reported that PF could suppress IL-1, TNF-α, and prostaglandin E2 production in FLS.

2.2. Inflammatory bowel disease

IBD is characterized by chronic inflammation of the colon and small intestine [20]. The main types of IBD are ulcerative colitis and Crohn's disease.

Previous studies have already demonstrated that PF could ameliorate IBD in animal models *in vivo* and cell models *in vitro* in recent years. PF mitigated dextran sulfate sodium-induced colitis model [21]. In the murine model of IBD, mice displayed diarrhea, bloody diarrhea, and body weight loss. The histological examination of the colon showed that colon length was decreased, and the inflammatory cells had infiltrated into the submucosa and mucosa of the colon. In contrast, PF-treated IBD mice exhibited notably less diarrhea, bloody diarrhea, and body weight loss. The colon length in the PF-treated group was normal and little inflammation was present in the colon. Authors have also described that PF suppressed the production of inflammatory mediators, including TNF-α and IL-6, in the colonic mucosa of mice with colitis. Furthermore, they explored the molecular mechanisms of PF in the treatment of IBD. The NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways were inhibited by PF, which alleviated IBD. Gu et al. [22] demonstrated that PF ameliorated trinitrobenzenesulfonic acid-induced ulcerative colitis. In the animal model of trinitrobenzenesulfonic acid-induced IBD, the mortality rate was high; more than half of the mice died within 1 week. After 1 week of PF administration, the survival rate of mice with IBD was significantly increased (65.87%–84.50%). Myeloperoxidase expression was reduced in the mucosa of the PF-treated group, indicating that PF inhibited the migration and infiltration of neutrophils into the mucosa. In addition, the researchers explored the PF suppression of the apoptosis pathway in mice with IBD. The level of B-cell lymphoma 2 in the colon tissue was upregulated after treatment, whereas the levels of Bax, caspase-3, caspase-9, and cytochrome c were downregulated after treatment. More recently, Zheng et al. [23] discovered that PF inhibited Th17/regulatory T cell differentiation and DCs maturation in trinitrobenzenesulfonic acid-induced ulcerative colitis. The decreased expression of major histocompatibility complex II, CD80, CD86, and IL-12 *in vivo* and *in vitro* suggested that PF inhibited DCs maturation. The reduced mRNA expression of IL-17 and Th17 proliferation indicated that PF inhibited Th17/regulatory T cell differentiation. The effects of PF on ulcerative colitis revealed by inhibiting maturation of DCs and thus decreasing the capacity of DCs to stimulate Th17/Treg differentiation. In addition to the studies *in vivo*, Wu et al. [24] indicated PF has an inhibitory effect on intestinal endothelial injury *in vitro*. The authors found PF significantly increased transepithelial electrical resistance (TEER) value, decreased intestinal epithelium FITC-dextran flux permeability, restored the expressions of occludin, ZO-1, and claudin5, inhibited LPS-induced expression of cyclooxygenase-2, iNOS, TNF-α, IL-6, and MMP-9; and suppressed NF-κB signaling via activating the Nrf2/HO-1 signaling pathways in ILPS-stimulated Caco-2 cells.

2.3. Psoriasis

Psoriasis is a chronic autoimmune papulosquamous disease characterized by abnormal keratinocyte proliferation [25]. Inflammatory cells, including antigen-presenting cells, Th17 cells, macrophages, and neutrophils, playing important roles in the pathogenesis of psoriasis. Inflammatory mediators, including TNF-α, IL-1β, IL-6, IL-12, and IL-17, are also involved in the exacerbation of psoriasis. Psoriatic skin exhibits marked inflammation with erythema, scaling, and thickening. Histological analysis showed a thickened epidermis, focal parakeratosis, and infiltration of lymphocytes into the dermis.

Reports of the anti-psoriatic effect of PF have recently been published [26,27]. PF administration ameliorated psoriatic lesions in an animal model of psoriasis, showing reduced erythema, rarer scaling, and thinner skin. The histological analysis of psoriatic skin after PF treatment revealed thinner epidermis, less parakeratosis, and reduced lymphocyte infiltration in the dermis. The researchers also discovered the cellular mechanisms of PF in the amelioration of psoriasis. PF suppressed the mRNA expression of IL-6, IL-17A, and IL-22, and concurrently inhibited the production of IL-22 protein in HaCat cells *in vitro*, which was probably related to the inhibition of the MAPK pathway [26]. Sun Y et al. [27] revealed that PF reduced the infiltration of neutrophils and macrophages in psoriatic skin. The inflammatory cytokines produced by neutrophils and macrophages, including TNF-α, IL-1β, IL-6, IL-12, IL-23, and iNOS, were decreased after PF treatment. In addition, they reported that PF decreased the production of Th1/Th17 cell-associated cytokines, such as interferon gamma (IFN-γ), IL-17, IL-21, and IL-22 *in vivo*. Chen T et al. [28] found that PF reduced the infiltration of T cells, DCs, and neutrophils, which alleviated the inflammation of the lesions in mice with psoriasis. Furthermore, they examined the function of PF on PBMCs isolated from patients with psoriasis. They demonstrated that PF could inhibit the viability of PBMCs and decrease the mRNA expression of inflammatory cytokines, including TNF-α, IFN-γ, IL-6, and IL-17, in PBMCs. Zhao et al. [29] reported that PF inhibited the proliferation and differentiation of keratinocytes. In addition, PF suppressed Th17 cell differentiation and decreased Th17-related cytokine expression through the

Table 1
Recent advances of Paeoniflorin for inflammatory disorders.

