Available online at www.sciencedirect.com
ScienceDirect
Chinese Journal of Natural Medicines 2019, **17**(2): 0081–0102
Chinese Journal of Natural Medicines

Progress in active compounds effective on ulcerative colitis from Chinese medicines

CAO Si-Yu [1Δ], YE Sheng-Jie [1Δ], WANG Wei-Wei [1, 2], WANG Bing [1, 2], ZHANG Tong [1, 2], PU Yi-Qiong [2*]

[1] *School of Pharmacy, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China;*
[2] *Experiment Center for Teaching and Learning, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China*

Available online 20 Feb., 2019

[ABSTRACT] Ulcerative colitis (UC), a chronic inflammatory disease affecting the colon, has a rising incidence worldwide. The known pathogenesis is multifactorial and involves genetic predisposition, epithelial barrier defects, dysregulated immune responses, and environmental factors. Nowadays, the drugs for UC include 5-aminosalicylic acid, steroids, and immunosuppressants. Long-term use of these drugs, however, may cause several side effects, such as hepatic and renal toxicity, drug resistance and allergic reactions. Moreover, the use of traditional Chinese medicine (TCM) in the treatment of UC shows significantly positive effects, low recurrence rate, few side effects and other obvious advantages. This paper summarizes several kinds of active compounds used in the experimental research of anti-UC effects extracted from TCM, mainly including flavonoids, acids, terpenoids, phenols, alkaloids, quinones, and bile acids from some animal medicines. It is found that the anti-UC activities are mainly focused on targeting inflammation or oxidative stress, which is associated with increasing the levels of anti-inflammatory cytokine (IL-4, IL-10, SOD), suppressing the levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8, IL-23, NF-κB, NO), reducing the activity of MPO, MDA, IFN-γ, and iNOS. This review may offer valuable reference for UC-related studies on the compounds from natural medicines.

[KEY WORDS] Ulcerative colitis; Chinese medicine; Flavonoids; Terpenoids; Alkaloids

[CLC Number] R965 **[Document code]** A **[Article ID]** 2095-6975(2019)02-0081-22

Introduction

Ulcerative colitis (UC), a chronic non-specific inflammatory disease of the colon and rectum, is confined to the colorectal mucosa and submucosal layer. Lesions, mostly located in the sigmoid colon and rectum, can extend to the descending colon, and even the entire colon. Additionally, UC is a long-term recurrent disease, with clinical manifestations that include diarrhea, purulent stools, and stomachaches. Since the severity of UC is different, it has a chronic course of repeated episodes. Moreover, UC has a great probability of being carcinogenic.

