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Research progress on *Prunella vulgaris* and its monomers in protecting against ulcerative colitis

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ABSTRACT

Prunella vulgaris is a traditional Chinese herbal medicine with many pharmacological effects, among which the anti-inflammatory effect is more significant. It is widely reported that *Prunella vulgaris* has anti-inflammatory, antioxidant, immune regulation, intestinal flora regulation and intestinal barrier protection effects on ulcerative colitis (UC). This paper collected relevant reports to further summarize the mechanisms and effective parts of *Prunella vulgaris* and its monomers in the treatment of UC and provided theoretical basis and reference for the application of *Prunella vulgaris* in UC.

1. Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease mainly caused by the interaction of multiple factors such as environment, genetics, infection and immunity.[1] In recent years, the incidence rate in our country has increased year by year, and its complex pathogenesis and recurrence make it difficult to treat thoroughly. At present, UC is mainly treated with western medicine, but it has many adverse reactions, such as fever, rash, angioedema, liver damage, bleeding tendency, etc.,[2,3] while traditional Chinese medicine treatment shows good therapeutic effect.

Prunella vulgaris is a multifunctional traditional Chinese herbal medicine. According to Chinese Ancient Books, *Prunella vulgaris* has the anti-inflammatory effect of dispersing knot and swelling. Modern pharmacological studies[4] have shown that there are many anti-inflammatory active components in *Prunella vulgaris*, including triterpenoids, flavonoids, organic acids and sterols, which display anti-inflammatory, antioxidant and immunoregulatory pharmacological activities. In this paper, the current related research was summarized to further analyze, and summarize the association between *Prunella vulgaris* and UC, as well as elucidate the active compounds and mechanisms of *Prunella vulgaris* against UC, thereby helping us comprehensively understand the anti-UC effect of *Prunella vulgaris* and providing theoretical basis for further research and application of *Prunella vulgaris*.

2. *Prunella vulgaris* in protecting against UC

Prunella vulgaris shows anti-inflammatory, antioxidant and immunomodulatory effects on UC. Zheng et al.[5] found that *Prunella vulgaris* capsule could significantly reduce the number of ulcers and congestion index, increase colon weight and intestinal weight index, and up-regulate $CD3^+$, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ T cells, suggesting that *Prunella vulgaris* capsule may play a role in immune regulation by regulating peripheral blood T-lymphocyte subsets. Further experiments showed that it significantly decreased the proinflammatory cytokine tumor necrosis factor-α (TNF-α) and increased the anti-inflammatory cytokine interleukin-13 (IL-13).[6] Wan et al.[7] found that *Prunella vulgaris* honey extract contained abundant phenolic acid compounds, which could significantly up-regulate expression of antioxidant protein, NADPH: quinone oxidoreductase 1 (NQO-1), thioredoxin reductase 1 (Txnrd1) and nuclear factor erythroid 2-related factor 2 (Nrf2), and tight junction protein zonula occludens-1 (ZO-1), thus alleviating the damage of sodium dextran sulfate (DSS) on intestinal epithelial cell barrier function. Harrbarg et al.[8] found that ethanol extract of *Prunella vulgaris* reduced serum levels of interleukin-10 (IL-10), C-X-C motif chemokine ligand 9 (CXCL9) and TNF-α. The activity of myeloperoxidase (MPO) and expression of chemokine (Ccl2, Ccl20, Cxcl1, Cxcl9) and adhesion molecules (VCAM-1, ICAM-1) in colon mucosa were decreased to reduce the severity of

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intestinal inflammation in mdr1a $^{(-/-)}$ mice. The plant and the spike of *Prunella vulgaris* are provided in Fig. 1.

3. *Prunella vulgaris* monomers in protecting against UC

3.1. Flavonoids

At present, the main flavonoids of *Prunella vulgaris* in protecting against UC are luteolin, quercetin, rutin, and kaempferol. The structures of these flavonoids[9] are provided in Fig. 2.