Inflammatory disorders	Object	Therapeutic effects/mechanisms	References
Rheumatoid arthritis	rats	PF increased the pain threshold and decreased the arthritic symptoms in RA rats; PF reduced the MDA concentration in serum, attenuated the activity of NF-κB p65 unit, TNF-α, IL-1β and IL-6, and reduced the cyclooxygenase-2 protein expression level in RA tissue.	[7]
Rheumatoid arthritis	rats	PF exhibited therapeutic effects on rats with arthritis by regulating PI3K/Akt/mTOR signal mediated by BAFF/BAFF-R, and down regulating the antibodies production further.	[8]
Rheumatoid arthritis	rats	PF diminished the secondary hind paw swelling and arthritis scores, inhibited lymphocytes proliferation, increased the levels of IL-4 and TGF-β1, and reduced IL-2 expression.	[9]
Rheumatoid arthritis	rats	PF reduced the levels of the inflammatory cytokines, IL-1β and TNF-α, thereby inhibiting inflammation and bone erosion.	[10]
Rheumatoid arthritis	mice	Oral PF reduced the polyarthritis index, paw swelling, delayed the onset of arthritis in Collagen induced Arthritis (CIA) mice, and downregulated IL-6, TNF-α and IL-1β. PF accumulates in the intestine and primarily modulates Th1 and Th17 responses in the mesenteric lymph nodes and Peyer's patches, rather than in the spleen, to exert anti-arthritis effects.	[11]
Rheumatoid arthritis	rats and FLS	PF can reduce the adjuvant arthritis (AA) rats' arthritis score, and the expression of mTOR, p-mTOR, IL-1, IL-6 and MMP3.	[12]
Rheumatoid arthritis	rats	PF ameliorated the symptoms in CIA rats, reduced the levels of pro-inflammatory cytokines and paw swelling, down-regulated the expressions of p-NF-κB p65 and p-MYPT1 by inhibiting Rho kinase activation in the joint synovial tissues.	[13]
Rheumatoid arthritis	mice and osteoclast precursor cells	PF ameliorated CIA through inflammatory response inhibition and bone destruction suppression. PF decreased osteoclast number through the altered RANKL/RANK/OPG ratio and inflammatory cytokines profile. PF inhibited osteoclast differentiation by down-regulating NF-κB activation.	[14]
Rheumatoid arthritis	rats	PF may treat RA by decreasing two key proteins, LIFR and ASPN.	[15]
Rheumatoid arthritis	rats	PF suppressed rat AA by inhibiting abnormal proliferation of synoviocytes and the production of IL-1, PGE2, IL-6, VEGF, GM-CSF, Gi, and cyclooxygenase-2.	[16]
Rheumatoid arthritis	rats and synoviocytes	PF inhibited FLS proliferation, and decreased G protein-coupled receptor kinase 2 expression in FLS *in vitro*.	[17]
Rheumatoid arthritis	rats and synoviocytes	PF decreased the production of IL-1, TNF-α, and PGE_2, and inhibited synoviocyte, thymocyte and splenocyte proliferation.	[18]
Rheumatoid arthritis	rats and synoviocytes	PF suppressed the inflammatory response and inflammatory mediators (IL-1, TNF-alpha and PGE_2) *in vivo*, and inhibited Gi expression and restored cAMP level and PKA activity in FLS of CIA rats *in vivo* and *vitro*.	[19]
Inflammatory bowel disease	mice and RAW264.7 cells	PF down regulated the activity of myeloperoxidase, the levels of TNF-α and IL-6, and the mRNA expression of proinflammatory mediators via decreasing the expression of Toll-like receptor 4 and suppressing the activation of NF-κB and MAPK pathways.	[21]
Inflammatory bowel disease	mice	PF exhibited anti-inflammatory effect (reducing myeloperoxidase expression, inhibiting migration and infiltration of neutrophils) via inhibiting MAPK/NF-κB pathway and apoptosis in mice.	[22]
Inflammatory bowel disease	$CD4^+$ T cells and mice	PF treated UC effectively through inhibiting maturation of DCs and thus decreasing the capacity of DCs to stimulate Th17/Treg differentiation.	[23]
Inflammatory bowel disease	Caco-2 cell	PF increased TEER value, decreased intestinal epithelium FITC-dextran flux permeability, and restored the expressions of occludin, ZO-1, and claudin5 in LPS-induced Caco-2 cell. PF inhibited LPS-induced expression of COX-2, iNOS, TNF-α, IL-6, and MMP-9. PF suppressed NF-κB signaling via activating the Nrf2/HO-1 signaling pathways in ILPS-stimulated Caco-2 cells.	[24]
Psoriasis	guinea pigs and HaCaT cells	PF ameliorated the lesion and decreased the Baker Score in psoriasis-like model of guinea pigs and inhibited the expression of IL-6, IL-17A, IL-22 by inhibiting the phosphorylation of p38 MAPK.	[26]
Psoriasis	mice	PF inhibited infiltration of neutrophils and macrophages, decreased the number of $F4/80^+CD68^+$ macrophages and their related cytokine production (TNF-α, IL-1β, IL-6, IL-12, IL-23 and iNOS), and decreased the production of Th1/Th17 cell-associated cytokines.	[27]
Psoriasis	human and mice	PF reduced infiltration of T cells, DCs and neutrophils, inhibited the viability of PBMCs and decreased the mRNA levels of inflammatory cytokines including TNF-α, IFN-γ, IL-6 and IL-17 in PBMCs.	[28]
Psoriasis	mice	PF inhibits imiquimod-induced psoriasis by regulating Th17 cell response and cytokine secretion via phosphorylation of Stat3.	[29]
Contact dermatitis	mice	PF inhibited inflammatory cells infiltration and thymocyte proliferation; PF reduced inflammatory cytokines (IL-2 and IL-17), but increased anti-inflammatory cytokines (IL-4 and IL-10).	[31]
Contact dermatitis	mice	PF inhibited DC migration, reduced the secretions of IFN-γ and IL-17 and increased IL-10 secretion.	[32]
Contact dermatitis	mice and RAW264.7 cells	PF inhibited TNF-α and cyclooxygenase-2 production in stimulated macrophages via the down regulation of ERK1/2 MAPK phosphorylation.	[33]
Contact dermatitis	DCs	PF may be effective in preventing and treating contact dermatitis *in vitro* and other inflammatory responses through inhibiting maturation of DCs and limiting their capacity to stimulate T cell responses.	[34]
Asthma	mice	PF reduce inflammation and airway hyperresponsiveness in allergic asthma mice might via regulating fatty acid metabolism, inflammatory response and the adhesion pathway at system level.	[36]
Asthma	mice	PF ameliorated scratching behaviors and writhing syndrome in asthmatic mice.	[37]
Asthma	mice	PF reduced IgE expression in serum and bronchoalveolar lavage fluid of mice with asthma, and reduced cytokines in the bronchoalveolar lavage fluid including IL-4 and IFN-γ.	[38]
Asthma	mice	PF decreased the expression of IL-5, IL-13, IL-17 and eotaxin in the asthmatic model by via inhibiting the activation of MAPK pathway.	[39]
Asthma	human airway smooth muscle cells	PF reduced the numbers of live human airway smooth muscle cells and their platelet-derived growth factor-BB-induced migration by inhibiting the PI3K/Akt signaling pathway.	[40]
Pulmonary fibrosis	mice	PF attenuates pulmonary fibrosis by suppressing type I collagen synthesis via inhibiting the activation of TGF-β/Smad pathway and increasing the expression of IFN-γ.	[41]

