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Review

Paeonol: pharmacological effects and mechanisms of action

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ABSTRACT

Paeonia suffruticosa possesses various medicinal benefits and has been used extensively in traditional oriental medicine for thousands of years. Paeonol is the main component isolated from the root bark of *Paeonia suffruticosa*. The pharmacological effects of *Paeonia suffruticosa* are mostly attributed to paeonol. Paeonol injection has been successfully applied in China for nearly 50 years for inflammation/pain-related indications. Currently, the dosage forms of paeonol approved by China Food and Drug Administration include tablet, injection, and external preparations such as ointment and adhesive plaster. So far, the clinical applications of paeonol are mainly focusing on the anti-inflammatory activity. Studies of other pharmacological activities of paeonol are developing rapidly, and which may play an important role in the future. Besides, substantial mechanisms of pharmacological action of paeonol have been clarified in recent years. In this review, we summarize the pharmacological effects anti-inflammatory, neuroprotective, anti-tumor, anti-cardiovascular diseases and associated mechanisms of action of paeonol up to date.

Paeonol also have a long history of clinical applications in modern China. The clinical application of paeonol injection can be traced back to as early as 1970s [1]. Currently, the dosage forms of paeonol approved by China Food and Drug Administration include tablet, ointment, adhesive plaster and injection (http://app1.sfda.gov.cn/datasearchcnda/face3/dir.html). According to the instructions for drug, oral and injection administrations of paeonol are effective on inflammation/pain-related indications such as fever, headache, neuralgia, muscle pain, rheumatoid arthritis and rheumatoid arthritis. The external preparations of paeonol can be used for various skin diseases such as eczema, dermatitis, itchy skin, mosquito and bedbug bites, as well as certain effect on allergic rhinitis and cold prevention. However, except the anti-inflammatory activity, other pharmacological activities of paeonol have not been applied in clinical yet.

The first reported pharmacological study of paeonol was fifty years ago [2]. However, most of the mechanisms of pharmacological action remained unknown due to a slow progress before the 21st Century. Recent years, a great deal of studies on pharmacology effects of paeonol were reported, as well as the mechanisms.

The article reviews the pharmacological effects anti-inflammatory, neuroprotective, anti-tumor, anti-cardiovascular diseases (Fig. 1) and associated mechanisms of action of paeonol up to date.

1. Anti-inflammatory

Many common diseases and frequently-occurring diseases in life belong to inflammatory diseases. Anti-inflammatory is the basic pharmacological action of paeonol. Paeonol blocked the lipopolysaccharides stimulated inflammatory responses in BV-2 [3] and RAW264.7 [3–6] inflammatory cells model.

1.1. Osteoarthritis and rheumatoid arthritis

One possible pharmacological treatment of osteoarthritis and rheumatoid arthritis is anti-cytokine therapy [7,8]. IL-1 [7], the first reported inflammatory and catabolic cytokine in the pathophysiology of osteoarthritis and rheumatoid arthritis, represents one of the possible attractive treatment targets. TNF-α [8], another potent proinflammatory cytokine, induces several other cytokines in the proinflammatory cascade. Therefore, the treatment strategies of osteoarthritis and rheumatoid arthritis include blocking the formation of active IL-1 and TNF-α. The anti-inflammatory effects and mechanisms of paeonol on IL-1β-induced osteoarthritis mice models were investigated [9,10]. Paeonol could negatively affect chondrocyte apoptosis and proliferation by inhibiting IL-1β-induced nitric oxide, prostaglandin E2 and reactive oxygen species production. Meanwhile, the overproduction of inducible nitric oxide synthase, COX-2 and matrix

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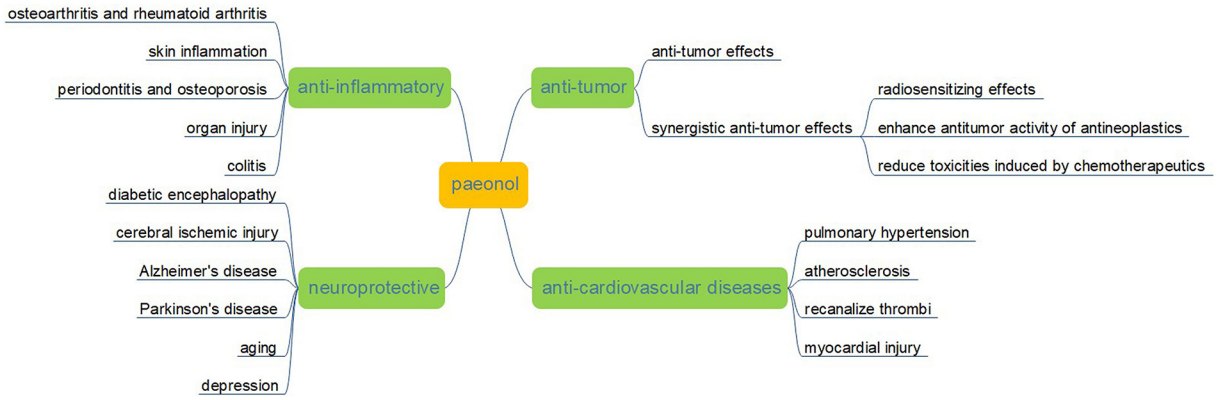

Fig. 1. Pharmacological effects of paeonol.

metalloproteinase-1/-3/-13 were also reversed by paeonol. Moreover, paeonol was found to inhibit NF-κB activation, PI3K, and AKT phosphorylation.

