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REVIEW ARTICLE

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Advances for pharmacological activities of *Polygonum cuspidatum* - A review

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ABSTRACT

Context: *Polygonum cuspidatum* Sieb. et Zucc (Polygonaceae), the root of which is included in the Chinese Pharmcopoeia under the name 'Huzhang', has a long history as a medicinal plant and vegetable. *Polygonum cuspidatum* has been used in traditional Chinese medicine for the treatment of inflammation, hyperlipemia, etc.

Objective: This article reviews the pharmacological action and the clinical applications of *Polygonum cuspidatum* and its extracts, whether *in vivo* or *in vitro*. We also summarized the main phytochemical constituents and pharmacokinetics of *Polygonum cuspidatum* and its extracts.

Methods: The data were retrieved from major medical databases, such as CNKI, PubMed, and SinoMed, from 2014 to 2022. *Polygonum cuspidatum*, pharmacology, toxicity, clinical application, and pharmacokinetics were used as keywords.

Results: The rhizomes, leaves, and flowers of *Polygonum cuspidatum* have different phytochemical constituents. The plant contains flavonoids, anthraquinones, and stilbenes. *Polygonum cuspidatum* and the extracts have anti-inflammatory, antioxidation, anticancer, heart protection, and other pharmacological effects. It is used in the clinics to treat dizziness, headaches, traumatic injuries, and water and fire burns.

Conclusions: *Polygonum cuspidatum* has the potential to treat many diseases, such as arthritis, ulcerative colitis, asthma, and cardiac hypertrophy. It has a broad range of medicinal applications, but mainly focused on root medication; its aerial parts should receive more attention. Pharmacokinetics also need to be further investigated.

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Introduction

Traditional Chinese medicine (TCM) has been used extensively for thousands of years, and the use of herbal medicinal products has been growing rapidly in many countries (Agbabiaka et al. 2018). For example, artemisinin and its derivatives, the most effective antimalarial drugs, are extracted from the sweet wormwood plant, *Artemisia annua* Linn (Compositae) (Yang et al. 2020). Numerous researchers have studied herbal medicine. An herbal medicine may have a variety of phytochemical constituents, each of which may have a different medicinal activity, so an herb can actually have a variety of therapeutic effects at the same time. Nowadays, people use herbal medicine alone or as a supplement to treat many diseases, such as cancer (Guo et al. 2021), cardiovascular (Xu et al. 2019), cerebrovascular, and nervous system diseases (Lu et al. 2020). Moreover, as the prevalence of TCM research increases worldwide, more pharmaceutical activities will be discovered (Acquaviva et al. 2021).

Polygonum cuspidatum Sieb. et Zucc (Polygonaceae) is a traditional Chinese herb that grows in Asia and North America. The roots of *Polygonum cuspidatum* (PC) are listed in the Pharmacopoeia of the People's Republic of China using the name of Huzhang. Resveratrol, polydatin, quercetin, emodin, and their derivatives are the primary active phytochemical components of PC. These phytochemical components of PC have undergone extensive research and are thought to be essential for PC's medicinal functions (Lachowicz and Oszmiański 2019; Wang, Feng et al. 2019). Moreover, PC has been known to have anti-inflammatory (Liu et al. 2018), antioxidant (Zeng et al. 2019), antiviral (Lin et al. 2015), antimicrobial (Yang et al. 2015), neuroprotective effects (Liu et al. 2015), etc. It is seen as a potential treatment for arthritis, ulcerative colitis (Liu et al. 2018), asthma (Zeng et al. 2019), cardiac hypertrophy (Ding W et al. 2014), etc. The main objective of this review is to provide a systematic elaboration of the therapeutic effects of PC on a variety of diseases, so as to promote the understanding of PC and the development PC-derived herbal medicinal products and supplements.

Phytochemical constituents

The phytochemical constituents isolated and identified from PC are mainly stilbenes, anthraquinones, flavonoids, and polyphenols. The distribution and contents of different types of

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phytochemical constituents showed remarkable differences among different plant parts of PC. Stilbene compounds, such as resveratrol and polydatin, are the main active components in PC. Anthraquinone compounds mainly include emodin and its derivatives. Stilbene and anthraquinone compounds are more concentrated in the rhizomes than in other tissues, which may explain why the PC root is used in traditional Chinese medicine. Flavonoids are mainly found in the leaves and the stems, whereas polyphenols are more concentrated in the flowers (Wang, Feng et al. 2019; Wu, Wang et al. 2019). The root of the PC is most widely used in traditional Chinese medicine to clear away heat and toxic materials. The other plant parts, such as the leaves, are also used due to the health benefits of the phytochemicals contained. The root, leaves, flowers, rhizomes, and fibers of PC can all be used as medicinal proposes.

Pharmacological activities

Anti-inflammation effect

Ethanol extract of PC (100, 200, 400 mg/kg) could prevent colon length shortening and tissue damage, and reduce the levels of inflammatory cytokines in serum of ulcerative colitis mice including interleukin 1β (IL-1β), IL-6, and tumor necrosis factor α (TNF-α). Ethanol extract of PC exerted the above therapeutic effect by regulating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signal pathway. Researchers discovered that polydatin, resveratrol, and emodin were the primary anti-inflammatory phytochemical components in PC ethanol extract (Liu et al. 2018). Emodin-8-*O*-β-D-glucoside (50, 100, 200 μmol/L), derived from the alcohol extract of PC, could reduce the lipopolysaccharide (LPS) induced inflammation of murine macrophage cell. The above study showed that emodin-8-*O*-β-D-glucoside had significant inhibitory effects on IL-6, IL-1β, and monocyte chemotactic protein-1 (MCP-1) (Li, Yu et al. 2019). Resveratrol and polydatin in PC could also inhibit the releasing of IL-6 and nitric oxide (NO) in the murine macrophage cell inflammatory model in another study, and this effect was related to the suppression on NF-κB and Janus kinase/signal transducer and activator of transcription (STAT) signaling pathway (Ma et al. 2015; Sun et al. 2015). Meanwhile, resveratrol could reduce inflammation by downregulating miR-155 and suppressing of cytokine signaling 1 (SOCS1) (Ma et al. 2017; Figure 1(a)).