(*continued on next page*)

Table 1 (*continued*)

Pulmonary fibrosis	mice and A549 cells	PF suppressed the early stages of TGF-β mediated epithelial-mesenchymal transition in alveolar epithelial cells via a Smad-dependent pathway involving the up-regulation of Smad7.	[42]
Chronic obstructive pulmonary disease	rats	PF attenuated oxygen stress by partially quenching reactive oxygen species and up regulating antioxidant enzymes via an Nrf2-dependent mechanism.	[44]
Sjogren's syndrome	human and mice	PF reduced lymphocyte infiltration, inhibited the mRNA expression of TNF-α, IL-6, B-cell activating factor, and decreased the serum level of anti-SSA antibody and anti-SSB antibody.	[46]
Sjogren's syndrome	Human	PF-mediated reduction of IL-1β and IL-6 was due in part to the reduced expression and activation of the ATP sensor purinergic receptor P2X ligand-gated ion channel 7 on primary SS PBMCs.	[48]
Diabetic nephropathy	rats	PF protected renal function may be mediated by its anti-inflammatory actions (down-regulating TGF-β, intercellular adhesion molecule-1, and type IV collagen) via inhibiting NF-κB signaling pathway.	[50]
Diabetic nephropathy	Rat HBZY-1 cells	PF showed nephroprotective functions by suppressing the oxidative stress and inflammation in mesangial cells; PF increased glutathione peroxidase and catalase activities, and reduced IL-6 and MCP-1 level.	[51]
Diabetic nephropathy	Mouse renal mesangial cells	PF down regulated NADPH oxidase activity, and reduced ROS, TGF-β1, and fibronectin levels.	[52]
Diabetic nephropathy	Rat HBZY-1 cells	PF reduced autophagy of mesangial cells through the receptor for advanced glycation end products/mTOR/autophagy pathway.	[53]
Diabetic nephropathy	mice and RAW264.7 cells	PF decreased the expression of TNF-α, IL-1β, and MCP-1 and prevented macrophage activation via inhibition of TLR2/4 signaling expression.	[54]
Diabetic nephropathy	mice	PF inhibited the viability, migration, and differentiation of high glucose-induced macrophages by the suppression of the toll-like receptor 2-dependent signal pathway.	[55]
Diabetic nephropathy	Mice and BMDMs	PF suppressed the expression of iNOS, TNF-α, IL-1β, and MCP-1 both *in vivo* and *in vitro* by inhibing the TLR4 signaling pathway.	[56]
Liver fibrosis	rats	PF inhibited ECM accumulation, collagen fiber deposition, hepatocyte necrosis, and neutrophil infiltration in the liver and decreased TNF-α and IL-1β expression in the serum.	[58]
Liver fibrosis	rats and HSC-T6 cells	PF alleviated liver fibrosis by inhibiting HIF-1α expression partly through mTOR pathway.	[59]
Liver fibrosis	rats	PF alleviated CCl4-induced liver fibrosis in a dose-dependent manner probably by restoring the balance between activated Smad 2/3 and Smad7.	[60]
Liver fibrosis	mice	PF inhibited the infiltration of inflammatory cells and decreased the expression of TNF-α and IL-13.	[61]
Liver fibrosis	mice	PF not only directly inhibited alternative activation of macrophages via reducing the phosphorylations of janus-activated kinase 2 and/or STAT6, but also indirectly suppressed alternative activation of macrophages through decreasing secretion of IL-13.	[62]
Cholestasis	rats	PF reduced the expression of IL-1β and p65, and inhibited neutrophil infiltration in the liver tissue of rats with cholestasis by reducing the over expressions of NF-kB and hepatocyte transporters.	[64]
Cholestasis	rats	PF exerted a dose-dependent protective effect on cholestatic liver injury in rats, and the mechanism of this activity was related to its attenuation of oxidative stress in liver tissue.	[65]
Cholestasis	rats	PF pretreatment significantly attenuated cholestasis and liver injury, largely reduced cell apoptosis in liver, and inhibited the expression of TNF-α, IL-1β, and IL-6.	[66]
Cholestasis	rats	Glycerophospholipid metabolism, ether lipid metabolism, and arginine and proline metabolism pathways were associated with the hepatoprotective effects of PF.	[67]
Cholestasis	rats	PF activated nuclear factor erythroid related factor-2 via the PI3K/Akt signaling pathway to alleviate cholestasis in rats.	[68]