3.1.1. Luteolin

Li et al.[10] found that luteolin promoted the entry of Nrf2 into the nucleus by activating the Nrf2 signaling pathway, and then up-regulated the mRNA levels of downstream target genes HO-1 and NQO1, inhibited the expression of proinflammatory factors TNF-α and IL-6, enhanced the colon antioxidant activity of mice, and regulated the oxidation/antioxidant balance to alleviate UC. UC is closely associated with inflammation and intestinal dysbiosis. Li et al.[11] proved that luteolin reduced the levels of (nuclear factor-kappa B) NF-κB, IL-17 and IL-23 and increased the levels of peroxisome proliferator-activated receptor γ (PPAR-γ) in UC rats, while reducing the increase in the ratio of lactobacillus and Prevotella9. Protection of intestinal barrier function plays an important role in prevention and treatment of UC. Nunes et al.[12] showed that luteolin significantly inhibited cytokine induced interleukin-8 (IL-8) production, cyclooxygenase-2 (COX-2) and induced nitric oxide synthase (iNOS) expression and nitric oxide (NO) overproduction in HT-29 colon epithelial cells. Li et al.[13] showed that luteolin protected the intestinal epithelial barrier function of human colorectal adenocarcinoma cells (CaCo-2) by increasing the expression of tight junction (TJ) proteins occludin (OCLN), senescence-associated epithelial membrane protein 1 (CLDN1) and ZO-1. A study[14] reported that luteolin could ameliorate colon tissue damage, and its anti-inflammatory, anti-apoptotic and anti-autophagy effects were related to the activation of ERK signaling pathways. Kim et al.[15] proved that after IκB degradation and activation of NF-κB, luteolin inhibited TNF-α induced IL-8 production in intestinal epithelial cells by blocking MAPK phosphorylation. In addition, other studies[16] found that these therapeutic effects were associated with the down-expression of HMGB1-TLR–NF–κB signaling pathway related proteins.

3.1.2. Quercetin

Preclinical evidence of quercetin against inflammatory bowel disease showed that quercetin could reduce histological score (HS), disease activity index (DAI), IL-1β, TNF-α, NO, MDA and MPO activities, increase colon length (CL) and weight change degree (WCD), and increase IL-10 and GSH levels and enhance SOD and CAT activities. The above changes involve the effects of anti-inflammatory, antioxidant stress, cellular protection, barrier protection, and microbial community regulation.[17] Cai et al.[18] found that quercetin down-regulated IL-6/STAT3 signaling pathway and reduced the level of inflammatory cytokines. Tang et al.[19] found that quercetin inhibited the proinflammatory response mediated by NOD-like receptor thermal protein domain associated protein 3 (NLRP3) by up-regulating the expression of silent mating type information regulation 2 homolog-1 (SIRT1), and improved the anti-inflammatory and neuro-recovery effects mediated by M2 macrophages, thereby improving the colonic injury. Kottakis et al.[20] proved that the combined use of quercetin and lycopene restored the biochemical parameters of UC induced by ochratoxin A(OTA) to near normal levels, that was, decreased MDA, NO, MPO and hydroxyproline levels and increased SOD and GSH levels. Liu et al.[21] also observed that quercetin reduced the levels of IL-17A and IL-22, increased the activity of CAT and SOD and the expression of ZO-1 and OCLN, reduced the abundance of Bacteroides, thereby reducing colon oxidative stress, inflammation and intestinal mucosa injury. Another study[22] showed that quercetin may enhance the intestinal integrity and antioxidant capacity of the liver. In addition, quercetin increased the types of bacteria producing butyrate, and the increase of acetyl-CoA-mediated butyrate accelerated carbohydrate and energy metabolism, decreased cell motility and endotoxemia, and increased intestinal barrier function.[23]

3.1.3. Rutin

Yue et al.[24] showed that rutin decreased the levels of IL-1β and IL-18 in serum and colon tissue, and expression of NLRP3, IL-1β, Cleavedcaspase-1, and Cleaved IL-1β in colon tissue. The damage of mucosal inflammation was inhibited by inhibiting the activation of NLRP3 inflammasome. Chu et al.[25] proved that rutin plays an important protective role in the formation of DSS induced colitis lesions by inhibiting Th1 and Th17 cell responses in the intestinal Lamina propria of mice. The colonic protective mechanism of rutin against UC was also associated with the ability to decrease MPO and alkaline phosphatase (AKP) activity,[26] down-regulate NF-κB signaling pathway,[27] and increase colonic glutathione levels.[28]

3.1.4. Kaempferol

Kaempferol is an effective anti-inflammatory component in *Prunella vulgaris*. Park et al.[29] found that the plasma levels of NO and human leukotriene B4 (LTB_4) were significantly reduced after 2.0 % kaempferol feeding. After 0.3 % kaempferol feeding, colon mucosal MPO activity was inhibited and TFF3, a marker of goblet cell function, was upregulated. Studies have found that kaempferol also significantly prevented intestinal barrier destruction by increasing the levels of ZO-1, OCLN, and

Fig. 1. The plant and the spike of *Prunella vulgaris*.