The protective effect of paeonol on IL-1β rheumatoid arthritis was also found to be mediated by PI3K/Akt/NF-κB signaling pathway [11–13]. The productions of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β), granulocyte macrophage colony-stimulating factor and the expressions of matrix metalloproteinase-1/-3, Toll-like receptor 4 were suppressed by paeonol. Fibroblast-like synoviocytes play an essential role in the pathogenesis of rheumatoid arthritis. Decreases in protein expression of miR-155 and its target forkhead box O_3 were the underlying molecular mechanism of the anti-inflammatory effect of paeonol against activated fibroblast-like synoviocytes [12].

1.2. Skin inflammation

Meng [14] studied the effect of paeonol on inflammation in an imiquimod-induced psoriasis-like mouse model. Paeonol suppressed the maturation and activation of dendritic cells by decreasing MyD88 and TLR8 proteins in the Toll-like receptor 7/8 signaling pathway which finally alleviated psoriasis-like skin lesions.

Solar ultraviolet is composed of short-wave UVC (200–280 nm), mid-wave UVB (280–320 nm) and long-wave UVA (320–400 nm). All UVC and 95% UVB can be blocked by the ozone layer efficiently [15]. The application of paeonol attenuated UVB-induced matrix metalloproteinase-1 production and promoted procollagen type I in hairless mice, which suggested paeonol a promising agent in protecting skin from UVB-induced photoaging [16]. UVA-induced skin inflammation is a great threat to human health. T-LAK cell-originated protein kinase plays an important role in UVA-induced skin inflammation. Paeonol inhibited UVA-induced increase of T-LAK cell-originated protein kinase activity and the secretion of IL-6 and TNF-α in Babl/c mouse [17].

Down-regulation of melanin synthesis and melanin transfer are required for recovery of pigmentary disorders. Inhibitions of tyrosinase and its transcriptional regulator microphthalmia-associated transcription factor play important roles in regulating melanin synthesis. The depigmenting effects of paeonol were investigated [18,19]. Paeonol induced the down-regulation of melanogenesis through inhibition of cAMP responsive element binding protein phosphorylation, leading to the expression reduction of microphthalmia-associated transcription factor and subsequently tyrosinase. The key kinase mediating the effect of paeonol on melanogenesis in B16F10 cells was JNK/SAPK.

1.3. Periodontitis and osteoporosis

Periodontitis is the most common chronic oral infectious disease, which is a risk factor for osteoporosis. Li [20]and Chang [21]studied the effects of paeonol on periodontitis-aggravated osteoclastogenesis. Paeonol significantly reduced the induced osteoclast formation through reducing inflammatory factors and alleviating oxidative stress in gingival tissues. Paeonol protected against alveolar bone lesion via regulating Nrf2/NF-κB/NFATc1 signaling pathway. Besides, paeonol exhibited the similar effects and mechanisms of action on the bone marrow-derived macrophage associated with osteoporosis in several studies [22,23].

1.4. Organ injury

The anti-inflammatory effects of paeonol on organ fibrosis were reported in recent studies [24–26]. The mechanisms of paeonol reduction of liver fibrosis [24] might be the inhibition of hepatic stellate cells proliferation and inducing mitochondrial apoptosis via disrupting the NF-κB pathway. The profibrogenic effect of transforming growth factor-β1 on lung fibroblasts was crucial for the pathogenesis of this disease. Paeonol treatment suppressed transforming growth factor-β1-induced cellular events [25], mediated through inhibition of the MAPKs/Smad3 signaling pathway. Paeonol delayed the progression of diabetic renal fibrosis [26], the underlying mechanism was probably associated with regulating the Nrf2/antioxidant responsive element pathway.