Chronic pain	rats	PF alleviated bee verom induced inflammatory response in rats.	[70]
Chronic pain	rats	PF inhibited the phosphorylation of ASK1and the expression of p-p38 and p-JNK. PF reduced the response of astrocytes and microglia to injury, decreased the expression of IL-1β, TNF-α, and CGRP.	[72]
Chronic pain	rats	PF inhibited the activation of astrocytes and microglia, and reduced levels of TNF-α, IL-1β, IL-6, and chemokine (C-X-C motif) ligand 1.	[73]
Chronic pain	mice	PF suppressed microglia activation in mice and decreased matrix metalloproteinase 2/9 expression in the spinal cord.	[74]
Chronic pain	mice and LY-PPB6 cells	PF suppressed the demyelination of peripheral nerves.	[75]
Chronic pain	rats	PF inhibited the ERK signaling pathway via the adenosine A1 receptor.	[76]
Chronic pain	rats and BV-2 cells	PF increased the suppression of cytokine signaling 3 and the expression of heat shock protein 70 in the spinal cord, and inhibited MAPK signaling pathway to alleviate neuroinflammation.	[77]
Sepsis	rats and RAW264.7 cells	PF inactivated inflammatory response in sepsis through inhibiting the activation of the NF-κB pathway by suppressing IκB kinase activity.	[79]
Sepsis	mice	PF protects mice against lethal LPS challenge through inhibiting TNF-α and IL-1β production and accelerating IL-10 expression.	[80]
Sepsis	mice	PF effectively improved cardiac function during endotoxemia in mice. This action is attributed to PF-induced reduction of inflammatory cytokine release and NF-kB activation, which possibly occurred via the activation PI3K/Akt signaling.	[81]

downregulation of phosphorylation of signal transducer and activator of transcription 3.

2.4. Contact dermatitis

Contact dermatitis, a type of skin inflammation induced by exogenous agents, consists of allergic contact dermatitis and irritant contact dermatitis [30]. The clinical manifestations of contact dermatitis are large, burning, and itchy rashes. Innate and adaptive immunity have been implicated in the pathogenesis of contact dermatitis. In an animal model of ear contact dermatitis, mice display ear swelling and the histological examination showed obvious edema, vascular congestion, and the infiltration of inflammatory cells.

PF has been found to ameliorate contact dermatitis [31,32]. In animal models of ear contact dermatitis, the ear swelling was significantly reduced after PF treatment. The histological examination of animals in the PF-treated group exhibited markedly reduced edema, vascular congestion, and inflammatory cell infiltration. Sun et al. [33] reported that PF inhibited TNF-α and cyclooxygenase-2 production in stimulated macrophages via the downregulation of ERK1/2 MAPK phosphorylation. PF reduced the expression of macrophage migration inhibitory factor in T cells. Wang et al. [31] demonstrated that PF treatment could suppress thymocyte proliferation in the mice with contact dermatitis. PF decreased inflammatory cytokines, including IL-2 and IL-17, but increased anti-inflammatory cytokines, including IL-4 and IL-10, produced by thymocytes and splenocytes. They found similar results in the serum of mice with contact dermatitis, in which PF upregulated IL-2 and IL-17 expression and downregulated IL-4 and IL-10 expression. Shi et al. [34] discovered the mechanism of the PF-mediated inhibition of DC functions *in vitro*. PF could suppress DC migration and maturation. The DC inflammatory cytokine IL-12 was decreased, whereas the anti-inflammatory cytokines IL-10 and transforming growth factor beta (TGF-β) were increased after PF treatment. Moreover, PF-treated DCs displayed the inhibition of co-stimulatory functions on T cells. PF-treated DCs exhibited an impaired capacity to activate T cell proliferation and inflammatory cytokine production, such as IFN-γ, in T cells. Subsequently, the same research group demonstrated the mechanism of PF in the inhibition of DC functions *in vivo* [32]. PF inhibited DC migration in the skin lesions and lymph nodes. Simultaneously, PF reduced T cell infiltration in the skin lesions and T cell proliferation in the lymph nodes.