In vitro, polydatin (15 μg/mL) could reduce the level of IL-1β and TNF-α in human monocytic cells gouty inflammation model and inhibit the expression of pro-inflammatory proteins including toll-like receptor 2 (TLR2), TLR4, and NF-κB (Zhu et al. 2017). In addition, polydatin (20 μmol/L) could also restrain the expression and secretion of MCP-1 in preadipocytes, then inhibited the proliferation and differentiation of preadipocytes. These results indicated that polydatin might treat obesity by regulating the inflammatory (Zheng et al. 2017). Li, Maimai et al. (2019) revealed that polydatin (20, 40, 80 mg/kg) could diminish the infiltration of inflammatory cells in the uterine tissue of endometritis mouse. The protective effect of polydatin might associated with the inhibitory effect on the expression of TNF-α, IL-1β, and IL-6, then suppressed the activation of NF-κB (Li, Maimai et al. 2019). In the mouse mastitis model induced by *Staphylococcus*, polydatin (15, 30, 45 mg/kg) could suppress the activation of the p38 mitogen-activated protein kinase (MAPK)/NF-κB signal pathway, thereby inhibiting the inflammation in breast tissue and reducing tissue damage (Jiang et al. 2017).

In vivo experiments showed that PC possessed the potential to treat arthritis (Figure 1(b)). PC could improve synovitis injury in collagen-induced arthritis (CIA) rats by regulating the peroxisome proliferator-activated receptor γ (PPARγ)/NF-κB signal pathway (Yang et al. 2019). In acute gouty arthritis (AGA) mouse model, ethanol extract of PC (90, 180, 360 mg/kg) could inhibit the production of IL-1β and TNF-α in the ankle cavity in a dose-dependent manner. Its mechanism might be ethanol extract of PC could regulate the expression of nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3)/apoptosis-associated speck-like protein (ASC)/caspase-1 signaling at gene and protein levels (Ma et al. 2019). Researchers found that the crude extract of PC (65, 130, 260 mg/kg) could also improve synovitis symptoms and reduce acute ankle joint swelling in AGA rats. This study further found that this therapeutic effect might be attributed to stilbene and anthraquinone in the crude extract of PC (Ren et al. 2016). In rats with rheumatoid arthritis (RA), polydatin (40, 80, 160 mg/kg) was found to reduce blood levels of TNF- and IL-1 and reduce joint inflammation. This anti-inflammatory effect of polydatin was likely to involve the inhibition of the Wnt/β-catenin signaling pathway (Zeng et al. 2018). In the CIA model, emodin could also alleviate RA by inhibiting synovium inflammation of the knee joint and promoting neovascularization. This effect might be related to emodin could suppress the TNF-α-hypoxia-inducible factor 1α (HIF-1α)-inducible nitric oxide synthase (iNOs)-NO signaling pathway (Wang, Yang et al. 2015; Pan, Wang et al. 2019). In addition, emodin could also alleviate the symptoms of RA rats by up-regulating Bax and Bcl-2

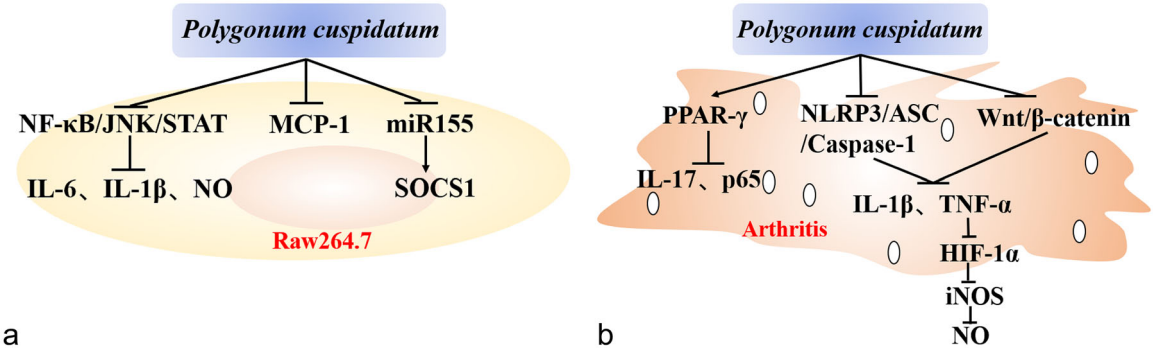

Figure 1. The main mechanism of anti-inflammatory effect of *Polygonum cuspidatum*. (a) In Raw 264.7 cells, the extract of *Polygonum cuspidatum* can decrease the expression of MCP-1, miR155 and the pathway of NF-κB/JNK/STAT directly, and also suppress the expression of IL-1β, IL-6 and NO, as well increase the expression of SOCS1. (b) The extract of *Polygonum cuspidatum* can also treat arthritis in different pathways. It can increase the expression of PPAR-γ, and then the IL-17 as well as p65 are inhibited. In addition, whether the NLRP3/ASC/Caspase-1 or the Wnt/β-catenin pathway can be activated by this plant, their downstream factors, such as IL-1β, TNF-α, HIF-1α, iNOS and NO are induced.

expression (Jin et al. 2018). 8-*O*-β-Glucopyranoside, another quinone compound extracted from the root of PC was found to significantly inhibit the proliferation of fibroblast-like synoviocyte and improve the foot swelling of CIA rats, therefore having therapeutic effects on arthritis (Geng et al. 2018).

The combination of PC and other drugs also showed remarkable anti-inflammatory effects. The combination of PC and *Cinnamomum cassia* Presl (Lauraceae) (Guizhi) alleviated symptoms and played a therapeutic role in rats with AGA. These two Chinese herbs could decrease the expression of pro-inflammatory genes including TLR2, TLR4, and myeloid differentiation factor 88 (MyD88), and reduce the level of IL-1β in the blood of AGA rats (Gu et al. 2015; Cheng and Jiang 2017). Zhang, Wang et al. (2015) found that PC ointment, an external medicine made in China, could reduce tissue inflammation caused by calcium extravasation. The effect was better than the classical medicine of magnesium sulfate (Zhang, Wang et al. 2015). Studies on the anti-inflammatory effects of PC and its extracts are listed in Table 1.

Antioxidant effect

The radical scavenging capacity and oxygen radical absorbance capacity assays indicated that the leaf of PC had the strongest antioxidant capacity, followed by the root and stem (Lachowicz and Oszmiański 2019). The supercritical carbon dioxide liquid extract of PC (10, 20, 50, 100, 250 mg/mL) could scavenge 1,1-diphenyl-2-picrylhydrazyl radical in a concentration-dependent manner. When the concentration was raised to 250 mg/mL, this PC extract had a remarkable capacity for ferric reduction (Lee et al. 2015). *In vitro* experiments revealed that 70% ethanol, ethyl acetate, and butanol extracts of PC strongly inhibited the production of reactive oxygen species by the enzyme xanthine oxidase (Sun, Zhao et al. 2014; Li et al. 2015).