Paeonol had beneficial effects against cigarette smoke-induced lung inflammation [27] through increasing extracellular and intracellular levels of reactive oxygen species, activating the MAPKs/NF-κB signaling, and inducing IL-8. Paeonol successfully attenuated inflammatory factors (TNF-α, IL-1β, IL-6) and coagulation reactions to protect against acute lung injury [28]. Besides, paeonol was proven to inhibit the expression, relocation and secretion of high-mobility group box 1[29]which played a critical role in the pathogenesis of acute lung injury through activating the NF-κB P65 pathway. Paeonol could inhibit the translocation and secretion of high-mobility group box 1 in lipopolysaccharides-induced RAW264.7 cells [4,5] by upregulating the expression of histone deacetylase 3. According to Du's [30] and Tang's [31] researches, paeonol significantly attenuated allergen-induced lung eosinophilic inflammation in the airway through the Toll-like receptor 4/NF-κB/MAPK signaling pathway.

Paeonol protected against acetaminophen-induced [32] and lipopolysaccharide/D-galactosamine-induced [33] acute liver failure. The hepatoprotect effects were attributed to anti-oxidant effects with increasing hepatic SOD, GSH-PX and GSH levels, inflammatory suppression with reducing TNF-α, MCP-1, IL-1β and IL-6 levels via NF-κB/MARK signaling pathway, and inhibition of hepatocyte apoptosis. Paeonol exhibited similar hepatoprotect effects on alcohol-induced liver injury [34,35] via SIRT1/Nrf2/NF-κB signaling pathway. As to the protective effects of kidney injury, paeonol could protect kidney from Pb-induced injury by inhibiting oxidative stress, endoplasmic reticulum stress and inflammation via the AMPK and GSK-3 pathway [36]. Paeonol could protect kidney from endotoxin-induced injury by attenuating inflammatory and suppressing Toll-like receptor 4 and NF-κB

Table 1
Anti-inflammatory mechanisms of action of paeonol (mainly via inhibiting proinflammatory factors, regulating enzymes, proteins and related signaling pathways).

Proinflammatory factors	IL (1β [6,11,12,20,22,28,32,34], 4 [30], 6 [6,11,12,17,20,22,28,32,34,38], 8 [27], 10 [6], 13 [30], 17 [38], 23 [14]), TNF-α [3,4,6,11,17,20,22,28,32,34], NO [9,34], PGE2 [9], GM-GSF [13], ROS [10,34], PAI-1 [28], IFN-γ [30], MCP-1 [32], TGF-β1 [38]
Enzymes, proteins and related signaling pathways	Enzymes: HDAC3 [5], INOS [9,40], COX-2 [9], MMP (1 [9,11,16], 3 [9,11], 13 [9]), PI3K [9,13], AKT [9,13], MAPKs(p38 and JNK/SAPK) [3,6,17,18,23,25,27,31–33,39,40], TOPK [17], MSK1 [17], ERK [6,23,39], Sirt1 [26], LKKα/β [32,37], HO-1 [34], NQO-1 [34], AMPK [36], GSK-3 [36] proteins: NF-κB [3,9,11,13,20,23,24,27,31,33,34,37,40], TLR(4 [11,31,37], 7 [14], 8 [14]), FOXO3 [12], MyD88 [14], H2AX [17], CREB [18], Nrf2 [20,26,34], NFATc1 [20], Smad3 [25], ARE [26], HGMB-1 [4,5,29], IkBα [6,32,37], STAT1 [40]

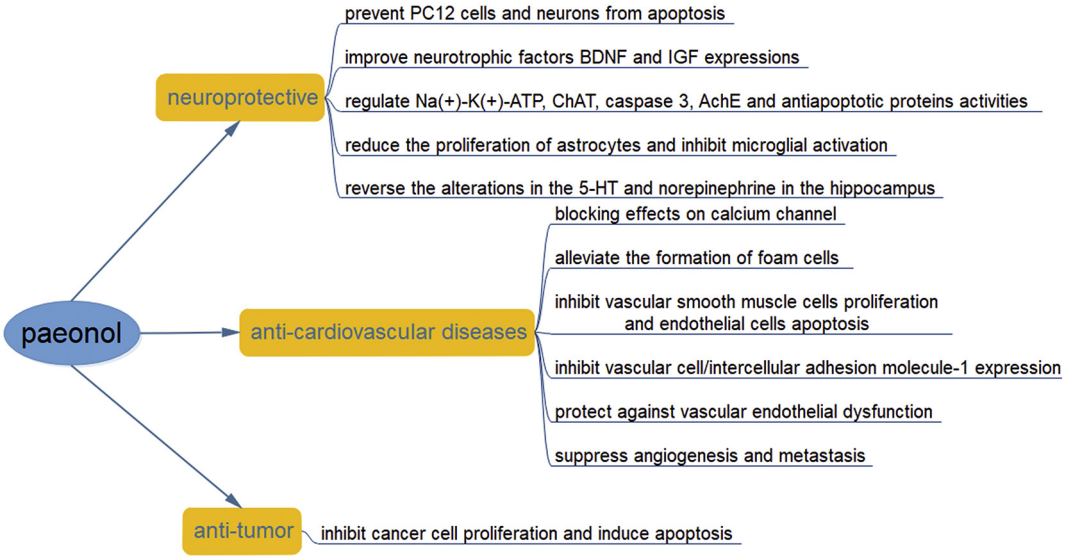

Fig. 2. Other pharmacological mechanisms of action of paeonol.

signaling pathway [37].