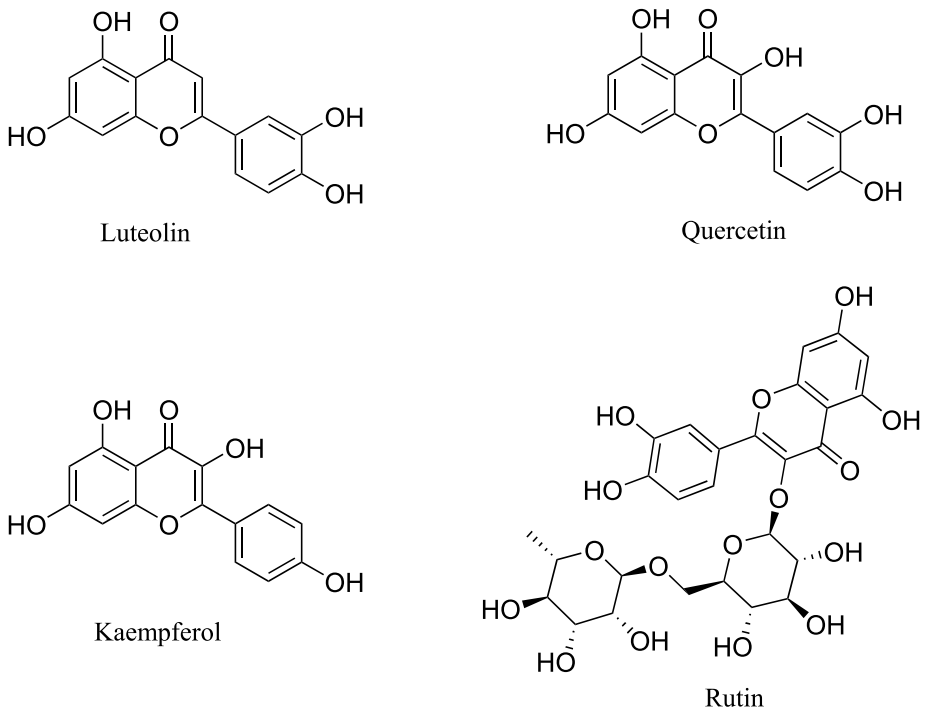

Fig. 2. Chemical structures of flavonoids.

claudin-1. In addition, kaempferol reduced levels of IL-1β, IL-6, and TNF-α, and down-regulated the transcription of a range of inflammatory signaling molecules while increasing the expression of IL-10 mRNA. Regulating the gut microbiota is an attractive alternative treatment strategy for UC.[30] Qu et al.[31] found that kaempferol increased the diversity and richness of intestinal flora in UC mice, and increased the relative proportion of Firmicutes and Bacteroides. It also decreased the relative abundance of Proteobacteria and pathogenic bacteria in its category, and increased the abundance of probiotics such as Ruminococcaceae and Prevotellaceae.

The above studies showed that the flavonoid components of *Prunella vulgaris* display a variety of therapeutic mechanisms for UC, including inhibiting intestinal inflammation, anti-oxidative stress, changing the diversity and composition of intestinal microbiota, and protecting the intestinal barrier.

3.2. Triterpenoids

The triterpenoids isolated from *Prunella vulgaris* are mainly ursolic acid (UA) and oleanolic acid (OA), which have been widely reported to play significant antioxidant and anti-inflammatory effects in the prevention of UC. The structures of triterpenoids[32] are provided in Fig. 3.