In vitro experiments showed that polydatin (50, 100 μmol/L) could prevent the apoptosis of human umbilical vein endothelial cells (HUVEC) induced by methylglyoxal *via* inhibiting oxidative stress and maintaining mitochondrial function (Pang et al. 2017). In an adriamycin-induced oxidative stress cardiomyopathy rat model, both polydatin and resveratrol (200 μmol/kg) could significantly promote the activities of total superoxide dismutase (T-SOD), catalase (CAT), and glutathione peroxidase (GSH-PX) in plasma and increase the content of GSH in myocardial tissue. These enzymes can prevent excessive levels of reactive oxygen species (ROS) and oxidative stress response in the body (Wang, Gao et al. 2015). Polydatin (0.2 g/kg) could also increase the level of SOD in the serum of atherosclerotic mice, ultimately improving the morphology of atherosclerotic vascular tissue and relieving lipid deposition (Hu et al. 2016). In the ovalbumin-induced asthmatic mice model, polydatin could increase the activity of SOD and CAT in bronchoalveolar lavage fluid and decrease the content of ROS and malondialdehyde (MDA). The mechanism might be related to activating the p38 MAPK/nuclear factor E2-related factor 2 (Nrf2) signal pathway (Zhao, Jiang et al. 2018; Zeng et al. 2019). Researchers found that polydatin could also reduce the ROS content in the fat tissue of the retrobulbar of Graves' orbitopathy mice model by stimulating the Kelch like-ECH-associated protein 1 (Keap1)/Nrf2 pathway in orbital fibroblasts (Li et al. 2020). The stimulation of PC on Keap1/Nrf2 could also reduce the ROS level in the liver tissue of rats with fructose-induced liver injury and inhibit fatty liver degeneration (Zhao, Yu et al. 2018). Figure 2 depicts the primary mechanisms of PC's antioxidant effect. Studies on the antioxidant effects of PC and its extracts are listed in Table 2.

Anticancer effect

In vivo experiments showed that PC (300 mg/kg) could inhibit osteosarcoma cell growth. PC could initiate apoptosis and S-phase cell cycle arrest in osteosarcoma cells through impeding protein kinase B (AKT)/extracellular signal-regulated protein kinase (ERK)/epidermal growth factor receptor (EGFR) pathway (Zhao, Pan et al. 2022). Crude extract of PC (25, 50, 100, 200, 400 μg/mL) could inhibit the activity of human breast cancer cells and ovarian cancer cells, as well as promote cancer cell apoptosis in a dose and time-dependent manner, with IC_{50} (50% of the maximum inhibitory concentration) values of 31.18 ± 1.95 μg/mL and 28.12 ± 1.07 μg/mL, respectively (Pan, Shi et al. 2019). PC ethanol extract (50, 100, 150, 200 μg/mL) could also suppress the cell viability of cisplatin-resistant human oral cancer cells *in vitro* and promote cancer cell apoptosis through the endogenous pathway (caspase-3/9) (Wang, Horng et al. 2019). *In vitro* experiments showed that when the concentration was higher than 25 mg/mL, supercritical carbon dioxide liquid extract of PC could significantly inhibit tyrosinase activity in melanoma cells. This PC extract might lower the amount of melanin in melanoma cells when the concentration reached 50 mg/mL. Moreover, this PC extract could also induce the release of TNF-α from human monocytic after 48 h of culture. TNF-α is a kind of inflammatory/killing cytokine, and such immune stimulation might promote PC extract's antitumor activity (Lee et al. 2015).

In vivo experiments showed that polydatin (50 mg/kg) could restrain the growth of human laryngeal cancer cells transplanted into nude mice and diminish the tumor weight by 40%. Researchers found that polydatin could inhibit the proliferation of cancer cells by suppressing the activation of the platelet-derived growth factor (PDGF)/AKT signaling pathway in a dose-dependent manner (Li et al. 2017). Polydatin could also induce the S-phase arrest of human acute monocytic leukemia cell line THP-1 dose-dependently and inhibit the proliferation of cancer cells. The mechanism might regulate Bcl-2, Bax, cyclin A, and cyclin D1 expression (Wang, Luo et al. 2016). Moreover, polydatin could also inhibit the proliferation of leukemia cell line K562 by regulating the AKT/mammalian target of rapamycin (mTOR)/P70S6K signaling pathway (Luo et al. 2016). In addition to these cancer cells, *in vitro* experiments also showed that polydatin could inhibit the growth of cervical cancer (Pan et al. 2017), lung cancer (Sun and Ye 2019), and breast cancer (Chen et al. 2017; Feng et al. 2019).

Resveratrol also showed a prominent anticancer effect. It could down-regulate Bcl-2 protein and up-regulate the expression of Bax protein, and induce human liver carcinoma cells into phase S and promote apoptosis (Gu et al. 2014). In addition, resveratrol could also inhibit the growth of the human gastric adenocarcinoma cells and arrest the cancer cells at the G0/G1 stage (Jing et al. 2016). Emodin (20 μmol/L) could inhibit the expression of transforming growth factor β2 (TGF-β2) and reduce the cell viability and colony formation of human ovarian cancer cells. This effect of emodin was mediated by activating forkhead box protein D3 (FoxD3) and miR-199a (Song et al. 2018). Rhein, an anthraquinone compound that can be isolated from PC, was found to suppress tumors *in vitro* by interfering with Pin1/c-Jun interaction (Cho et al. 2017). Moreover, rhein could also reverse the adriamycin resistance in the hepatoma cell line in a dose-dependent manner and increase adriamycin in the cells. Moreover, 20 μmol/L rhein could enhance the sensitivity to

Table 1. Anti-inflammatory effects of PC and its compounds.