1.5. Colitis

Colitis is an inflammatory disease of the colon caused by various causes which is very harmful to patients, and may lead to the loss of life. Paeonol significantly decreased the disease activity index, colon weight/length ratio, macroscopic and histopathological scores of acid-induced ulcerative colitis in rats [38]. The inflammatory factors (IL-17, IL-6) and transforming growth factor β1 were decreased in paeonol-treated groups with a-dose dependent manner. The mechanism study of paeonol on dextran sulfate sodium-induced colitis [39] showed that paeonol and its metabolites blocked the phosphorylation of MAPK/ERK 1/2 and p38. The application of paeonol enema attenuated trinitrobenzene sulfonic acid-induced colitis [40] through inhibiting mRNA expression induced by costimulation of TNF-α and IFN-γ via MAPKs/NF-κB/STAT1 pathway.

Table 1 summarizes anti-inflammatory mechanisms of action of paeonol as mentioned above.

2. Neuroprotective effects

Chen [41] studied the effect of paeonol on electrophysiological behavior of a central neuron (right parietal 4) of the giant African snail. Paeonol elicited a bursting firing pattern of action potentials in the right parietal 4 neuron. *N*-methyl-D-aspartate receptor is one of the most important receptors in learning and memory. Paeonol protected rat hippocampal neurons against oxygen-glucose deprivation-induced injury by targeting on *N*-methyl-D-aspartate receptors [42]. PC-12 cells are common nerve cell lines which exhibit reversible neuronal response to nerve growth factor. Paeonol could prevent PC12 cells from apoptosis [43,44], block hippocampal cell death and reduce the release of neurotoxic and proinflammatory factors in activated microglial cells [45,46]. Inflammatory processes mediated by microglial activation play an important role in numerous neurodegenerative diseases. The inhibitory effects of neuroinflammation by paeonol in microglia cells were found to be regulated by related proteins [47,48]. All the above revealed the possible neuroprotective effects of paeonol.

Paeonol plays remarkable roles in numerous central nervous system disorders such as diabetic encephalopathy, cerebral ischemic injury, Alzheimer's disease, Parkinson's disease, aging and depression.

2.1. Diabetic encephalopathy

Diabetic encephalopathy is described as cognitive impairment, neurophysiological and structural changes in the brain caused by diabetes mellitus. Using streptozotocin-induced diabetic encephalopathy rats model [49], the treatment of paeonol significantly increased Na(+)-K(+)-ATP enzyme and ChAT activities, and significantly decreased AchE activity in hippocampal tissue. Also, paeonol could attenuate apoptosis of neurons and caspase 3 expression, improve two neurotrophic factors BDNF and IGF expressions, and ameliorate Aβ deposition in the hippocampus and cerebral cortex. The mechanisms might be associated with the modulating advanced glycation end products/advanced glycation end products/NF-κB pathway [50]. In addition, according to a minireview [51], the expression of the hippocampal BDNF that has been already shown to exert significant neuroprotective and pro-cognitive effects in Alzheimer's disease.

2.2. Cerebral ischemic injury

Paeonol could reduce cerebral infarction volume and improve neurological deficits [52–54] through downregulating the expression of Toll-like receptor 2/4, Iba1, NF-κB, pAkt, Nrf2, HO-1 and superoxide dismutase, meanwhile reducing the number of IL-1β-immunoreactive and TUNEL-positive cells. In addition [53], paeonol treatment reduced