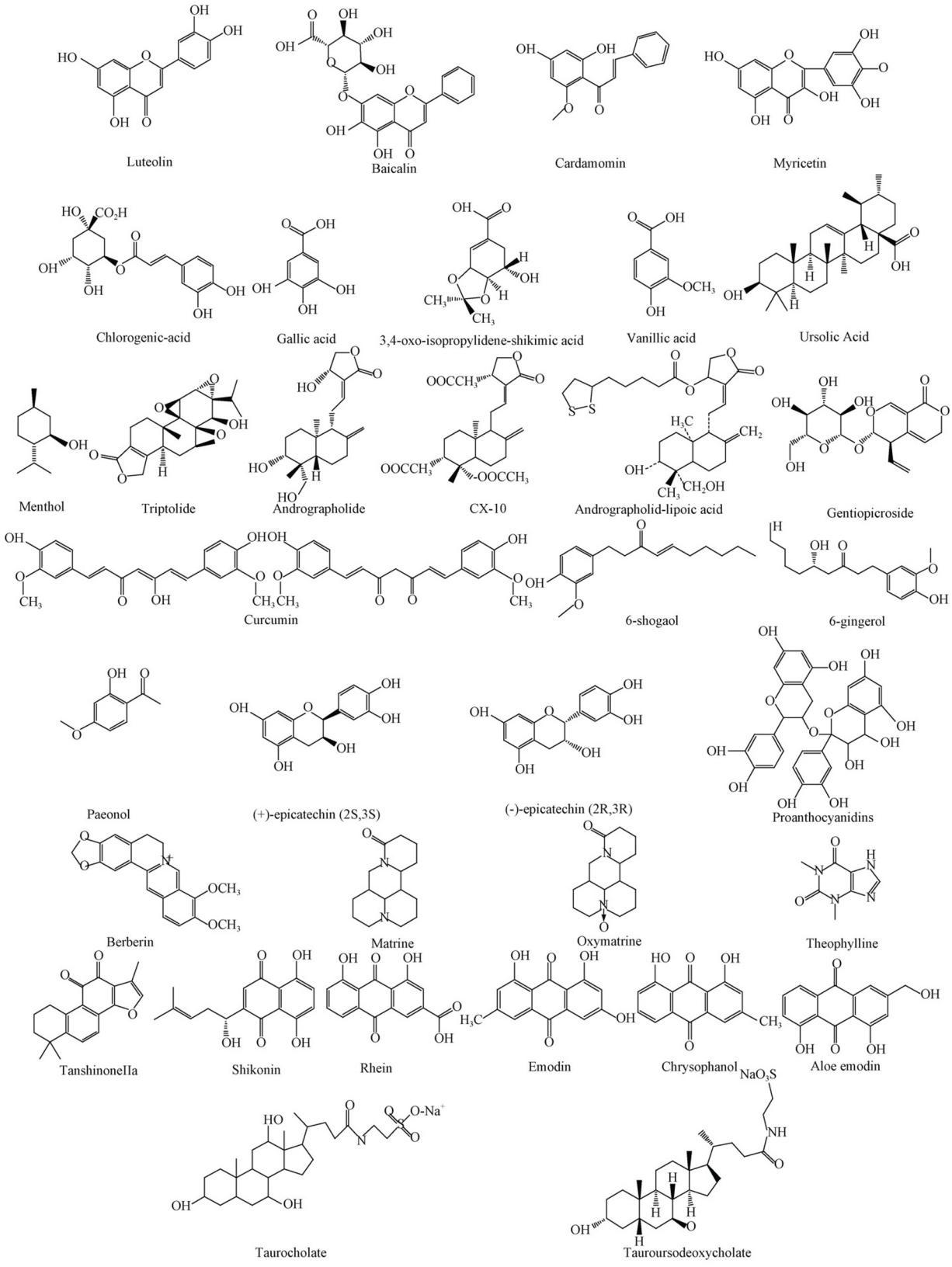
From the updated studies, the current drugs commonly used to treat UC include aminosalicylates, immunomodulators, steroids and some biologics. However, all of them can easily lead to significant loss of patient compliance, and potential toxic or side effects [1-2]. Many researchers are now turning to natural Chinese medicine for seeking effective compounds that can be used against UC.

Traditional Chinese medicine (TCM) has a long history of treating UC. Treatment using TCM can help relieve abdominal pain and inflammation. Moreover, some active compounds extracted from TCM can potentially interact with other natural drugs or even Western medicines [3]. In recent years, the efficacy of TCM in treating inflammatory bowel disease (IBD) has been extensively characterized in preclinical and clinical studies and widely reported [4]. This review summarizes some types of active compounds for treating UC that are extracted from TCM, mainly including flavonoids, acids, terpenoids, phenols, alkaloids, quinones, and bile acids

[Received on] 10-Sep.-2018
[Research Funding] The work was supported by National Natural Science Foundation of China (No. 81303233), Shanghai Committee of Science and Technology (No. 18401931400), and Budget Program of Shanghai University of Traditional Chinese Medicine (No. 2016YSN22), and College Student Innovation Program Project of Shanghai University of Traditional Chinese Medicine (SHUTCM).
[*Corresponding author] Tel: 86-21-51323068, E-mail: puyiq@163.com
[Δ] These authors contribute to this work equally.
These authors have no conflict of interest to declare.

from some animal medicines, which have been reported to have potential in alleviating UC via direct or indirect action with bacteria, cytokines, channels, or migration of enterocytes. The current knowledge about the anti-UC activity of natural compounds extracted from TCM in this review has covered the studies published since 2009.

The chemical structures of the major compounds effective on UC extracted from Chinese medicines are shown in Fig. 1.