Pharmacological effects	Mechanism	Extracts/ compounds	Minimal active concentration/dose	Model	Reference
Anti-inflammatory activity	Prevented colon shortening and tissue damage; reduced levels of IL-1β, IL-6, and TNF-α	Ethanol extract	100 mg/kg/day, p.o., for 8 days	Dextran sulfate sodium mice established Ulcerative colitis mice	Liu et al. 2018
	Decreased the levels of IL-6, IL-1β, and MCP-1	Emodin-8-*O*-β-D-glucoside	50 μmol/L	Lipopolysaccharide induced inflammatory model of peritoneal macrophages (RAW264.7 murine macrophages)	Li, Yu et al. 2019
	Decreased the levels of NO and IL-6	Resveratrol	1 μmol/L	Lipopolysaccharide induced inflammatory model of peritoneal macrophages (RAW264.7 murine macrophages)	Ma et al. 2015
	Inhibited the release of IL-6 and NO	Polydatin	100 μg/mL	Lipopolysaccharide induced inflammatory model of peritoneal macrophages (RAW264.7 murine macrophages)	Sun et al. 2015
	Suppressed the expression of IL-6 and TNF-α; inhibited JAK/STAT and MAPK signaling pathway	Resveratrol	1 μg/mL	Lipopolysaccharide induced inflammatory model of peritoneal macrophages (RAW264.7 murine macrophages)	Ma et al. 2017
	Decreased levels of IL-1β, TNF-α; inhibited expression of TLR2, TLR4, and NF-κB	Polydatin	15 μg/mL	Monosodium urate induced THP-1 gouty inflammation model	Zhu et al. 2017
	Inhibited expression and secretion of MCP-1	Polydatin	20 μmol/L	3T3-L1 preadipocytes	Zheng et al. 2017
	Inhibited the expression of TNF -α, IL-1 β, IL-6, and NF-κB activation	Polydatin	20 mg/kg, i.p.	Lipopolysaccharide-induced endometritis in BALB/c mice	Li, Maimai et al. 2019
Anti-inflammatory activity	Suppressed TLR2 expression and p38 MAPK, NF-κB phosphorylation	Polydatin	45 mg/kg, i.p.	Staphylococcus aureus-induced mastitis in BALB/c mice	Jiang et al. 2017
	Reduced inflammatory cell infiltration, promoted the expression of IL-17, and inhibited p65	PC	4 g/kg/day, i.g. for 12 weeks	Bovine collagen II-induced rheumatoid arthritis in SD rats	Yang et al. 2019
	Reduced levels of IL-1β, IL-6, and TNF-α in joint synovium and inhibited NLRP3/ASC/caspase-1 pathway	Ethanolic extract	90 mg/kg/day, i.g., for 6 days	Sodium urate crystals induced acute gouty arthritis in C57BL/6 mice	Ma et al. 2019
	Reduced swelling degree and UA levels	Extract (containing 56.14% anthraquinones and stilbene)	65 mg/kg/day, i.g., for 14 days	Uric acid sodium solution induced gouty arthritis in SD rats	Ren et al. 2016
	Reduced arthritis scores and downregulated Wnt/β-catenin signaling pathway	Polydatin	40 mg/kg/day, i.g., for 28 days	Complete Freund's adjuvant induced rheumatoid arthritis in SD rats	Zeng et al. 2018
	Relieved inflammation of synovium and promoted angiogenesis	Emodin	0.8 mg/kg, i.g., for 28 days	Bovine collagen II and incomplete Freund Adjuvant induced rheumatoid arthritis in Wistar rats	Wang, Yang et al. 2015
Anti-inflammatory activity	Inhibited TNF-α/HIF-1α/iNOS/NO signaling pathway	Emodin	40 mg/kg/day, i.g., for 20 days	Bovine collagen II and incomplete Freund Adjuvant induced rheumatoid arthritis in Wistar rats	Pan, Wang et al. 2019
	Upregulated Bax mRNA expression and downregulated bcl-2 mRNA expression	Emodin	40 mg/kg/day, i.g., for 20 days	Bovine collagen II and incomplete Freund Adjuvant induced rheumatoid arthritis in Wistar rats Wistar rats	Jin et al. 2018
	Inhibited cell proliferation and TGF-β, NF-κB/MAPK signaling pathway	Physcion8-*O*-β glucopyranoside	IC50 = 49.76 μg/ml	MH7A RA-derived fibroblast-like synoviocyte cell	Geng et al. 2018
	Decreased paw swelling and arthritis indices and decreased levels of TNF-α, IL-1β, and IL-6		20 mg/kg	Collagen-induced arthritis (CIA) rats	

(*continued*)

Table 1. Continued.

Pharmacological effects	Mechanism	Extracts/ compounds	Minimal active concentration/dose	Model	Reference
	Decreased the level of IL-1β and suppressed the expression of TLR2, TLR4, and MyD88	PC combinated with *Ramula Cinnamomi* (Guizhi)	3.5 g/kg/day, i.g., for 7 days	Monosodium urate induced Acute Gouty Arthritis in SD rats	Gu et al. 2015
	Suppressed the expression TLR2, TLR4	PC combinated with *Artemisia Herba artemisiae* (Yinchen)	1:3 (10 g/kg), i.g., for 10 days	Monosodium urate induced Acute Gouty Arthritis in Wistar rats	Cheng and Jiang 2017
	Relieved inflammatory cell infiltration, edema, and necrosis	PC cream (containing 230 g of knotweed powder)	external use, for 5 days	Calcium extravasation injure model in New Zealand rabbits	Zhang, Wang et al. 2015

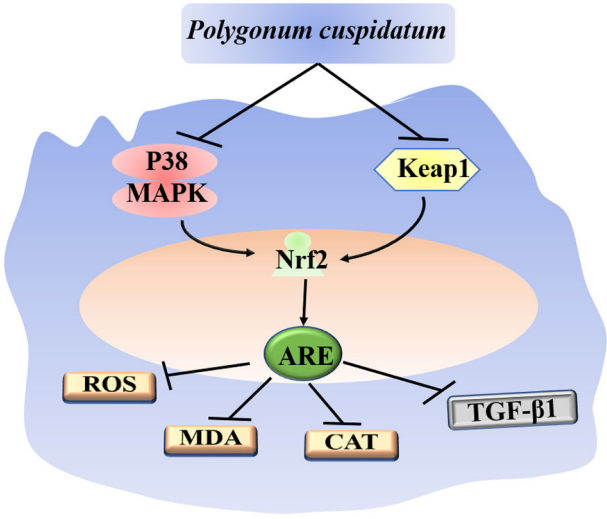

Figure 2. The main mechanism of the antioxidant effect of *Polygonum cuspidatum* Sieb. *et* Zucc. The component of this plant can inhibit the expression of p38 MAPK and Keap1, then Nrf2 is upregulated, which will activate the ARE gene, further induce the expression of ROS, MDA, CAT and TGF-β1.

adriamycin of the hepatoma cell line by 7.24 times (Wu, Cao et al. 2019). These studies may provide a new direction for the treatment of drug resistance in cancer cells.