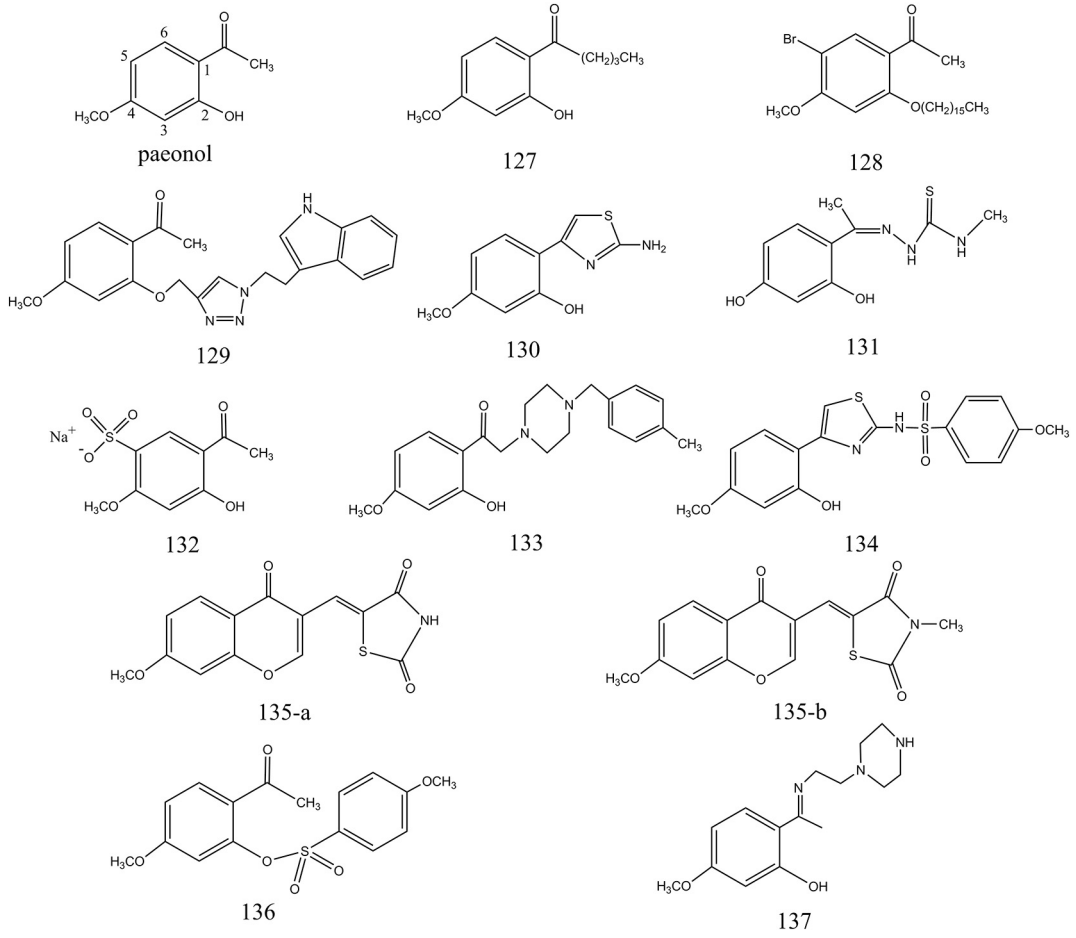

Fig. 3. Structures of paeonol and paeonol derivatives.

Table 2
Pharmacological activities of paeonol derivatives.

Type of paeonol derivatives	IC_{50} or effective concentration	Pharmacological activities	References
Ketone side chain extension	IC_{50}:2.67 μM (HeLa cells); 4.74 μM (MCF-7 cells)	Antiproliferative effect	[127]
Alkyl ether analogs	IC_{50}: scavenging activity 1.8 mM ($\cdot O_2^-$); 6.5 mM (DPPH); 0.1 mM ($\cdot$OH); 4.6 mM ($ABTS^+$)	Exhibit substantial inhibition on enzyme activity of COX-2, PGE2	[128]
Tryptamine hybrid analogs	25 mM (inhibit iNOS, COX-2, IL-6, TNF-α, IL-1β and MCP-1 mRNA expression)	Inhibit LPS and caused NO generation in BV2 cells, resulted in less cellular toxicity	[129]
Aminothiazole-like analogs	10 $\mu g \cdot mL^{-1}$ (inhibit IL-6 secretion in LPS-activated A549 cells)	Comparable inhibition of MCP-1/IL-6 and superior elimination of neutrophil infiltration and protein exudation compared to others	[130]
Thiosemicarbazone-like analogs	IC_{50}: 0.006 mM (inhibit tyrosinase activity)	Inhibitory activity on tyrosinase, displayed as a reversible competitive inhibitor	[131]
Paeononlsilatie sodium	50 $mg \cdot kg^{-1}$ (i.p., Alzheimer's disease rat model)	Alleviate behavioral damage and hippocampal dendritic injury	[132]
Donepezil-like analogs	IC_{50}:0.61 μM (inhibit AChE activity)	Effectively inhibit AChE activity and hydrogen peroxide-induced neuronal PC12 cell death	[133]
Aminothiazole-like analogs	IC_{50}:4.0 μM (AGC cells); 4.4 μM (HT-29 cells); 5.8 μM (HeLa cells)	Antiproliferative effect, superior to 5-fluorouracil against AGS and HT-29 cells along with lower cytotoxicity to fibroblasts	[134]
Chromonylthiazolidines-like analogs	IC_{50}: 44.1 $\mu g \cdot mL^{-1}$ (KB cells)[a]; 32.8 μg·mL-1 (MCF7 cells)[b]	Selective cytotoxic effects against human epidermoid carcinoma and breast cancer cell lines	[135]
Phenylsulfonyl-like analogs	IC_{50}: 0.36 μM (HepG2.2.15 cells)	Exhibit an apparent inhibition effect on HBV gene expression and propagation in cell model	[136]
Piperazin-like analogs	50 $\mu g \cdot mL^{-1}$	Promote differentiation of RAW264.7 cells into osteoclasts rather than inhibit it the way paeonol did	[137]

[a] IC_{50} correspond to compound 135-a in Fig. 3.
[b] IC_{50} correspond to compound 135-b in Fig. 3.

the proliferation of astrocytes in the boundary zone, and inhibited microglial activation in the ischemic core and boundary zone regions. The mechanism of action might include subacute/chronic microglial activation and astrocyte proliferation.