2.5. Asthma

Asthma is a common long-term autoimmune disease that affects approximately 8% of the population [35]. Wheezing, coughing, and chest tightness are the classical symptoms of asthma. The pathological characteristics are mucosa hyperemia, edema, and inflammatory cell infiltration, including eosinophils and mast cells. Airway smooth muscle cells, eosinophils, and mast cells contribute to asthmatic airway inflammation. Besides inflammatory cells, some inflammatory mediators, such as IgE, leukotrienes, and histamine, also contribute to the pathogenesis of asthma.

Several studies have demonstrated that PF possesses anti-asthmatic effects. Shou et al. [36] revealed PF had a beneficial effect on asthma, which may be achieved through regulating fatty acid metabolism, inflammatory response and the adhesion pathway at system level. Lee et al. [37] found that PF decreased the scratching behaviors and writhing syndrome in mice with asthma. However, they found that PF did not reduce IgE expression in mice with asthma. They also showed that PF did not inhibit the expression of TNF-α and IL-4 *in vitro*. In contrast, Zhang et al. [38] demonstrated that PF reduced IgE expression in serum and the bronchoalveolar lavage fluid (BALF) of mice with asthma. Eosinophils in BALF and lung tissue were also reduced in PF-treated mice. The asthma-related inflammatory cytokines in BALF, including IL-4 and IFN-γ, were decreased after treatment. Later, Sun J et al. [39] also explored that PF downregulated eosinophils and IgE production in mice with asthma. PF inhibited the production of pro-inflammatory mediators, such as IL-5, IL-13, IL-17, and eotaxin, in BALF and lung tissue via the suppression of the MAPK signaling pathway. More recently, Zhou H et al. [40] demonstrated that PF treatment significantly reduced airway smooth muscle cell proliferation and migration through the inhibition of the PI3K/Akt signaling pathway.

2.6. Pulmonary fibrosis

Pulmonary fibrosis is characterized by progressive fibrosis in the lung. It has been demonstrated that PF effectively reduced bleomycin-induced pulmonary fibrosis in mice. Ji et al. [41] found that PF markedly increased the survival rate of mice with pulmonary fibrosis. The mean survival rate was raised from 50.0% to 87.5% after treatment. Histopathological examination revealed that PF reduced interstitial fibrosis, inflammatory cell infiltration, and alveolitis in the lung. Decreased expression of type I collagen and alpha-smooth muscle actin after treatment indicated that PF suppressed myofibroblast activation. In addition, they studied the molecular mechanisms of PF in the treatment of pulmonary fibrosis. The anti-fibrotic cytokine IFN-γ was increased and TGF-β was decreased in the lung tissue in PF-treated mice. Collagen enzymes, such as collagenase-1, were inhibited by PF and alleviated pulmonary fibrosis. Ji et al. [41] also revealed that PF inhibited Smad2/3 phosphorylation and Smad4 expression, but increased Smad7 expression. Thus, they concluded that PF ameliorated pulmonary fibrosis through the inhibition of the TGF-β/Smad signaling pathway. Ji et al. [42] demonstrated that PF attenuated pulmonary fibrosis *in vitro*. PF downregulated alpha-smooth muscle actin and vimentin expression, but upregulated E-cadherin in alveolar epithelial cells. The TGF-β mediated epithelial-mesenchymal transition in alveolar epithelial cells was suppressed by PF treatment.

2.7. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is regarded as largely irreversible and progressive airway obstruction caused by smoking, air pollution, and bronchiectasis [43]. Reactive oxygen species (ROS), elastase, and other serine proteinases that originate from inflammatory cells are correlated with the development of COPD. Lin et al. [44] identified that PF ameliorated COPD through the reduction of oxidative stress. Rats were exposed to cigarette smoke for at least 12 weeks to induce COPD. In the PF-treated group, COPD rats exhibited better lung function parameters than vehicle-treated group. The lung function parameters, including peak expiratory flow, maximal mid-expiratory flow, the ratio of forced expiratory volume in the first 0.1 s, and forced vital capacity were better in the low-dose and high-dose PF-treatment groups than the vehicle-treated group. The histopathological examination of lung tissue indicated that the inflammatory cells around bronchioles, such as neutrophils and lymphocytes, were reduced by PF treatment. The edema of lung tissue was also alleviated. Furthermore, they detected that PF reduced oxidative stress in rats with COPD. The levels of ROS and MDA in the serum of rats with COPD, considered as markers of oxidative stress, were inhibited by PF administration. The antioxidant enzymes in the lung tissue, including heme oxygenase 1, γ-glutamylcysteine synthetase, superoxide dismutase, nuclear factor erythroid related factor-2, and activating transcriptional factor 4 were increased in the PF-treated group.

2.8. Sjogren's syndrome

Sjogren's syndrome (SS) is an autoimmune connective tissue disease manifested as dry eyes and dry mouth that results from damage to the lacrimal and salivary glands [45]. Inflammatory cells, such as T cells, B cells, and monocytes, play important roles in the pathogenesis of SS. Autoantibodies to SSA, SSB antigens, and inflammatory cytokines, such

as TNF-α and IL-6, are also involved in the development of SS.