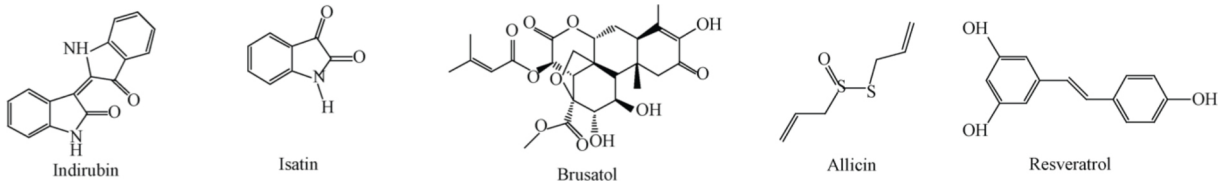


Fig. 1 Chemical structures of the major compounds effective on UC extracted from traditional Chinese medicines

Flavonoids

Luteolin

Luteolin, an active compound in leaves, stems and branches of *Reseda odorata* L. flowers of *Lonicera japonica* Thunb., and other plants such as *Capsicum annuum* L., *Ghrysanthemum indicum* L. and *Perilla frutescem* (L.) Britt., has a variety of pharmacological activities, such as anti-inflammatory, anti-allergy, urate, anti-tumor, antibacterial, and antiviral. Luteolin acts as an anti-inflammatory agent against colon cancer by effectively suppressing inducible nitric oxide synthase (iNOS) and COX-2 expression levels in azoxymethane (AOM, a derivative of DSS)-colitis mice [5]. Moreover, luteolin inhibits DSS-induced NF-κB-dependent enterocyte COX-2 expression. *In vitro* studies have shown that luteolin blocked TNF-α induced COX-2 gene expression and Prostaglandins E2 (PGE_2) enzyme secretion in HT29 cells, and sensitizes HT29 cells to TNF-α induced caspase-3 processing/activity and DNA fragmentation which is associated with the blockade of TNF-α induced NF-κB transcriptional activity and simultaneously decreases expression of downstream target genes C-IAP1 and C-IAP2. To sum up, the inhibitory effect of luteolin on NF-κB in the lamina propria mononuclear cells (LPMNC) by the strong impact of abundantly translocated luminal antigens by enhancing injury, which leads to the enhancement of NF-κB activation (EGFP expression) in mononuclear cells from the colonic lamina propria, while cecal EGFP expression was attenuated [6].

Baicalin

Baicalin is abundant in roots and seeds of *Scutellaria baicalensis* Georgi. It displayed significant effects on reducing the severity of DSS-induced UC in mice and showed significantly suppressed levels of IL-33 and NF-κB p65, while IκBα levels were increased. Baicalin treatment effectively alleviated DSS-induced chronic UC, and the protective mechanisms may involve the inhibition of IL-33 expression and subsequent NF-κB activation [7]. Moreover, baicalin regulates immune balance and relieves the UC-induced inflammation reaction by promoting the proliferation of $CD4^+$ and $CD29^+$ cells and modulates immunosuppressive pathways [8]. Additionally, baicalin simultaneously down-regulates the expression of migration inhibitory factor (Mφ), quantity of Mφs, and levels of Mφ-related cytokines, including macrophage chemotactic factor-1 (MCP-1, CCL2) and macrophage inflammatory protein-3α (MIP-3α) in UC rats [9].

Cardamonin

Cardamonin is a naturally occurring chalcone found in high concentration in conventional Chinese medicines, such as roots of *Alpinia katsumadai* Hayata [10]. It is reported to have protective effects such as anti-inflammation [11] and inhibition of NO release and iNOS expression [12]. *In vivo*, cardamonin reduced the levels of myeloperoxidase (MPO), iNOS, NF-κB, TNF-α, and MDA. Immunohistochemistry revealed the down-regulation of COX-2 and caspase-3 levels [13]. *In vitro* study has showed that the inhibitory effect of cardamonin on LPS-induced iNOS induction is due to a direct effect on transcription factor binding to DNA.

Myricetin

Among the known flavonoids, myricetin (3, 3', 4', 5, 5', 7-hexahydroxyflavone) is one of the major flavonoids found in several foods, including onions (*Allium cepa* L.), grapes (*Vitis vinifera* L.) and red wine. Myricetin has several beneficial effects, including anti-inflammatory [14], antioxidant [15], analgesic and anticarcinogenic effects [16-17]. Myricetin decreased the production of NO, MPO and MDA, while increasing the activity of SOD and GSH-Px. Furthermore, the levels of the cytokines IL-1β and IL-6 were significantly decreased. The anti-colitis effects of myricetin may be attributed to its anti-inflammatory and antioxidant actions [18].

Acids

Chlorogenic acid

Chlorogenic acid (CGA) is a phenolic acid produced by caffeic acid and gallic acid. CGA is extracted from the dry buds or open flowers of *Lonicera japora'ca* Thunb., and is also commonly found in other Chinese herbs, such as *Lonicera japonica* Thunb., *Crataegus pinnatifida* Bge., and *Eucommia almodies* Oliv..