2.3. Alzheimer's disease

Alzheimer's disease is a progressive neurodegenerative disease with insidious onset. Recent studies [55–59] reported that paeonol had the ability to improve impaired learning and memory. Paeonol increased

acetylcholine and glutathione levels, restored superoxide dismutase and Na(+), K(+)-adenosine triphosphatase activities in D-galactose-treated mice model [55]. Paeonol effectively inhibited neuroapoptosis and improved isoflurane-induced cognitive dysfunctions [56] through regulating the expression of antiapoptotic proteins (Bcl-2, Bcl-xL, xIAP, c-IAP-1, c-IAP-2, survivin), histone deacetylases, and improving acetylation of HK39 and HK412. In addition, isoflurane-induced activation of JNK/p38 MAPK signaling and suppression of ERK signaling were effectively regulated by paeonol.

Paeonol also enhanced spontaneous presynaptic transmitter release [57] which was with therapeutic potential in neurotransmitter deficits found in Alzheimer's disease. Moreover, paeonol protected against Aβ-induced impairment of long-term potentiation in mouse hippocampal neurons.

2.4. Parkinson's disease

Parkinson's disease is a common neurodegenerative disease associated with inflammation. Thus, the effect of paeonol on Parkinson's disease may due to attenuate inflammation. Shi [60] studied the underlying mechanisms of paeonol on a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine/probenecid-induced mouse model. Paeonol decreased oxidative stress, the levels of microglia and IL-1β. Meanwhile, paeonol treatment improved dopaminergic neurodegeneration.

Astrocytes exert neuroprotective effects and play an important role in the maintenance of the neuronal environment. Besides, astrocyte dysfunction increases the susceptibility of neurons to cytotoxicity. Thus, targeting astrocytes may be neuroprotective approaches in Parkinson's disease [61]. Ye [62] found that paeonol protected cells from apoptosis by repressing the activation of the JNK/ERK related signaling pathway induced by 1-methyl-4-phenylpyridnium ion in astrocytes.

2.5. Aging

Aging can cause the deterioration of various organ functions, including the nervous system. To some extent, anti-aging can be used as a treatment for neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Oxidative stress is known to increase the risk for many diseases associated with aging [63]. Paeonol could decrease oxidative injury in Hepatocellular Carcinoma Rats [64] and oxidative stress-induced premature senescence in endothelial cells [65]. Paeonol protected endothelial cells against oxidative stress-induced premature senescence by modulating the expressions of Sirt1 protein and its substrates.

Senescent human fibroblasts facilitate epithelial-mesenchymal transition in premalignant epithelial cells. According to Yang's study [66], paeonol significantly reduced the clonogenic, migratory, and invasive capacities of premalignant HaCaT cells. Meanwhile, paeonol notably altered pluripotency of epithelial-mesenchymal transition-associated markers via the modulation of ERK and transforming growth factor-β1/Smad pathway. Additionally, Paeonol significantly decreased intracellular reactive oxygen species levels in aging MRC-5 cells via regulation of nuclear translocation of Nrf2, and which suggested the anti-aging efficiency.

2.6. Depression

The effects of paeonol on lipopolysaccharide-induced depressive-like behavior were investigated [67]. Paeonol administration could effectively reverse the alterations in the concentrations of 5-HT and norepinephrine in the hippocampus. Meanwhile, brain-derived neurotrophic factor, TrkB and NF-κB in hippocampal were downregulated by paeonol. Zhu [68] confirmed the antidepressant effects of paeonol in chronic unpredictable mild stress rats. Brain-derived neurotrophic factor -Rac1/RhoA pathway might be involved in attenuation of chronic unpredictable mild stress-induced behavioral and neuronal damage by paeonol, and which might represent a novel therapeutic agent for depression.

3. Anti-tumor

Paeonol is a broad-spectrum antitumor agent, which is widely used in the treatment of various tumors in Asia. Paeonol exhibits antitumor effects either through inhibiting the activity of cancer cells or reducing toxicities induced by chemotherapeutics. Besides, paeonol also show synergistic anti-tumor effects when combined with chemotherapy drugs or radiotherapy.