Resveratrol-4-*O*-D-(2′-galloyl)-glucopyranoside is one of the active compounds isolated from PC. Xie et al. (2014) revealed that this compound could inhibit the activity of human hepatoma cells and slow tumor growth in mice transplanted with hepatoma cells. The mechanisms included the regulation of the c-Jun-N-terminal kinase (JNK)/ERK signaling pathway, and this effect was dose- and time-dependent (Xie et al. 2014). Another active compound in the ethyl acetate (EtOAc) extract of PC, 2-ethoxystypandron, could also restrain the cell growth of human hepatoma cells in a dose-dependent manner. This effect of 2-ethoxystypandron was linked to its inhibition of STAT3 signaling and the induction of hepatoma cell cycle arrest (Li, Zhang et al. 2019). 2-Methoxystypandron, another EtOAc extract of the PC roots was found to be an inhibitor of JAK2 and IκB kinase. 2-Methoxystypandron could also inhibit the activation of STAT3 induced by IL-6 and suppress the growth of cervical cancer cells. Even a concentration of 10 μmol/L could completely inhibit the growth of cancer cells (Kuang et al. 2014). 2-Methoxy-6-acetyl-7-methyljuglone, the active component of PC, could significantly reduce the proliferation of 16 types of cancer cell lines *in vitro*, and its IC_{50} value was less than 5.5 μmol/L (Sun et al. 2016). Studies on the anticancer effects of PC and its extracts are listed in Table 3.

Neuroprotection effect

The main components of PC have shown significant neuroprotective effects in many neurological diseases. Polynapstilbene B, resveratrol, (-)-epicatechin, procyanidin B 2, 3-*O*-gallate, and 2′-*O*-galloyl-peceid were isolated from PC. These components could significantly relieve the damage of PC12 cells caused by rotenone at 10 μmol/L *in vitro*, among which resveratrol had the most potent inhibitory effect (71.7%) (Liu et al. 2015). Studies observed that physcion 8-*O*-β-glucopyranoside, isolated from PC, could alleviate the symptoms of dementia rats and reduce the increase in escape time of dementia rats in Morris water maze by 44.8% (Xu et al. 2015).

The chronic and unpredictable mild stress (CUMS) rat model was established to investigate the effect of resveratrol on depression. Long-term use of resveratrol could significantly prevent behavioral changes induced by CUMS, such as spatial learning and memory disorders (Liu, Zhang et al. 2014). In addition, resveratrol could up-regulate the cAMP-response element-binding protein (CREB) and brain derived neurotrophic factor (BDNF) and modulate the mRNA levels of Bcl-2 and Bax in the hippocampus of CUMS rats (Wang, Xie et al. 2016; Shen et al. 2018). Resveratrol also had an antidepressant effect by regulating serum corticosterone levels. When trans-resveratrol was combined with piperine, a bioavailability enhancer, the minimum effective dose of trans-resveratrol could be reduced to 20 mg/kg (Liu, Xie et al. 2014; Xu et al. 2016). In addition to alleviating symptoms of depression, resveratrol (10, 100 nmol/L) significantly reduced hypoxia-induced degradation of IκB-α, phosphorylation of p65 NF-κB protein, ERK1/2, and JNK, thereby inhibiting microglial activation (Zhang, Yuan et al. 2015).

Hepatoprotective effect

Continuous gavage of PC water extract (80, 160 mg/kg) for 11 weeks could decrease liver lipid accumulation in fructose-fed rats with metabolic syndrome by targeting the Keap1/Nrf2 pathway (Zhao, Chen et al. 2022). In addition, polydatin (50, 100 mg/kg) could also reduce alanine transaminase and aspartate aminotransferase in serum of mice with alcohol induced hepatic injury (Koneru et al. 2017). Furthermore, polydatin (6.25 mg/mL) could alleviate hepatic steatosis in zebrafish larvae induced by ethanol. This effect of polydatin might correlate with the improvement of

Table 2. Antioxidant effects of PC and its compounds.

Pharmacological effects	Mechanism	Extracts/compounds	Minimal active concentration/dose	Model	Reference
Antioxidant activity	Promote radical scavenging	Supercritical carbon dioxide fluid extraction	10 mg/mL	DPPH assay	Lee et al. 2015
	Inhibited xanthine oxidase	70% Ethanol extracts	IC_{50} = 2.06 mg/mL	HPLC method for *in vitro* screening	Sun, Zhao et al. 2014
	Inhibited xanthine oxidase	Ethyl acetate and butanol extractions	K_m = 40 μg/mL, 100 μg/mL	HPLC method for *in vitro* screening	Li et al. 2015
	Inhibited methylglyoxal-induced cell apoptosis and activated Akt pathway	Polydatin	50 μmol/L	Methylglyoxal-induced HUVEC apoptosis	Pang et al. 2017
	Promote the activities of T-SOD, CAT, and GSH-Px in plasma; increased the GSH in myocardial tissue	Polydatin and resveratrol	200 μmol/kg, i.g., for 15 days	Doxorubicin induced oxidation model in SD rats	Wang, Gao et al. 2015
	Reduced ROS level and promoted SOD activity	Polydatin	0. 2 g/kg/day, i.g., for 28 days	High fat diet induced $ApoE^{-/-}$ mice model of coronary atherosclerosis	Hu et al. 2016
	Activated p38 MAPK/Nrf2 signaling pathway	Polydatin	30 mg/kg/day, i.p., for 7 days	Ovalbumin-induced Asthma BALB/c mice	Zhao, Jiang et al. 2018
	Inhibited activity of ROS, TGF-β1, and Nrf2	Polydatin	100 mg/kg	Ovalbumin-induced Asthma BALB/c mice	Zeng et al. 2019
Antioxidant activity	Reduced ROS level and activated Keap1/Nrf2/ARE pathway	Polydatin	10 μmol/L	H2O2-induced oxidative stress in orbital fibroblasts	Li et al. 2020
			50 mg/kg/day, i.g., for 4 weeks	Adenovirus expressing the thyroid-stimulating hormone receptor (TSHR) A-subunit (Ad-TSHR289) induced Graves' orbitopathy mice	
	Reduced ROS level, inhibited Keap1 and activate Nrf2 pathway	Polydatin	40 μmol/L	Fructose induced BRL-3A and HepG2 cells injury	Zhao, Yu et al. 2018
			7.5 mg/kg, i.g., for 7 weeks	Fructose induced liver oxidative stress, inflammation, and lipid deposition in SD rats	

ethanol and fat metabolism, inhibition of oxidative stress and DNA damage (Lai et al. 2018).