3.2.1. Ursolic acid

Zhuang et al.[33] found that UA significantly inhibited the increase of disease activity index (DAI) score, colon length shortening and histological injury in UC mice, and reversed the increase of serum amyloid A (SAA) level and colon IL-6 level induced by DSS. Further studies showed that UA against mice colitis induced by DSS by blocking IL-6/STAT3 signaling pathway. Sheng et al.[34] also observed that early prevention of UA could effectively reduce serum and colon IL-6 levels, and down-regulate the three classic inflammatory pathways (MAPK, IL-6/STAT3 and PI3K signaling pathway) in DSS-induced UC mice. Liu et al.[35] found that when DSS induced colon injury, the levels of interleukin-1β (IL-1β) and TNF-α were increased, the content of malondialdehyde (MDA) was increased, and the activity of superoxide dismutase (SOD) in colon homogenate was decreased, while UA treatment significantly alleviated these changes. It also reduced the level of NF-κB p65 in colon tissue. Additionally, in the SDS-induced drosophile UC model,[36] UA mitigated the accumulation of reactive oxygen species (ROS) and MDA, up-regulated the activities of total superoxide dismutase (T-SOD) and catalase (CAT), and down-regulated the JNK/JAK/STAT signaling pathway.

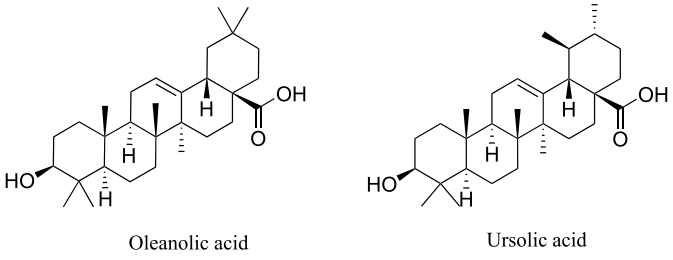

Fig. 3. Chemical structures of triterpenoids.

3.2.2. Oleanolic acid

Kang et al.[37] found that DSS induced mice to increase Th17 cell differentiation and inhibit Treg cell differentiation, while OA reversed this change, thereby inhibiting the expression of proinflammatory cytokines TNF-α, IL-1β and interleukin-17 (IL-17), and increasing the expression of interleukin-10 (IL-10). Gutierrez et al.[38] also found the similar mechanism. OA significantly reduced the serum levels of intestinal fatty acid binding protein (iFABP), an indicator of intestinal mucosal epithelial damage, and sCD14, a marker of monocyte activation, as well as the proinflammatory mediators in serum and colon tissue. In terms of oxidative stress, OA prevented the accumulation of lipid peroxidation and superoxide anions in intestinal tissues, while inducing the expression of ROS scavenger Sestrin-3. Studies have shown that kidney homogenates of mice that ingestion triterpenoids such as UA and OA had strong antioxidant effects on glucose-induced glutathione loss and MDA and oxidized glutathione production.[39] Additionally, Xie et al.[40] found that total triterpenoids (TTP) of *Prunella vulgaris* could inhibit the secretion of TNF-α and IL-6 in RAW264.7 cells, and significantly inhibited the expression of Janus kinase 2 (Jak2), signal transduction and activator of

transcription 3 (STAT3). It was further proved that triterpenoids of *Prunella vulgaris* had anti-inflammatory effects.

The above experiments showed that the triterpenoid components UA and OA in *Prunella vulgaris* can reduce intestinal damage, reduce the development of inflammation, and have preventive and therapeutic effects on UC by exerting their anti-inflammatory and antioxidant functions.

3.3. Organic acids

Rosmarinic acid (RA) and caffeic acid (CA) are the main organic acids in *Prunella vulgaris* which shows significant antioxidant effect. The structures of organic acids[41] are provided in Fig. 4.

3.3.1. Rosmarinic acid

Marinho et al.[42] found that RA-loaded nanovesicles reduced MPO activity and TNF-α production, and down-regulated the protein expression of inflammasome components. Formiga et al.[43] found that oral administration of p-C (para-cymene) and RA reduced MDA and MPO levels, restored glutathione (GSH) levels, enhanced SOD fluorescence intensity, reduced IL-1β and TNF-α, and maintained the basic level of IL-10. These results indicated that p-C and RA protected the intestinal barrier through their antioxidant and immunomodulatory effects. Mai[44] found that RA inhibited NF- κB from entering the nucleus by enhancing HO-1 level to regulate the polarization of macrophages towards M2, directly inhibited the migration of bone marrow micrometastasis (BMM) *in vitro* and enhanced its phagocytosis, which confirmed that RA improved the immunological mechanism by regulating the polarity, migration and phagocytosis of macrophages. In addition, there were studies[45] confirmed that RA inhibited dual activation of NF-κB and STAT3 to inhibit DSS induced UC in mice.