PF was found to ameliorate SS. Li et al. [46] demonstrated that PF alleviated inflammation in SS mice. Lymphocyte infiltration, including T cells and B cells, in the salivary tissue was reduced by PF treatment. Inflammatory mediators in the salivary tissue, such as TNF-α, IL-6, and B-cell activating factor, were also inhibited by PF. Anti-SSA and anti-SSB autoantibodies were lower after treatment. Qian et al. [47] used confocal laser scanning microscopy to reveal that PF increased intracellular Ca^{2+} concentration in isolated salivary gland cells. Building on experiments in animal models of SS, Yu et al. [48] identified that PF inhibited the inflammatory production of inflammatory cytokines in PBMCs isolated from patients with SS. They discovered that PF significantly decreased the expression of the pro-inflammatory cytokines, IL-6 and IL-1β, in activated PBMCs. The purinergic receptor P2X ligand-gated ion channel 7 is involved in NLRP3 inflammasome activation and cytokine productions in PBMCs, and purinergic receptor P2X ligand-gated ion channel 7 levels are higher in patients with SS than in the healthy population. They found that PF could reduce purinergic receptor P2X ligand-gated ion channel 7 expression in PBMCs isolated from patients with SS. This mechanism may explain the anti-inflammatory effects of PF in the treatment with SS.

2.9. Diabetic nephropathy

Diabetic nephropathy (DN) is a common complication of diabetes and the incidence is increasing owing to the global epidemic of diabetes. Researchers have implicated plenty of inflammatory mediators and signaling pathways in the pathogenesis of DN, especially TNF-α, IL-1β, iNOS, monocyte chemoattractant protein-1 (MCP-1), TGF-β, and intercellular adhesion molecule-1 [49]. Chronic inflammation and oxidative stress participate in the podocyte injuries, such as a decreased density of podocytes, in diabetic glomerular injury.

PF exerts protective effects on DN. Fu et al. [50] identified that PF treatment effectively protected renal function, showing decreased blood glucose and urinary albumin, and ameliorated glomerular hypertrophy in rats with diabetes. The expression of inflammatory mediators in the tissue of diabetic kidneys, including TGF-β, intercellular adhesion molecule-1, and type IV collagen, were downregulated after PF treatment via the inhibition of the NF-κB signaling pathway in the renal cortex. They also found that PF could reduce the MCP-1 level in the serum and to inhibit macrophage infiltration in the glomeruli to alleviate kidney inflammation. Zhang et al. [51] suggested that PF showed nephroprotective functions through the suppression of oxidative stress and inflammation in mesangial cells. The antioxidative enzymes in the mesangial cells, such as glutathione peroxidase and catalase, were increased by PF administration. The IL-6 and MCP-1 levels in the mesangial cells were decreased in a dose-dependent manner by PF. Subsequently, the results conducted by Sun J et al. [52] showed that PF downregulated NADPH oxidase activity, ROS, TGF-β1, and fibronectin levels in glucose-treated mesangial cells also supported the antioxidative and anti-inflammatory effects of PF. Chen et al. [53] reported that PF reduced autophagy of mesangial cells through the regulation of the receptor for advanced glycation end products/mammalian target of rapamycin (mTOR)/autophagy pathway. More recently, researchers have focused on the effects of PF on macrophages in the treatment of DN. Zhang et al. [54] discovered that PF inhibited macrophage activation *in vitro* and *in vivo*. The inflammatory cytokines produced by macrophages, such as TNF-α, IL-1β, and MCP-1, were diminished after PF treatment. Shao et al. [55,56] found that PF could ameliorate the onset and clinical symptoms of DN in mice. PF decreased the viability, migration, and differentiation of high glucose-induced macrophages by the suppression of the toll-like receptor 2-dependent signal pathway in mice. At the same time, PF could influence Bone Marrow-Derived Macrophages (BMDMs) by suppressing iNOS expression as well as the production of TNF-α, IL-1β, and MCP-1 both *in vivo* and *in vitro*. These effects might be attributable to the inhibition of the TLR4 signaling pathway.

2.10. Liver fibrosis

Liver fibrosis is characterized by the accumulation of extracellular matrix (ECM) in the liver [57]. Hepatic stellate cells are activated and secrete excessive ECM, leading to in liver fibrosis. Viral hepatitis, alcoholic liver disease, and schistosomiasis are regarded as the main causative factors of liver fibrosis.

Several studies have already demonstrated that PF attenuated liver fibrosis in animal models. Chen X et al. [58] found that PF could significantly increase the survival rate of rats with dimethylnitrosamine-induced liver fibrosis. PF effectively improved liver function through the downregulation of alanine aminotransferase, aspartate aminotransferase, and alkaline phosphate expression. Liver histological examination showed that PF decreased ECM accumulation, collagen fiber deposition, hepatocyte necrosis, and neutrophil infiltration in rats with liver fibrosis. In addition, they revealed that PF decreased TNF-α and IL-1β expression through the inhibition of macrophage activation in the liver. Subsequently, Zhao et al. [59] reported that PF ameliorated liver fibrosis through the inhibition of hepatic stellate cell (HSC) activation. PF induced HSC apoptosis and suppressed hypoxia-inducible factor 1-alpha through the mTOR-dependent pathway. Li et al. [60] indicated that PF improved liver function in rats with liver fibrosis through the modulation of the TGF-β/Smad signaling pathway.