3.1. Anti-tumor effects

The antitumor effects of paeonol on skin [69], gastric [70–72], colon [73–75], breast [76,77], hepar [78,79], ovarian [80], prostate [81], esophagus [82], bone [83] cancer cells and oral carcinogenesis [84] were reported. Paeonol inhibited B16F10 melanoma metastasis [69]through inhibition of cell proliferation and induction of apoptosis. The evident anti-inflammatory effects by reducing proinflammatory cytokines secretion (TNF-α, IL-1β, IL-6, and TGF-β) were similar to previous introduction on anti-inflammatory via NF-κB/STAT3 pathways. The antitumor activities of paeonol on gastric cancer cell line BGC823 [70], MFC, and SGC-790 [71,72] cells were investigated. Paeonol could downregulate the protein expression levels of matrix metalloproteinase-2/-9 to inhibit the growth, migration and invasion of BGC823 cells in a concentration-dependent manner. Also, paeonol reduced the expression of Bcl-2 and increased the expression of Bax in MFC and SGC-790 cells. The gastric cancer-related epidermal growth factor receptor 2 gene was decreased by paeonol via inhibiting the activation of the NF-κB signaling pathway. Paeonol promoted human colon tumor cell *N*-acetyltransferase activity and 2-aminofluorene-DNA adduct formation [73]. The production of prostaglandin E2 and the expression of cyclooxygenase-2 were inhibited by paeonol on human colorectal cells [74]. Paeonol reduced LoVo human colon cancer cell viability, blocked the cell cycle at the G1 to S transition, induced apoptosis and upregulated the runt-related transcription factor 3 gene expression [75].

Breast cancer is one of the most prevalent types of malignant tumor and increases rapidly in Asian countries. The antitumor effect of paeonol on mice bearing EMT6 breast cancer [76] was via induction of apoptosis, regulation of Bcl-2 and Bax expression, and activation of caspase-8/-3. Paeonol downregulated HO-1 by regulating the expression of BACH1 and Nrf2, and CXCL4/CXCR3-B signals might be involved in the mechanism of apoptosis [77]. Human hepatocellular carcinoma cell lines BEL-7404, SMMC-7721, and MHCC97-H activities were inhibited by paeonol [78]. In addition, paeonol induced DNA fragmentation in the HCC cell line BEL-7404. The anti-tumor effect against hepatoma cells were likely mediated via induction of tumor cell apoptosis and stimulation of IL-2 and TNF-α production [79]. Yin [80] studied the antitumor effect of paeonol on ovarian cancer cells, paeonol could induce apoptosis of ovarian cancer cells via activation of caspase 3 and down-regulation of survivin. The anti-proliferative effects of paeonol on human prostate cancer cell lines DU145 and PC-3 might be related to the inhibition of the PI3K/Akt pathway [81].

3.2. Synergistic anti-tumor effects

Paeonol had radiosensitizing effects on human ovarian cancer [85] and lung adenocarcinoma [86]. Paeonol treatment enhanced apoptosis of SKOV-3 and OVCAR-3 cells that were exposed to radiation [85]. Paeonol effectively enhanced the sensitivity of ovarian cancer cells to radiation by significantly altering regulation of the proteins of PI3K/Akt pathway, in addition to downregulating VEGF and HIF-1α. Paeonol had a radiosensitizing effect on lung adenocarcinoma both in vitro and in

vivo [86]. The mechanisms could be related to the inhibition of the PI3K/Akt signaling pathway and its downstream proteins: COX-2 and survivin.

Paeonol also showed synergistic anti-tumor effects when combined with chemotherapy drugs. The synergistic effects included enhancing antitumor activity of antineoplastics and reducing toxicities induced by chemotherapeutics. Paeonol, in combination with cisplatin, had a significantly synergistic growth-inhibitory and apoptosis-inducing effect on oesophageal cell line [87] and human hepatoma cell lines [88]. Paeonol enhanced the antitumor activity of epirubicin [89] in a synergistic manner against breast cancer cells via inhibiting p38/JNK/ERK MAPKs.

Paeonol could act as reversal agents for cancer [90–92]. The frequent use of paclitaxelas in the treatment of breast cancer could lead to resistance. Paeonol down-regulated paclitaxel resistance by reducing the activity of the SET/PP2A/Akt pathway [90] and the expressions of P-gp, MRP1, BCRP [91] in MCF-7/PTX cells. Paeonol reversed endoplasmic reticulum stress-induced resistance to doxorubicin in human hepatocellular carcinoma cells [92] by targeting COX-2 mediated inactivation of PI3K/AKT/CHOP.

Besides, paeonol reduced the toxicities induced by chemotherapeutics. Paeonol alleviated epirubicin-induced hepatotoxicity [93], nephrotoxicity [94] and cardiotoxicity [89,95] by inhibiting the PI3K/Akt/NF-kB pathway. The paeonol-treated group showed prolonged survival and marked attenuation of cisplatin-induced acute renal failure in mice [96]. The toxicities-reducing effect was associated with the inflammatory organ injury protective effect as described above.