Some study showed that CGA reduced MPO, TNF-α levels and scavenge intracellular ROS by inhibiting H_2O_2-induced IL-8 production in Caco-2 cells in the colon tissue, and significantly suppressed nuclear factor NF-κB transcriptional activity, nuclear translocation of the p65 subunit, and phosphorylation of IκB kinase (IKK), lead to the upstream of IKK, and the suppression of protein kinase D (PKD) [19-21]. CGA attenuated the weight loss, increased DAI, and suppressed the serious cellular injury and inflammatory intestinal diseases via suppressing the secretions of IFN-γ, TNF-α, and IL-6 and colonic infiltration of $F4/80^+$ macrophages, $CD177^+$ neutrophils, and $CD3^+$ T-cells by inhibiting the active NF-κB signaling pathway. Moreover, CGA can relieve intestinal injury, inhibit the permeability of intestinal mucosa and alleviate the reduction in fecal microbiota, such as *Firmicutes* and *Bacteroidetes* in

DSS-induced mice, while increase the proportion of the-mucin-degrading bacterium *Akkermansia*; however, CGA does not exert strong antimicrobial effects [19]. Furthermore, *in vitro*, CGA reduces the level of reactive oxygen species in IPEC-J2 cells. And simultaneous application of CGA and *Lactobacillus plantarum* 2142 supernatant leads to the protection against lipopolysaccharide (LPS)-induced inflammation and oxidative stress [22].

Gallic acid

Gallic acid (GA), which exists widely in plants, such as *Rheum palmatum* L., *Eucalyptus robusta* Smith, and *Cornus officinalis* Sieb. et Zucc., has biological activities, such as anti-oxidation, anti-bacteria, anti-viral, and anti-tumor.

GA relieves DSS-induced ulcerative colitis via reducting the neutrophilic infiltration in the colon accompanied by a decreased expression of $CD68^+$ and inhibiting the activation of p-STAT, preventing the decrease of IκBα expression resulted in decreasing the expression levels of iNOS and COX-2, and *in vitro* inhibiting the nuclear translocation of p65-NF-κB in RAW264.7 macrophages in colonic mucosa [23]. A study showed that mango is rich in polyphenols especially high abundant in GA. The mango extract (only total polyphenolics) treatment resulted in decreasing the Ki-67 labeling index in the central and basal regions, and at the mRNA and protein level, it attenuated the expression of TNF-α, IL-1β, and iNOS. Moreover, the expression levels of PI3K, AKT, and mammalian target of rapamycin (mTOR) were reduced, while miR-126 was upregulated *in vivo*. Moreover, mango extract suppressed the protein expression levels of p-NF-κB, NF-κB, 3-kinase (PI3K, p85β), HIF-1α, p70 ribosomal protein S6 kinase (p70S6K1), and RPS6 protein in LPS-treated CCD-18Co cells *in vitro* [24]. Another study showed that Mango extract suppressed the ratio of phosphorylated/total protein expression of the insulin-like growth factor-1 receptor (IGF)-1R-AKT/mTOR axis and down-regulates the mRNA expression of gene *Insr, Igf1* and *pik3cv* [25].

3, 4-Oxo-isopropylidene-shikimic acid

3, 4-Oxo-isopropylidene-shikimic acid (ISA) is a derivative of shikimic acid extracted from Illicium verum Hook. Some study has illustrated that ISA exerts the anti-inflammatory effect on colitis induced by TNBS in rats. It is reported that the protective effect of ISA is probably associated with the reducing granulocyte infiltration, the depressing MDA, NO levels and iNOS activity, the enhancing GSH level as well as GSH-Px and SOD activities in the colon tissues of experimental colitis [26]. These protective effects were associated with a reduced level of NF-κB p65 subunit in the nucleus and changes in the expression of IκBα. The anti-inflammatory activity of ISA may be mediated, at least in part, by inhibition of the expressions of certain pro-inflammatory mediators which are regulated by the oxidative stress sensitive NF-κB signaling pathway [27].

Vanillic acid

As a benzoic acid derivative, vanillic acid (VA) is used as a flavoring agent. It is an oxidized form of vanillin produced during the conversion of vanillin to ferulic acid. Moreover, the highest quantity of VA in plants is found in the roots of *Angelica sinensis* (Oliv.) Diels.