3.3.2. Caffeic acid

UC is associated with epithelial dysfunction and mucosal immune response. Xiang et al.[46] found that Caffeic acid (CA) exerted direct suppressive effects on the activation of bone marrow-derived macrophages (BMDMs) upon the exposure of TLRs agonists *in vitro*, suggesting that CA could attenuate UC through interfering with the activation of macrophages. Wan et al.[47] found that CA treatment significantly reduced the levels of proinflammatory cytokines and MDA, enhanced the total antioxidant capacity (T-AOC) and increased the levels of IL-10, superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and CAT in serum. Activation of the Nrf-2/HO-1 pathway has been shown to have antioxidant and anti-inflammatory properties and to prevent intestinal barrier damage by enhancing OCLN expression. By inhibiting the activation of NF-κB signaling pathway, CA could significantly inhibit the secretion of IL-6, TNF-α and IFN-γ, as well as colonic infiltration of $CD3^+$T cells, $CD177^+$ neutrophils and $F4/80^+$ macrophages.[48]

The above studies proved that organic acids in *Prunella vulgaris* had significant antioxidant, macrophage polarization regulation and inflammation inhibition activities in UC.

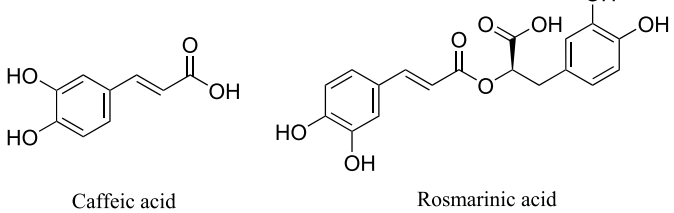

Fig. 4. Chemical structures of organic acids.

3.4. Sterols

The sterols of *Prunella vulgaris* mainly consist of β-sitosterol and stigmosterol, and β-sitosterol has been studied more. The structures of sterols[49,50] are provided in Fig. 5.

Feng et al.[51] found that β-sitosterol and stigmosterol significantly inhibited colon shortening, reduced fecal hemoglobin content, reduced the severity of distal colitis, and significantly inhibited the activation of NF-κB. Kim et al.[52] found that β-sitosterol inhibited the increased expression of HFD-induced proinflammatory cytokines and the activation of NF-κB in the colon. Additionally, β-sitosterol inhibited the binding of lipopolysaccharide (LPS) to Toll-like receptor 4 (TLR4) in the NF-κB pathway. Studies showed that β-sitosterol decreased the levels of TNF-α, IL-6 and IL-1β in the intestinal tissues of mice in a concentration-dependent manner, significantly increased the expression of antimicrobial peptides and decreased the survival rate of Lactobacillus Firmicutes bacteroides.[53] Lee et al.[49] also proved that β-sitosterol inhibited colon shortening, decreased the expression of proinflammatory cytokines (TNF-α, IL-1β and IL-6) and the cyclooxygenase (COX-2), and the activation of NF-κB, suggesting that β-sitosterol could alleviated UC by inhibiting the NF-κB pathway. The above studies proved that inhibition of NF-κB signaling pathway and regulation of intestinal flora are the main mechanisms by which β-sitosterol alleviates intestinal inflammation of UC.

4. Analysis of the effective parts of *Prunella vulgaris* in protecting against UC

Prunella vulgaris and its monomers have significant anti-oxidant and anti-inflammatory effects on UC. However, *Prunella vulgaris* is mainly used for medicine with its spike, and a large number of non-medicinal parts cannot be effectively utilized and are discarded. By comparing the distribution of anti-UC components and their anti-inflammatory and anti-oxidant activities in different parts of *Prunella vulgaris* as well as their extraction, more evidence is provided for the full utilization of *Prunella vulgaris* on UC.