Schistosomiasis is an important etiological factor of liver fibrosis. Abd et al. [61] revealed that PF prevented liver fibrosis in mice with schistosomiasis. Histopathological findings showed that fibrocellular granuloma diameters were decreased in PF-treated mice. The infiltration of inflammatory cells in the granuloma, including neutrophils, lymphocytes, and eosinophils, were also suppressed by PF treatment. As a result, inflammatory cytokines in the serum, such as TNF-α and IL-13, were reduced in the PF-treated group. Furthermore, Chu et al. [62] revealed that PF mitigated schistosomiasis-induced liver fibrosis through the inhibition of macrophage activation. The expression of Janus kinase/STAT signaling pathway and IL-13 in macrophages was inhibited by PF.

2.11. Cholestasis

Cholestasis is the retention of biliary constituents and these retained bile salts cause itchiness and jaundice in the skin. The severity of the clinical manifestations of was correlated with inflammatory cytokines [63].

PF has been shown to suppress inflammation and ameliorate cholestasis in animal models. Zhao et al. [64] discovered that PF reduced the expression of the inflammatory cytokine IL-1β and the inflammatory signaling protein p65 in the liver tissue of rats with cholestasis. The serum levels of aspartate aminotransferase and alanine aminotransferase were reduced by PF treatment. Other hepatic enzymes, such as γ-glutamyl transpeptidase and alkaline phosphatase, were also decreased. The histological examination of liver tissue indicated that PF mitigated neutrophil infiltration, edema, and congestion to alleviate inflammation in the liver. The same research group also explored if PF could suppress oxidative stress in rats with cholestasis [65]. The levels of nitric oxide, MDA, and NADPH oxidase 4 (NOX4) in liver tissue were inhibited by PF administration, whereas the antioxidant glutathione was increased. As a result, PF inhibited ROS in the liver tissue of rats with cholestasis. Later, Zhou HQ et al. [66] reported that PF treatment decreased the expression of inflammatory cytokines, including TNF-α, IL-1β, and IL-6, in the liver tissue of rats with cholestasis. PF also inhibited cell apoptosis in the liver, protecting liver function through the downregulation of Bax, caspase-3, and caspase-9 expression and the upregulation of B-cell lymphoma 2 expression. Chen Z et al. [67] used the Kyoto encyclopedia of genes and genomes analysis to uncover the molecular mechanism of action of PF in cholestasis. They

found that several pathways, such as glycerophospholipid metabolism, ether lipid metabolism, and arginine and proline metabolism, were associated with the hepatoprotective effects of PF. They also demonstrated that PF activated nuclear factor erythroid related factor-2 via the PI3K/Akt signaling pathway to alleviate cholestasis in rats [68].

2.12. Chronic pain

Chronic pain is a global common health problem. It may seriously interfere with the quality of life of patients and lead to many social and psychological problems. Neuroinflammation is critical in the pathogenesis of pain [69].

Several previous studies have demonstrated that PF could alleviate pain through the inhibition of neuroinflammation [70–72]. PF administration significantly increased the pain threshold pressure. The parameters of pain threshold, including paw withdrawal threshold and paw withdrawal latency, in rats with chronic constriction injury were higher in the PF-treated group. PF exerted analgesic effects on bee venom-induced nociception and hypersensitivity in rats via anti-inflammation and activation of opioid receptors. Zhou JY et al. [73] found that PF inhibited the activation of astrocytes and microglia in rats with chronic constriction injury. The levels of inflammatory cytokines in the spinal cord, such as TNF-α, IL-1β, IL-6, and chemokine (C-X-C motif) ligand 1, were markedly decreased after PF treatment. Similar Results were found in the study of Zhou D et al. [72]. The authors indicated PF reduced the response of astrocytes and microglia to injury, decreased the expression of IL-1β and TNF-α, and downregulated the expression of calcitonin gene related peptide (CGRP) induced by Chronic constrictive injury in rats, which via inhibiting the phosphorylation of ASK1 and the expression of p-p38 and p-JNK. Fan YX and Hu L et al. [74] revealed that PF suppressed microglia activation in mice with plantar incision and decreased matrix metalloproteinase 2/9 expression in the spinal cord. The c-Fos protein, which was increased after the stimulation of neurons was suppressed by PF. Andoh et al. [75] demonstrated that PF suppressed the demyelination of peripheral nerves induced by the chemotherapeutic agent paclitaxel. Zhang et al. [76] indicated that PF inhibited the ERK signaling pathway via the adenosine A1 receptor. PF suppressed p-ERK and c-Fos expression in the lumbosacral dorsal horn. The adenosine A1 receptor antagonist blocked the anti-nociceptive effect of PF, which indicated that PF could ameliorate pain through the activation of the adenosine A1 receptor. Fan YX and Qian C et al. [77] reported that PF induced heat shock protein 70/TLR4 signaling. PF increased the suppression of cytokine signaling 3 and the expression of heat shock protein 70 in the spinal cord, and inhibited MAPK signaling pathway to alleviate neuroinflammation.