VA has been proved that has the anti-colitis, anti-mutagenic, anti-angiogenetic, anti-sickling, and anti-analgesic effects. It exhibited the reduction of weight loss and colon shortening, and exerted anti-inflammatory effects via reducing IL-6 level and COX-2 levels, and significantly suppressing the activation of transcription NF-κB p65 in DSS-treated colon tissues [28].

Ursolic acid

Ursolic acid (UA), which was isolated from an ethanol extract of *Cornus officinalis* Sieb.et Zucc. seed, potently inhibited nuclear factor κ light-chain enhancer of activated B cells activation in LPS-stimulated peritoneal macrophages.

UA inhibited phosphorylation of IRAK1, TAK1, IKKβ, and IκBα as well as activation of NF-κB and MAPKs in LPS-stimulated macrophages. It suppressed LPS-stimulated IL-1β, IL-6, TNF-α, COX-2, and iNOS expression as well as PGE2 and NO levels. UA not only inhibited the Alexa Fluor 488conjugated LPS-mediated shift of macrophages but also reduced the intensity of fluorescent LPS bound to the macrophages transiently transfected with or without MyD88 siRNA. Oral administration of UA has significantly inhibited TNBS-induced colon shortening, MPO activity, COX-2 and iNOS expression as well as NF-κB activation in mice. It may ameliorate colitis by regulating NF-κB and MAPK signaling pathways *via* the inhibition of LPS binding to TLR4 on immune cells [29].

Terpenoids

Menthol

Menthol is a monoterpene-based partial agonist of TRPV3 channel, and shows lower (−65%) activation of the TRPV3 channel compared with that by camphor. Menthol can be extracted from some Chinese medicinal plants, such as *Mentha haplocalyx Briq, Lysimachia christinae* Hance, and *Perilla frutescens* (L.) Britt.

Menthol is an aromatic compound with high anti-inflammatory activity. It is reported to has potent anti-inflammatory and antioxidant activities *in vitro* and *in vivo* [30-31]. In a study to investigate the effectiveness of menthol on acetic acid-induced acute colitis in rats, menthol displayed similar effectiveness with dexamethasone; significantly reduced body weight loss, macroscopic damage score, ulcer area, colon weight, and colon length; and improved hematocrit in rats with colitis. Moreover, histopathological examination confirmed the anti-colitis effects of menthol. Menthol also significantly reduced the colonic levels of TNF-α, IL-1β, IL-6, and MPO in the inflamed colons [32].

Triptolide

Triptolide, an epoxy two terpene compound extracted from the root, leaf, flower, and fruit of *Tripterygium wilfordii* Hook. f, has anti-inflammatory and immunosuppressive ef-

fects [33]. Triptolide inhibits the migration, proliferation, and colony formation of colon cancer cells *in vitro*, decreases the incidence of colon cancer formation in mice by reducing the secretion of IL-6, IL-1β [34-35], the levels of JAK1, IL-6R, and phosphorylated STAT3; triptolide prohibited Rac1 protein (Rho GTP-bound) activity and blocked cyclin D1 and CDK4 expression, thereby leading to G_1 arrest [36]. Furthermore, triptolide decreased extracellular matrix (ECM) deposition and collagen production in the colon, and inhibited the expression of collagen Iα1 transcripts and collagen I protein in the isolated subepithelial myofibroblasts of rats with colonic fibrosis. Besides, triptolide was indicated that can inhibit the expression of IL-8 and monocyte chemotactic protein (MCP)-1, and matrix metallo proteinases-3 (MMP-3) in period study [33].

Andrographolide

Andrographolide exists in the whole plant or leaf of the *Andrographis paniculata* (Burm.f.) Nees., which is a natural antibiotic drug that dispels heat, detoxifies, diminishes inflammation, and relieves pain. The active compound has a special curative effect for bacterial and viral upper respiratory tract infections and dysentery.

Clinical trials show that andrographolide decreased the levels of proinflammatory factors IL-1β, TNF-α, IL-6 and IL-17A in patients' serum and in the colon tissues, and the percentages of Th17 cells in $CD4^+$ cells, and suppressed the levels of IL-17A, IL-23, ROR-γt (key transcription factor of Th17 cells) and STAT3 in the colon tissues [37-38]. Moreover, an andrographolide derivative AL-1 (the andrographlide- lipoic acid conjugate), presented a significant reduction in DAI, which inhibits inflammatory response by decreasing the level of inflammatory cytokines and MPO activity. AL-1 attenuates the expression levels of p-IκBα, p-p65 proteins, cytochrome c oxidase subunit (COX)-2 and NF-κB, and increased the expression of peroxisome proliferator-activated receptor (PPAR)-γ, thereby alleviating colon injury [39]. Another andrographolide derivative CX-10 (a hemi chemical synthesized from andrographolide) reduced the expression of IL-6 and TNF-α and the activity of MPO in colonic tissues, and the expression of NF-κB, p65 and p-IκBα proteins, while increasing the expression of IκBα and regulated down the phosphorylation of p38 mitogen-activated protein kinase (MAPK), ERK and JNK [40].