4.1. Distribution of anti-UC components in different parts of Prunella vulgaris

Many studies have shown that *Prunella vulgaris* spike contains most active components, including triterpenes, flavonoids, phenolic acids, sterols, etc., indicating that the spike is the main effective part of *Prunella vulgaris* protecting against UC.[54] With further research, it was found that rosmarinic acid and caffeic acid are also abundant in stems and leaves.[55] *Prunella vulgaris* seeds also contain abundant ursolic acid and oleanolic acid.[56] There is little difference in triterpenoid and flavonoid components between the stem, leaf, and spike of *Prunella vulgaris*, indicating that seed, stem and leaf may also have potential effect for protecting against UC[57] (Table 1).

4.2. Activities of anti-UC components in different parts of Prunella vulgaris

There is a correlation between the anti-inflammatory and anti-oxidative activity of various parts and the content of phenolic acids and flavonoids in *Prunella vulgaris*. DPPH free radical scavenging results showed that there was no significant difference in the antioxidant activity between the spike and the stem and leaf, but that was significantly higher than the seed, indicating that the anti-inflammatory and anti-oxidative activity of the spike, stem, and leaf are equivalent.[55] Therefore, the stem and leaf of *Prunella vulgaris* have potential utilization value. With the improvement of the extraction methods of active ingredients from *Prunella vulgaris*, it is feasible to use whole *Prunella vulgaris* as a medicine.[60]

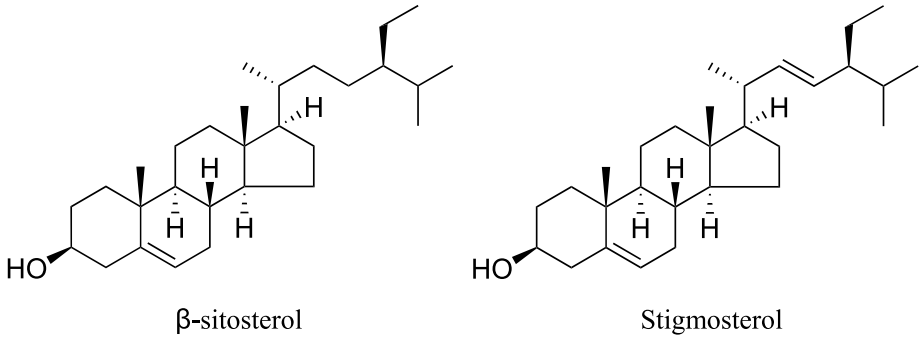

Fig. 5. Chemical structures of sterols.

Table 1
Active compounds and distribution of *Prunella vulgaris* in protecting against UC.

Group	Compounds	Plant Part	Ref.
Flavonoids	Luteolin	Spike, Stem, Leaf	57
	Quercetin	Spike, Stem, Leaf	57
	Rutin	Spike, Stem, Leaf	57
	Kaempferol	Spike, Stem, Leaf	57
Triterpenoids	Ursolic acid	Spike, Stem, Leaf, Seed	56,58
	Oleanolic acid	Spike, Stem, Leaf, Seed	56,58
Organic acids	Rosmarinic acid	Spike, Stem, Leaf	55
	Caffeic acid	Spike, Stem, Leaf	55
Sterols	β-Sitosterol	Spike	59
	Stigmosterol	Spike	59

4.3. Extraction methods of anti-UC components of Prunella vulgaris

Experiments have shown that there are significant differences in the content of flavonoids, triterpenes, and organic acids in different solvent extracts of *Prunella vulgaris*, and the effects of different solvent extracts from *Prunella vulgaris* also vary.[61] The flavonoids in *Prunella vulgaris* are mainly extracted with ethanol, and ethanol extracts of different concentrations can show significant anti-oxidant effects, among which 70 % ethanol extract of *Prunella vulgaris* have relatively high antioxidant activity.[62–66] Ethyl acetate can also be used for the extraction of flavonoids.[60] The triterpenoid components extracted with high concentration methanol mainly exert anti-oxidant stress and anti-inflammatory effects.[67–70] Organic acids extracted by water, ethanol or methanol have significant anti-inflammatory effects[71,72] (Table 2).

Table 2
Extraction methods and activities of anti-UC components in *Prunella vulgaris*.