Cardioprotective effect

Ding W et al. (2014) have found that polydatin is essential in preventing pressure overload-induced cardiac hypertrophy and heart failure. The mechanism might be polydatin could inhibit the Ca^{2+}-calcineurin pathway without affecting myocardial contractility (Ding W et al. 2014). Furthermore, trans-polydatin could also decrease the expression of angiotensin, inhibit the activity of renin and angiotensin-converting enzyme, and protect against myocardial ischemia injury (Ming et al. 2017). This suggested that PC might be a new cardiac protective drug.

Blood vessel protective effect

The extracts of PC root (100, 350 mg/kg) could inhibit the increase of retinal vascular permeability in diabetic rats, suggesting that oral administration might help to suppress the development of retinopathy in diabetic patients (Sohn et al. 2016). *In vitro*, it was shown that polydatin (1, 3, 10 μmol/L) could restore abnormal vasodilation induced by high glucose levels in a dose-dependent manner. When the concentration of polydatin was 10 μmol/L, it could recover vascular endothelial function to the same level as the normal glucose group. The effect of polydatin was related to activating the PPAR protein-NO pathway (Wu et al. 2015). Researchers discovered that quercetin (0.1, 0.5, 1 μmol/L) could protect human brain microvascular endothelial cells injured from hypoxia and reoxygenation. Regulating the Keap1/Nrf2 pathway and endoplasmic reticulum stress might be important for the protective effect of quercetin. Such effects suggest that quercetin may protect small vessels and thus be a potential treatment for cerebral small vessel disease (Li et al. 2021).

Antiviral effect

Procyanidin c-13,3′,3″-tri-*O*-gallate was isolated from the ethanol extract of PC and could activate the transcription of HIV-1 in a concentration and time-dependent manner. This suggested that procyanidin c-13,3′,3″-tri-*O*-gallate could be combined with highly active antiretroviral therapy to eliminate inactive potential HIV (Wang, Yang et al. 2015). The aqueous extract of PC, with resveratrol and emodin as the most effective active compounds,

Table 3. Anticancer effects of PC and its compounds.

Pharmacological effects	Mechanism	Extracts/compounds	Minimal active concentration/dose	Cancer	Reference
Anticancer activity	Initiated apoptosis and S-phase cell cycle arrest through impeding Akt/ERK/EGFR pathways	PC dissolved in saline	300 mg/kg	Osteosarcoma	Zhao, Pan et al. 2022
	Inhibited the activity of human breast cancer and promoted apoptosis	Crude extract	$IC_{50} = 31.18 \pm 1.95$ μg/mL $IC_{50} = 28.12 \pm 1.07$ μg/mL	Breast cancer Ovarian cancer	Pan, Shi et al. 2019
	Anti-human oral cancer, stimulated caspase-9 and -3 activities	Ethanol extract	50 μg/mL	Oral cancer	Wang, Horng et al. 2019
	Anti-laryngeal cancer and inhibited the PDGF/AKT signaling pathway	Polydatin	2 μmol/L	Laryngeal cancer	Li et al. 2017
	Reduced mean tumor volume		50 mg/kg		
	Anti-leukemia, induced S-phase cell cycle arrest, and upregulated cyclin D1 and Bcl-2	Polydatin	IC_{50} (48 h) = 50 μmol/L	Acute leukemia	Wang, Luo et al. 2016
	Anti-leukemia and inhibited Akt/mTOR/p70S6K signaling pathway	Polydatin	IC_{50} (24 h) = 80 μmol/L	Acute leukemia	Luo et al. 2016
	Anti-cervical cancer and inhibited PI3K/AKT/mTOR pathway	Polydatin	50 μmol/L	Cervical cancer	Pan et al. 2017
	Anti-hepatoma and inhibited AKT/NF-κB pathway	Polydatin	IC_{50} (72 h) = 34.89 mg/L	Lung cancer	Sun and Ye 2019
	Inhibited the proliferation of human breast cancer and downregulated VEGF and MMP-9	Polydatin	0.2 μmol/L	Breast cancer	Chen et al. 2017
Anticancer activity	Induced phase S cell cycle arrest and downregulated CREB and cyclin D1	Polydatin	1.5 μmol/L	Breast cancer	Feng et al. 2019
	Inhibited the proliferation of cells, downregulated the expression of Bcl-2 and upregulated Bax	Resveratrol	25 μmol/L	Liver cancer	Gu et al. 2014
	Induced cell blockage at phase S	Resveratrol	12.5 μmol/L	Liver cancer	Gu et al. 2015
	Decreased the survival rate of cells and rested the cells at the G0/G1 phase	Resveratrol	IC_{50} (24 h) = 127 μmol/L	Gastric cancer	Jing et al. 2016
	Anti-ovarian cancer, promoted FOXD3 expression, activated miR-199a, and suppresses the expression of TGF-β2	Emodin	20 μmol/L	Ovarian cancer	Song et al. 2018
	Increased accumulation of DOX in SMMC-7721/DOX cells	Rhein	20 μmol/L	Liver cancer	Wu, Cao et al. 2019
	Inhibited human hepatoma cells activity	Resveratrol-4-*O*-D-(2′-galloyl)-glucopyranoside	2.5 μmol/L	Liver cancer	Xie et al. 2014
	Reduced mean tumor volume and weight in mice		10 mg/kg		
	Anti-hepatoma and inhibited STAT3 signaling	2-Ethoxystypandrone	$IC_{50} = 3.69 \pm 0.51$ μmol/L $IC_{50} = 5.58 \pm 0.89$ μmol/L	Liver cancer	Li, Zhang et al. 2019
	Induced death of tumor cells and inhibited STAT3 and NF-κB pathways	2-Methoxystypandrone	10 μmol/L	Cervical cancer, Breast Cancer, Glioma, Ovarian cancer, Prostate cancer, Lung cancer	Kuang et al. 2014
	Induced multiple forms of cell death in cancer cells and activated JNK/iNOS/NO pathways	2-Methoxy-6-acetyl-7-methyl-juglone	$IC_{50} < 5.5$ μmol/L	Lung cancer, Melanoma, Breast cancer	Sun et al. 2016

was found to inhibit the replication of the H1N1 influenza virus *in vitro*, with an IC_{50} value of 312 g/mL (Lin et al. 2015). Both the ethanol and aqueous extracts of PC were able to inhibit 3-chymotrypsin-like (3CL) protease and prevent the interaction between spike-protein and angiotensin-converting enzyme II, which in turn prevented the entry of SARS-CoV-2 wild-type and omicron pseudotyped viruses into intact zebrafish larvae. The researchers further found that among the 9 major phytochemical constituents in these PC extracts, only gallic acid significantly inhibited viral entry into HEK293T cells in a dose-dependent manner, with an IC_{50} value of 23.5 μmol/L (Lin et al. 2022). Other studies have shown that EtOAc extract from the root of PC (12.5 μg/mL) could suppress the expression of Epstein-Barr virus lytic proteins and transcriptional genes, and the transcriptional inhibition rates of lytic genes BRLF1 and BZLF1 are 95.29% and 95.31%, respectively (Yiu et al. 2014).