Gentiopicroside (Gent)

Gentiopicroside (Gent), as a secoiridoid compound isolated from *Gentiana lutea* L., has been the subject of numerous reports on the choleretic, anti-hepatotoxic, adaptogenic, and anti-inflammatory properties.

MPO activity in the DSS-induced colitic colon was effectively suppressed by oral administration of Gent. Furthermore, Gent treatment significantly reduced the overproduction of pro-inflammatory cytokines and chemokines. The oral administration of Gent significantly reduced the mRNA expression of TNF-α, IL-1β, IL-6, and down-regulated the overexpression of COX-2 and iNOS proteins. Therefore, it was concluded that the protective effect of Gent in experimental colitis is related to the suppression of inflammatory factors activation [41].

Phenols

Curcumin

Turmeric belongs to the family Zingiberaceae and has been used as medicine in India and China for thousands of years [42]. Curcumin, a natural hydrophobic polyphenol derived from the rhizomes of turmeric (*Curcuma longa* L.) [43], is known for its multiple pharmacologic activities [44] in NF-κB-mediated inflammation, oxidative stress-mediated inflammation, and ER stress-mediated apoptosis and inflammation [45]. Curcumin has recently received increasing attention for UC therapy because it efficiently down-regulates inflammatory cytokines, scavenges free radicals, and promotes mucosal healing [46-48]. *In vivo*, curcumin can be a therapeutic agent for blocking NF-κB activation [49], and alleviate visceral hyperalgesia and reverse increasing expression of TRPV1 and p-TRPV1 in rats modeled by DSS. *In vitro*, in the HEK293 cell line stably expressing TRPV1, curcumin inhibited phorbol myristate acetate-induced upregulation of membrane TRPV1. By downregulating the colonic expression and phosphorylation of TRPV1 on the afferent fibers projected from the peptidergic and non-peptidergic nociceptive neurons of the dorsal root ganglion, oral administration of curcumin alleviated visceral hyperalgesia in DSS-induced colitis rats [50]. Moreover, for the therapeutic effect of curcumin on DSS- induced ulcerative colitis, the expression levels of TNF-α and MPO in the colon tissue was determined with ELISA, and colon p-p38MAPK and p38MAPK mRNA expression levels were evaluated by immunohistochemistry and RT-PCR. Curcumin displayed a therapeutic effect, which was probably enacted by inhibiting the p38MAPK signaling pathway, thereby reducing the release of TNF-α [51]. Furthermore, curcumin plus soy oligosaccharide was reported to decrease TNF-α and IL-8 expression and reduce colonic mucosa inflammation and tissue damage [52].

Gingerols

Ginger (*Zingiber officinale* Rosc.) has been used for centuries for the treatment of various illnesses that involve inflammation and which are caused by oxidative stress. It is well acknowledged that gingerols consist of 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol, which share analogous structural features. It has reported that the three gingerols (6-gingerol, 8-gingerol, and 10-gingerol) have a strong and relatively equal efficacy in the treatment of colitis [53].

6-gingerol, a component of gingerols extracted from ginger, has been reported to improve ulcerative colitis. It has been reported that 6-gingerol can suppress the induction of UC in mice, *via* antioxidant and anti-inflammatory activities [54]. *In vitro*, 6-gingerol can attenuate colitic symptoms evoked by dextran sulfate sodium, significantly elevated superoxide dismutase activity, decrease malondialdehyde levels and mye-

loperoxidase activity in the colon tissue, and markedly reduce the content of TNF-α and IL-1β in the serum [53].

6-shogaol, which can be extracted from Zingiber officinale Rose., has proved to have antioxidative, anti-inflammatory, and anticarcinogenic properties [55-57]. It is recently demonstrated that a specific population of ginger-derived nanoparticles (NPs) may effectively reduce colitis [58-60]. In another study, the NPs exhibited very good biocompatibility both *in vitro* and *in vivo*. They underwent efficient receptor-mediated uptake by colon-26 cells and activated Raw 264.7 macrophage cells *in vitro*, targeted colitis tissue, alleviated colitis symptoms, and accelerated colitis wound repair by regulating the expression levels of pro-inflammatory (TNF-α, IL-6, IL-1β, and iNOS) and anti- inflammatory (Nrf-2 and HO-1) factors in *vivo* [61].