Group	Plant Part	Solvent	Activity	Ref.
Flavonoids	Spike	50 % Ethanol	Anti-oxidation	62
	Spike	65 % Ethanol	Anti-oxidation	63,64
	Spike,	70 % Ethanol	Anti-oxidation	65
	Spike	20 % Ethanol	Anti-oxidation	66
	Whole plant	Ethyl acetate	Anti-oxidation	67
Triterpenoids	Seed	80 % Methanol	Anti-inflammation	56
	Spike	70 % Methanol	Anti-inflammation	68
	Spike	Methanol	Anti-oxidative stress	69
Triterpenoids&Organic acids	Aerial part	80 % Methanol	Anti-inflammation	70
Organic acids	Stem, Leaf	Water	Anti-inflammation	71
	Fruits	Methanol	Anti-inflammation	72
	Spike	70 % Ethanol	Anti-oxidation	73

4.4. Colon targeting study of Prunella vulgaris

Prunella vulgaris is a kind of traditional Chinese medicine that can be used as both medicine and food. However, some components have the disadvantages of poor absorption and low bioavailability. How to improve the oral bioavailability and enhance the efficacy of *Prunella vulgaris* and its monomers plays an important role in the development and utilization of *Prunella vulgaris* in UC. In recent years, much progress has been made in the research of new dosage forms and targeted drug delivery. The oral colon-specific drug delivery system (OCDDS) is a drug delivery system that, after oral administration, does not release drugs in the stomach, duodenum, jejunum, and front end of the ileum, but releases drugs after being transported to the ileocecal region, exerting local and systemic therapeutic effects. In recent years, progress has been made in the study of colon specific release through improved preparation processes. For example, the effective part of *Prunella vulgaris* colon targeting tablet has a high distribution of rosmarinic acid in rat colon tissue, which has the release characteristics of colon targeting drug delivery systems.[74] The preparation process of pH dependent time-delay colon localization pellets achieves colon localization effects *in vitro*.[75,76] ROS responsive nanoparticles (NPs) can target the delivery of luteolin, which is beneficial for ROS clearance and selective accumulation of luteolin in the colon.[77] Quercetin supported microcapsules enhanced anti-inflammatory and antioxidant effects and chitosan nanoparticle delivery system enhanced quercetin's therapeutic value.[78,79] Therefore, in-depth research on the colon localization of *Prunella vulgaris* and its monomers is expected to make it an effective therapeutic drug for UC.

5. Conclusion and prospects

According to current studies, triterpenoids, flavonoids, organic acids and sterols are the main active components of *Prunella vulgaris* against UC, of which flavonoids have been studied more, showing multiple mechanisms of action, involving anti-inflammatory, antioxidant stress, flora regulation and protection of intestinal barrier. The research of triterpenoids is mainly focused on its anti-inflammatory and antioxidant effects and its mechanism is mainly about the STAT signal pathway, and its other mechanisms of action on UC awaits further study. The research characteristics of organic acids lie in the effects of rosmarinic acid and caffeic acid on the polarization of macrophages to M2 type, and inhibition of their infiltration and function. The main mechanism of sterols is their inhibitory effect on the NF-κB signaling pathway (Fig. 6). By analyzing the anti-UC components and activities of different parts of *Prunella vulgaris*, it was found that in addition to spike, the stem and leaf of P*runella vulgaris* may also become effective anti-UC parts. With the in-