Orthoquin, a natural product extracted from the root of PC, could react with oxygen to produce singlet oxygen and short-lived reactive oxygen species. These oxygen species can damage large molecules such as proteins, lipids, and nucleic acids near the virus, then inhibit viral replication. Orthoquin could inhibit herpes simplex virus infection in a light-dependent manner (Monjo et al. 2018). Resveratrol (30 g/mL) and polydatin (200 g/mL) were both shown to have anti-human enterovirus-71 properties *in vitro* and to be able to protect rhabdosarcoma cells. Compared to polydatin, resveratrol exhibited a stronger antiviral effect (Zhang, Li et al. 2015).

Antibacterial and antifungal effects

Different extracts from PC have extraordinary bacteriostatic effects. The methanol extract of PC root could significantly suppress the activity of bacterial neuraminidase and alleviate the symptoms of the host. In particular, the active ingredient emodin-1-*O*-β-D-glucopyranoside in PC extract demonstrated a robust inhibitory effect on activity of bacterial neuraminidase at a low concentration (IC_{50} = 0.43 μmol/L) (Uddin et al. 2016). The ethanol extract of PC had inhibitory effects on *Bacillus subtilis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, with minimum inhibitory concentration (MIC) values of 100, 50, and 100 μg/mL. This effect of PC extract suggested that it can treat bacterial infection caused by snakebite (Liu, Nielsen et al. 2014). The ethyl ether fraction of PC also showed a broad antimicrobial spectrum against the tested clinical drug-resistant isolates, with the MIC between 0.2 ~ 1.63 mg/mL, which was 3 to 10 times more effective than crude PC extract. The ethyl ether fraction of PC at 2 times the MIC could completely kill 3×10^5 CFU/mL *Staphylococcus aureus* within 1 h (Su et al. 2015). In addition, the ethyl ether fraction of PC had anti-methicillin-resistant *Staphylococcus aureus* activity, as it could destroy the integrity of bacterial cell walls and cell membranes. It was found that emodin (32 g/mL) was the main component of ethyl ether fraction of PC to reduce the activities of the methicillin-resistant *Staphylococcus aureus*. Emodin could inhibit the expression of biofilm-related genes, reduce the release of extracellular DNA, and thus inhibit the formation of *Staphylococcus aureus* biofilm in a dose-dependent manner (Cao et al. 2015). Moreover, the extracts of PC could also be used as a chemical stabilizer that binds to the surface of silver nanoparticles to enhance their antibacterial effect (Sun, Qu et al. 2014).

Studies have shown that PC had different antifungal activities against superficial fungi: *Trichophyton rubrum* (MIC = 50 μg/mL), *Trichophyton mentagrophytes* (MIC = 100 μg/mL), *Microsporum canis* (MIC = 50 μg/mL), *Epidermophyton floccosum* (MIC = 50 μg/mL), *Trichophyto schoenleinii* (MIC = 50 μg/mL), *Microsporum gypseum* (MIC = 100 μg/mL), *Trichophyton tonsurans* (MIC = 50 μg/mL), and *Trichophyton violaceum* (MIC = 50 μg/mL) (Yang et al. 2015).

Other pharmacological effects

The water extract of PC (100, 250 mg/kg) significantly reduced the corneal irregular score and increased the volume of tears after extra orbital lacrimal gland resection in dry-eye rats. Park et al. (2018) have proved that this effect of PC extract might be related to the increased expression of mucin-4 and the inhibition of oxidative stress and inflammation (Park et al. 2018). PC and its extracts also have a strong regulatory effect on carbohydrate and lipid metabolism. The α-glucosidase and protein-tyrosine phosphatase 1B (PTP1B) were essential in insulin metabolism. *In vitro*, it was found that the crude EtOAc extract of PC could inhibit the activity of α-glucosidase and PTP1B, with IC_{50} values of 8.33 ± 1.42 and 16.21 ± 0.38 μg/mL, respectively (Zhao et al. 2017). Ethanol extract from the root of PC (100, 350 mg/kg) could inhibit the expansion and proliferation of glomerular mesangial matrix in diabetic rats, thus preventing diabetic nephropathy (Sohn et al. 2014).

In addition, resveratrol (20, 50, 100 μmol/L) could up-regulate the expression of type II collagen in superficial chondrocytes and middle chondrocytes, indicating that it could be used in the treatment of arthritis (Maepa et al. 2016). In a clinical test, the plant was found to have the ability to inhibit platelet aggregation. When healthy subjects took a supplement (80 mL) containing 10% resveratrol, the platelet aggregation induced by the platelet-activating factor could be suppressed significantly (Gavriil et al. 2019). The inhibitory effect of polydatin on angiogenesis allowed it to be used to treat angiogenesis-related diseases, including retinopathy, rheumatoid arthritis, and psoriasis (Hu et al. 2019). Emodin is considered as a potential therapeutic drug for lung cancer induced-cachexia, because feeding with emodin-enriched PC extract (2% of feed supplement) could increase the weight and reduce gastrocnemius muscle atrophy of A549 tumor-bearing BALB/c-nu mice. *In vivo* and *in vitro* mechanism research showed that emodin in this PC extract could inhibited transcription factor 4 (TCF4)–TWIST1 (a bHLH-domain-containing transcription factor) interaction, then suppress parathyroid hormone-related protein (PTHrP) expression (Fang et al. 2022).

Summary of pharmacologic effects

PC has been prescribed for medicinal purposes for thousands of years in China. In addition to anti-inflammatory, antioxidative, anticancer, and neuroprotective properties, PC and its phytochemical constituents had protective effects on the heart, kidney, liver, and other organs. PC can be a valuable alternative to various diseases, including inflammation, cancer, cognitive impairments, depression, fatty liver disease, and diabetes. Identifying the best therapeutic effect of one or more phytochemical constituents of PC and analyzing its mechanisms of action would help with the development of PC-related medicines. In addition, the above studies on the pharmacological activities of PC and its phytochemical constituents were all animal or cell experiments, and the therapeutic effects and safety need to be verified in future clinical studies.