Paeonol

Paeonol, 20-hydroxy-40methoxyacetophenone, is the main active component isolated from Cynanchum paniculatum and Aaeoina suffruticosa [62-63]. Paeonol has shown significant anti-inflammation [64-66], anti-tumor [67-68], and anti-oxidant properties [69].

Paeonol was reported to reduce the activity of myeloperoxidase in the colon and inhibit the proliferation of iNOS, the expression of iNOS-mRNA induced by TNF-α+IFN-γ, and the activation of NF-κB and STAT1 signalling pathway in CW-2 and Jurkat cell lines, which was possibly contributed to its anti-inflammation and anti-UC properties. In addition, in the DSS-induced UC model of mice treated with paeonol, the anti-inflammatory and anti-oxidative activities of paeonol and its metabolite were related to the blocking of the MAPK/ERK/p38 signaling pathway [70]. Moreover, paeonol can reduce the levels of IL-17 and IL-6 in rat serum and increased the levels of TGF-β1 and inhibit colitis inflammation by regulating the balance of Treg/Th17 via downregulating Th17 cells and upregulating Treg cells [71].

Epicatechin

Epicatechin can be extracted from *Acacia catechu* (L. f.) Willd. and *Hippophae rhamnoides* L. Ficus carica fruit, a source of bioactive functional ingredients, have been traditionally used for its medicinal benefits as they improve the digestive system, treating constipation and used as a natural laxative. A recent study was investigated the ameliorative effect of Ficus carica L. aqueous extract (FCAE) on delayed gastric emptying and ulcerative colitis-improved motility disturbances in DSS-induced acute colitis in rats [72]. As a compound extracted from Ficus carica fruit, epicatechin can ameliorate ulcerative colitis as well. In C57BL/6J mice model with DSS-induced UC, epicatechin can decrease the disease activity index and colon macroscopic damage index scores, reduce body weight loss, and significantly relieve colon contracture and crypt damage. Besides, TNF-α, IL-6, NO, MPO, and MDA were reduced, whereas antioxidant enzymes showed increased activity. Furthermore, the effects of inhibited NF-κB activation have been demonstrated *in vivo* and *in vitro*. It is inferred that the inhibitory effect on DSS-induced acute UC of epicatechin is mainly related to its antioxidant effects and the inhibition of inflammatory molecules *via* the NF-κB pathway [73].

Proanthocyanidin

Proanthocyanidin, is a kind of naturally occurring oligomers and polymers of flavan-3-ol monomer units widely available in fruits, vegetables, nuts, seeds, flowers, and bark of *Cynanchum paniculatum* (Bge.) Kitag. and many other plants [74].

Grape seed extract proanthocyanidins (GSPs) are naturally occurring polyphenol that possesses antioxidant and anti-lipid peroxidation activities. It is reported that GSPs exerted a protective effect on TNBS-induced recurrent colitis in rats by modifying the inflammatory response, inhibiting inflammatory cell infiltration and antioxidation damage, promoting damaged tissue repair to improve colonic oxidative stress, and inhibiting the activity of iNOS to reduce the production of NO [75]. As for therapeutic effects in TNBS-induced UC rats, GSPs was effective on either acute or recurrent colitis.

Alkaloids

Berberine

Berberine is an isoquinoline alkaloid and mainly originates from the roots and stems of *Berberis julianae C. K. Schneid*, which has the highest reported content of berberine at about 4.5%. As an antibacterial drug, the clinical effects of berberine are mainly for intestinal infections and dysentery. Moreover, berberine can attenuate pro-inflammatory cytokine-induced intestinal epithelial barrier dysfunction, preserve barrier function, and reduce and occlude the tight junction (TJ) protein zona occludens (ZO)-1, which prevents pro-inflammatory cytokine-disruption of barrier function in HT-29 cells and Caco-2 cells by modulating TJ proteins *in vitro*. Berberine increases the levels of superoxide dismutase and catalase in the colon and serum samples and reduces the levels of myeloperoxidase, reduces the macromolecule leak caused by cell layer exposure to cytomix and H_2O_2. In addition, berberine attenuates the T helper (Th)1/Th2/Th17 response and promotes Treg response in UC and leads to increased TNF-α, interleukin (IL)-23, and IL-6 mRNA expression levels. Furthermore, berberine may regulate transcription (STAT)3 to balance Th17 and Treg, reversed the up-regulation of IL-17 secretion from $CD4^+$cells of spleens and mesenteric lymph node cells (MLNs) [76-78]. Besides, compared with 5-ASA treatment alone, the combination of berberine and 5-ASA therapy more pronouncedly reversed the up-regulation of the mRNA level in colonic TNF-α, as well as nuclear NF-κB and Janus kinase (JAK)2 phosphorylation by DSS; and more significantly inhibited lymphocyte TNF-α secretion [79]. Moreover, combination of berberine and 5-ASA therapy has less serious toxic effects on the spleen [80].