4. Anti-cardiovascular diseases

Calcium channel is closely related to the occurrence of many cardiovascular diseases such as myocardial injury, arrhythmia and heart failure. The blocking effects of paeonol on calcium channel were confirmed nearly thirty years ago [97]. L-type calcium channel is an important target in cardiovascular diseases, which was reported to be significantly inhibited by paeonol [98]. Paeonol also shortened the action potential duration, in a manner not associated with the blockade of the calcium current, or the enhancement of potassium currents [99]. An intracellular calcium channel regulatory mechanism might be responsible to the potent vasodilatory effect of paeonol [100]. Treatment with paeonol significantly lowed the blood pressure, increased the renal arterial blood flow and the carotid arterial blood flow in spontaneously hypertensive rat [101]. Paeonol ameliorated the hypoxia-induced pulmonary arterial smooth muscle cells proliferation via ERK1/2 signaling pathway [102], and which represented a potential novel therapeutic approach for the treatment of pulmonary hypertension.

Foam cell formation is the most important pathological sign in the whole process of atherosclerosis, which is primarily caused by impaired cholesterol efflux or uncontrolled uptake of oxidized low-density lipoprotein (ox-LDL) in macrophages [103]. Paeonol alleviated the formation of foam cells by upregulation of the ATP-binding membrane cassette transport protein A1 and downregulation of the cluster of differentiation 36 [104,105]. ox-LDL plays a vital role in the initiation and progression of atherosclerosis. Lipid peroxide produced during LDL oxidation could directly damage endothelial cells. Paeonol suppressed ox-LDL induced endothelial cells apoptosis, probably via inhibition of LOX-1-ROS-p38MAPK-NF-κB signaling pathway [106]. Besides, paeonol promoted miR-126 [107], miR-30a [108] and miR-21 [109] expression to inhibit monocyte adhesion to ox-LDL-injured vascular endothelial cells. ox-LDL induced typical foam-cell formation of vascular smooth muscle cell, which gave rise to a significant number of foam cells as well [110]. Paeonol protected against vascular smooth muscle cell proliferation [111–113] by up-regulating autophagy, activating the AMPK/mTOR signaling pathway and inhibiting the Ras-Raf-ERK1/2 signaling pathway.

Vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 produced by vascular endothelial cells are key molecules in the development of atherosclerosis. Paeonol inhibited vascular cell adhesion molecule-1 [114,115] and intercellular adhesion molecule-1 [115,116] expression by the attenuation of p38, ERK and NF-κB signal transduction pathways. Vascular endothelial dysfunction is the earliest detectable manifestation of atherosclerosis. Endoplasmic reticulum stress in endothelial cells leads to endothelial dysfunction which is commonly associated in the pathogenesis of several cardiovascular diseases. Paeonol protected against tunicamycin-induced vascular endothelial dysfunction [117,118] by reducing the endoplasmic reticulum stress-associated reactive oxygen species level and improving nitric oxide bioavailability via the AMPK/PPARδ signaling pathway. Inflammatory injury of the endothelium could lead to endothelial dysfunction as well, and paeonol reduced Lipopolysaccharides-induced endothelial dysfunction by inhibiting Toll-like receptor 4 signaling [119].

Paeonol had the potential to suppress angiogenesis and metastasis [120] partially through the inhibition of Akt signaling pathway and matrix metalloproteinase activity, and recanalize thrombi [121] by the upregulation of vascular endothelial growth factor 165 via the phosphorylated-ERK1/2 MAPK signaling pathway. Paeonol attenuated myocardial ischemia/reperfusion-associated injuries [122,123], suggesting that paeonol might be useful in treating myocardial infarction.

From the above descriptions, the mechanisms of other pharmacological effects of paeonol are more or less related to the anti-inflammatory activity. Besides, other relevant mechanisms are also involved (Fig. 2).

5. Summary

We concluded the pharmacological effects and associated mechanisms of action of paeonol up to date. In addition, paeonol also showed antianaphylatic activity [124], platelet aggregation-inhibiting activity [125], and reduced early neointimal hyperplasia [126].

The multiple pharmacological effects were attributed to the functional groups. According to Wang's research [127], 4-methoxy group was the synergistic group of paeonol's anti-tumor activity and ketone carbonyl side chain was essential functional group of paeonol's anti-tumor activity. A series of paeonol derivatives were synthesizing in recent years (Fig. 3). The derivatives exhibited pharmacological effects such as anti-inflammatory [128–131], anti-Alzheimer's disease [132,133] and anti-cancer [127,134,135] as well, conferring lower cytotoxicity and higher activity. Moreover, paeonol derivatives showed anti-HBV activity [136] and reverse effect on osteoclastogenesis compared with paeonol [137](Table 2). Paeonol derivatives are worth to be intensively studied further.

Declarations of interest

None.

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