Clinical application

This review summarized the dosage and compatibility of PC in prescriptions of past dynasties and found that the effective dosage of PC mainly was between 10 g and 30 g. When the dosage was $\leq$ 30 g, it primarily removes dampness and jaundice, clears heat, and helps with body detoxification; when the dosage was greater than 10-90 g, it promotes blood circulation and dredged channels. The most commonly drugs compatible to be used with PC supplements were blood-activating and stasis-dissolving drugs, heat-clearing drugs, blood-enriching drugs, Qi-tonic drugs, and water-dampening drugs (Bai et al. 2016), which were used to treat severe moldy sugarcane poisoning, cirrhosis ascites, carotid atherosclerosis, etc. In addition, PC could also be made into a tincture to treat burns or made into an ointment to assist in the treatment of periappendiceal abscess (Liu, Zheng et al. 2014; Xia and Yang 2014; Wang, Yang et al. 2015; Li, Bei et al. 2016; Chen et al. 2018). Compatible drugs and appropriate dosage for different diseases should be carefully selected when clinicians prescribe the medicine.

The information on proprietary Chinese medicines with PC as the main component in the State Drug Administration (https://www.nmpa.gov.cn) was also queried. The results included Huzhangye capsules (approval number: Z20026314), Huzhangfanshi liniments (approval number: Z20025342), Huzhangshangtong tincture (approval number: Z20025395), Compound Huzhang tablets (approval number: Z45022334), Compound *Rhizoma Polygoni Cuspidati* burn oil (approval number: Z10920021), and Compound paracetamol and chlorphenamine maleate capsules (approval number: H13023540). Huzhangye capsules were used to treat dizziness, headaches, and other symptoms related to hypertension (Zhao 2016). It was safe and effective in treating primary hypertension with liver Yang hyperactivity when used in combination with nifedipine. Its antihypertensive mechanism might be related to the protection of vascular endothelial cells (Ding and Gao 2021). Experimental findings also indicated that Huzhangye capsules were more effective in improving the symptoms of benign paroxysmal positional vertigo when combined with manual reduction (Zhang et al. 2020). Compound Huzhang tablets could clear heat and remove phlegm, relieve coughs and asthma; it could also be used to prevent liver damage from psychotropic drugs (Yang and Liu 2014). Compound paracetamol and chlorphenamine maleate capsules, which was made according to the principle of combining Chinese and western medicine to treat cold, contain acetaminophen, chlorpheniramine maleate, and PC. Huzhangshangtong tincture, Huzhangfanshi liniments, and Compound *Rhizoma Polygoni Cuspidati* burn oil are all external drugs. Huzhangshangtong tincture was used to treat traumatic injuries (Liu 2016), and the latter two were used to treat mild water and fire burns (Liu et al. 2012).

Pharmacokinetics

Most of the current pharmacokinetic studies on PC focused on its active ingredients. This review discussed the pharmacokinetic studies of four richest ingredients in PC. Resveratrol was characterized by low solubility and high intestinal permeability, with a plasma bioavailability of about 1% after oral administration. Glucuronides and monosulfates were the main metabolites in plasma (Huang et al. 2019; Briskey and Rao 2020; Zhang et al. 2021). After oral administration, resveratrol was swiftly metabolized in the liver and intestine, mostly into sulfate conjugates and glucuronides, and excreted through the urine (Honari et al. 2019). It has also been reported that the above metabolites could be converted back to resveratrol by intestinal microbes (Zhang et al. 2021). Polydatin, a glucose derivative of resveratrol, was mainly metabolized to resveratrol in the small intestine and liver, then metabolized to glucuronidation forms, but polydatin could still be detected in plasma and urine (Lou et al. 2021; Montanari et al. 2021; Sunsong et al. 2021). Animal experiments showed the mutual transformation between polydatin and resveratrol in rats after oral administration of polydatin and resveratrol at the same dosages, respectively (Wang, Gao et al. 2015).

After oral administration of PC, emodin also rapidly underwent phase II metabolism to form its glucuronide. The parent form of emodin was of low concentration in the body, which was only detectable in the liver and the brain (Di et al. 2015; Dong et al. 2016). A study in mice showed that plasma glucuronidated emodin peaked 1 h after intragastric administration of emodin and was eliminated within 12 h. Female mice appeared to metabolize emodin faster than male mice (Sougiannis et al. 2021). Studies have shown that quercetin was present in a conjugated form whose primary form was glycoside in human blood after a single oral dose (Li, Yao et al. 2016). After oral administration of 200 mg of quercetin, the C_{max} and T_{max} were 2.3 ± 1.5 μg/mL and 0.7 ± 0.3 h, respectively (Batiha et al. 2020). Quercetin aglycones were absorbed in the small intestine mainly through passive diffusion and transported by organic anion transport peptides, followed by methylation, vulcanization, and glucuronidation in the small intestine and liver (Li, Yao et al. 2016). After metabolized by the liver, it could enter the circulation or be metabolized by the kidney and finally excreted from urine (Guo and Bruno 2015; Li, Yao et al. 2016).

In general, the primary components of PC were rapidly metabolized by the small intestine and liver after entering the body. More studies should be carried out on improving drug solubility, controlling drug release, preventing drug degradation, changing the means of administration, and preventing metabolism for enhancing the bioavailability of drugs.

Conclusions and future perspectives

PC has been used in the clinical practice for thousands of years and has extensive pharmacological activities. This review summarized its phytochemical constituents, pharmacological actions, the clinical application, and pharmacokinetics. PC and its main components have a wide range of pharmacological activities and are used for antipyretic, antibacterial, anticancer, cardiovascular and cerebrovascular protection, etc. It could be an effective therapeutic drug for various related diseases, such as arthritis, ulcerative colitis, asthma, and cardiac hypertrophy. PC can exert its therapeutic effects on a variety of systems and pathways since it contains a variety of phytochemical ingredients.

The synergistic therapeutic effect of the main phytochemical constituents in PC and the herb-drug interaction should also be further explored, which can guide the clinical drug use and standardized drug preparation. Many active ingredients that come from the roots of PC have been studied. The phytochemical constituents and pharmacological effects of flowers or leaves have been less studied, which limits the clinical use of PC. In the future, more research on other parts of PC should also be done to expand the understanding of PC.

Pharmacokinetic studies showed that the poor bioavailability of PC and its main phytochemical constituents affected its medicinal properties. Contemporary technology should be used to develop biological preparations of compounds with improved

bioavailability and tested them in animals or even humans for early application in the clinical treatment. Although PC has been reported to be nephrotoxic in some cases, its contributions to the clinical treatment are undeniable. With more research being done on PC, its pharmacological effects and safety will be better known, allowing for more widespread therapeutic application of these plants.

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