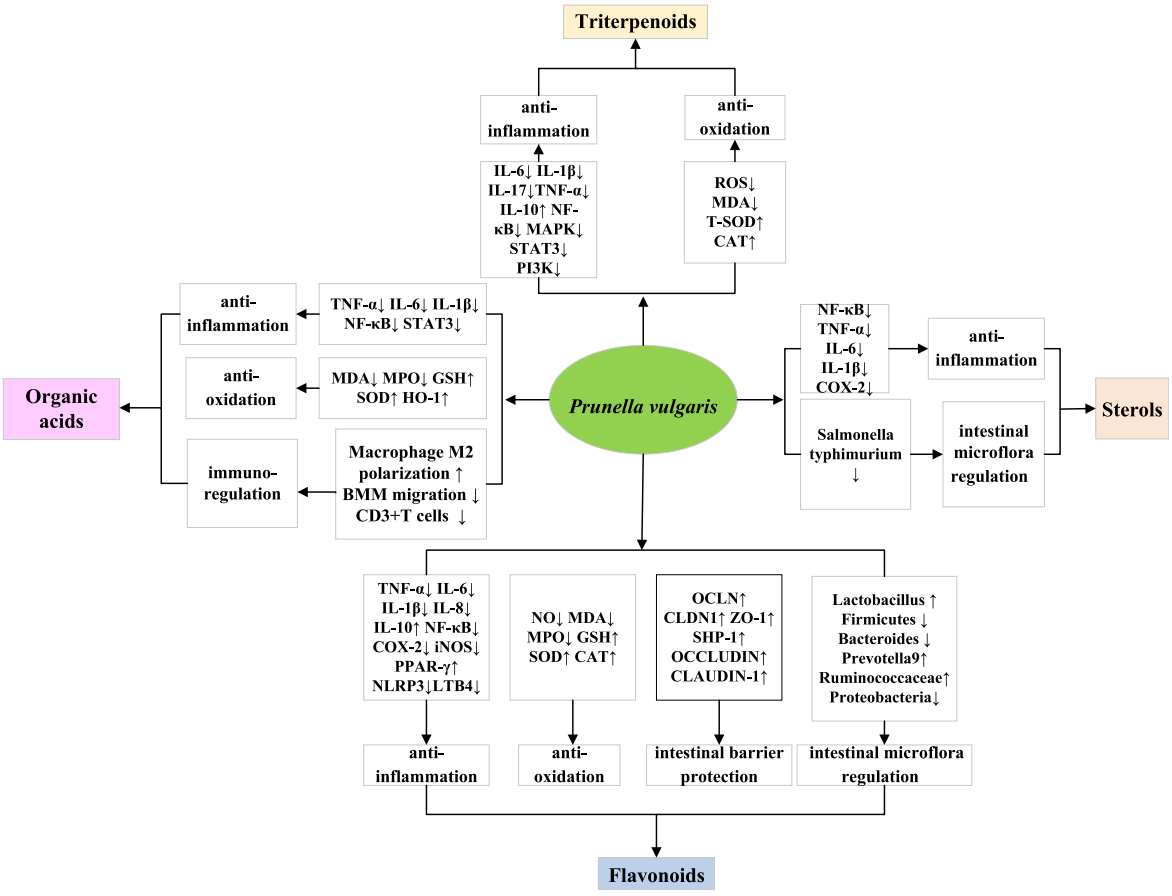

Fig. 6. Pharmacological effects and mechanisms of *Prunella vulgaris* in protecting against UC.

depth research on the targeted release of *Prunella vulgaris* and its monomers in the colon, the development and utilization of *Prunella vulgaris* in UC shows broad prospects.

Additionally, recent studies have shown that vascular endothelial growth factor A (VEGFA) was one of the key targets of the treatment of UC. It was found that VEGFA is overexpressed in colitis mice and inflammatory bowel disease patients,[80] and inhibition of VEGF may lead to ulceration and perforation of intestinal mucosa, so it is speculated that *Prunella vulgaris* and its monomers may prevent or alleviate UC by regulating VEGFA.[81,82] PI3K/AKT signaling pathway is the key pathway for the prevention of UC. The downstream target of PI3K is protein kinase B (AKT), and NF-κB is one of the important downstream transcription factors of AKT. Activated AKT can activate IκB, resulting in the shedding of IκB from NF-κB and its ubiquitination. The activated NF-κB enters the nucleus, activates the target gene to release inflammatory mediators, and induces inflammatory response.[83] Therefore, inhibition of PI3K/Akt pathway can indirectly inhibit the NK-κB pathway, thereby reducing the inflammatory response of UC. Studies have shown that inhibition of the activation of PI3K/Akt pathway can reduce VEGFA gene expression to alleviate UC in mice.[84] Therefore, PI3K/Akt pathway may be a potential mechanism of *Prunella vulgaris* and its monomers in protecting against UC, providing new research ideas for future studies of *Prunella vulgaris* against UC.

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CRediT authorship contribution statement

Jinyin Fu: Writing – original draft. **Yue Yuan:** Visualization. **Xiaojia Li:** Supervision. **Peng Lin:** Methodology. **Shuibin Wang:** Funding acquisition. **Mingzhu Xiao:** Writing – review & editing.

Declaration of Competing Interest

These authors have no conflicts of interest to declare.

Acknowledgments

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