2.13. Sepsis

Septic shock is a status of immune system disturbance triggered by microorganisms [78]. The innate imbalance and adaptive immune responses are involved in the development of septic shock. Excessive inflammatory cytokines result in injury to endothelial cells. Multiple organ dysfunction is a severe complication of sepsis. Therefore, it is important to modulate the disturbed immune response of sepsis.

PF has been shown to modulate the imbalance of the immune response in response to sepsis. Jiang et al. [79] showed that PF elevated the survival rate of experimental rats with sepsis in a dose-dependent manner. The hemodynamics were ameliorated by PF treatment. The hemodynamic parameters, including aortic blood flow, mesenteric blood flow, and mean arterial pressure were improved in the PF-treated rats. As a result, serum lactate was also downregulated after treatment. The pro-inflammatory mediators in the serum, including TNF-α, IL-6, triggering receptor expressed on myeloid cells-1, high mobility group box-1 protein, and endotoxins were inhibited, whereas the anti-inflammatory cytokine IL-10 was increased in the PF-treatment group. PF suppressed TNF-α, IL-6, and HMGB1 expression *in vitro* in activated macrophages via the inhibition of the NF-κB pathway. Cao et al. [80] revealed that PF mitigated multiple organ dysfunction in sepsis. PF improved pulmonary and renal functions in mice with sepsis. The lung wet-dry weight ratio and serum creatinine level were reduced by PF treatment. The histopathological examination of the lung and kidney showed that PF reduced inflammatory cell infiltration, apoptosis, and necrosis to alleviate inflammation. Zhai et al. [81] revealed that PF protected cardiac function in mice with sepsis through the inhibition of NF-κB activation. The cardiac functions containing the ejection fraction, fractional shortening, left ventricular internal diameter at systolic and diastolic phases were higher in PF-treated mice than the vehicle-treated mice. PF also decreased the serum levels of lactate dehydrogenase, creatinine kinase, and cardiac troponin-I in mice with sepsis mice. Apart from cardiac enzymes, the inflammatory cytokines in the heart tissue, including TNF-α, IFN-γ, IL-1β, IL-6, IL-12, and iNOS, were inhibited by PF. In addition, inflammatory cytokines in the serum, including TNF-α, IFN-γ, IL-1β, IL-6, IL-12, and MCP-1, were inhibited.

2.14. In vitro studies of PF in inflammatory cells

Inflammatory cells, such as macrophages, monocytes, and dendritic cells (DCs), play important roles in the pathogenesis of inflammatory disorders. Previous studies have demonstrated the anti-inflammatory effects of PF on the regulatory functions of inflammatory cells *in vitro* [82–88].

2.14.1. Monocytes and macrophages

PF was shown to inhibit the inflammation of monocytes and macrophages. Dai et al. [82] reported that PF suppressed the proliferation of PBMCs. The inflammatory cytokine IL-17 was decreased by PF treatment, whereas the anti-inflammatory cytokine IL-10 was increased. Wang et al. [83] discovered that PF suppressed the phagocytic function of monocytes and reduced tumor necrosis factor alpha (TNF-α) and prostaglandin E2 expression in activated monocytes. The production of HLA-DR and CD80 in activated monocytes was also inhibited by PF. Jin et al. [84] found that PF inhibited intercellular adhesion molecule-1 expression in lipopolysaccharides-induced monocytes possibly by the suppression of the nuclear factor-kappa B (NF-κB) signaling pathway. PF inhibited the inhibitor of NF-κB degradation and the inhibitor of NF-κB kinase phosphorylation of monocytes in a dose-dependent manner. Huang et al. [85] observed that PF inhibited TNF-α and IL-6 expression in lipopolysaccharide-induced macrophages. They also conducted a genome-wide microarray analysis and found that PF altered 68 genes in activated macrophages. Zhai et al. [86] found that PF inhibited nitric oxide and inducible nitric oxide synthase (iNOS) expression through the suppression of the NF-κB signaling pathway in activated macrophages.

2.14.2. B cells

PF reduced the proliferation and division of lipopolysaccharide-stimulated B cells. Zhang et al. [87] reported that PF inhibited the inflammatory activities of B cells through the downregulation of the NF-κB/extracellular regulated protein kinase (ERK) signaling pathways. The expression of the CD86 and CD69 proteins on B cells were inhibited by PF. In addition, PF suppressed immunoglobulin (Ig) production by B cells derived from antibody-secreting cells. IgM and IgG production were reduced by PF in a dose-dependent manner.

2.14.3. Dendritic cells and Th17 cells

Shi et al. [88] indicated that PF inhibited DC activation. PF inhibited IL-6 expression in stimulated DCs. The IL-6 signal transducer and activator of transcription 3 signaling pathway in DCs was also suppressed by PF. Subsequently, the decreased expression of IL-6 inhibited the differentiation of Th17 cells.

3. Conclusion

The prevalence of inflammatory disorders has increased over the past few decades, particularly in developed countries. Therefore, it is very important to find new approaches for the treatment of inflammatory disorders. PF, one of the main bioactive constituents of *P. lactiflora*, has shown effective anti-inflammatory and immunosuppressive properties in many studies. We have systematically reviewed the therapeutic properties of PF in this article. In the future, we believe more rigorous randomized and controlled trials will provide crucial information to the clinical applications of PF.

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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