Matrine and oxymatrine

Matrine and oxymatrine are extracted from the dried

roots, plants, and fruits of *Sophora flavescens* Ait. by using organic solvents, such as ethanol. Matrine can decrease the levels of superoxide dismutase (SOD) and malondialdehyde (MDA) in the colon mucosa cells, and has an inhibitory effect on lipopolysaccharide (LPS)-induced release of NO from macrophages. Matrine significantly decreases TNF-α, IL-1β, IL-4, and IL-10 levels. Additionally, matrine can heal ulcer cells and reduce the lesion areas in inflammatory cell infiltration, fibrosis, and edema [81]. Moreover, matrine can protect the colonic mucosa by reducing the overexpression of colonic mucosa proteins NOD2 and NF-κB p65 and decreasing IL-6 level [82]. Oxymatrine might attenuate UC by regulating the β2-adrenocepto (β2AR)-β-arrestin2-NF-κB and the delta opioid receptor (DOR)-β-arrestin1-Bcl-2 signal transduction pathway. The expression of NF-κB p65, DOR, β-arrestin1 and Bcl-2 protein and mRNA were significantly decreased while the expressions of β2AR and β-arrestin2 were significantly increased [83-84]. Oxymatrine ameliorated UC through pro-apoptotic, down-regulating the Th1 and Th17 cells differentiation *via* phosphoinositide 3-kinase (PI3K)/AKT pathway [85].

Theophylline

Theophylline (1, 3-dimethyl-2, 6-dioxypurine), which can be extracted from Viridis tea and Camellia crassicolumna [86], is a non-specific phosphodiesterase inhibitor. Theophylline showed anti-inflammatory activity both *in vitro* and *in vivo* [57, 87-88]. *In vivo*, studies showed that theophylline attenuated the response to allergen [89] and reduced bronchial mucosal eosinophils in patients with mild asthma [90]. Moreover, theophylline treatment also reduced myeloperoxidase (MPO) activity and tumor necrosis TNF-α, IL-1β and IL-6 concentrations in the inflamed colon [91].

Quinones

Tanshinone IIa

Tanshinone IIa, is obtained from the dry roots and rhizomes of *Salvia miltiorrhiza* Bge. and the root of *Salvia sclarea* L.. Clinical study showed that tanshinone IIa presented a therapeutic role in UC by reducing DAI, enhancing the macrophage phagocyte system and the function of natural killer (NK) cell's suppression of non-specific immunity killing effects while improving humoral immunity, and activating interferon cytokine production to increase T cell and NK cell activity. Besides, tanshinone IIA sulfonate injection can significantly reduce the level of CRP protein [51]. Moreover, tanshinone IIa improved intestinal permeability, decreases the neutrophil (PMN) infiltration and activation of intestinal mucosa by the decreased production of MPO, reactive oxygen species (ROS), and inflammatory cytokines and suppress neutrophil migration to inhibit the adhesion of PMN and endothelial cells in DSS-treated mice [92]. *In vitro*, tanshinone IIa is an efficacious the pregnane X receptor (*PXR*, a known target of abrogating inflammation in IBD) agonist, as mediated by the transactivation of *PXR*. Tanshinone IIa induced *CYP3A4* mRNA and protein expression in LS174T cells and HepG2 cells to inhibit the mRNA expression of inflammatory mediators such as TNF-α, IL-6, iNOS, and MCP [93].

Shikonin

Shikonin, obtained from the root of plants *Lithosperraum erythrorhizon* Sieb. et Zucc. and *Arnebia euchroma* (Royle) I.M. Johnst., has anti-cancer, anti-inflammatory, and anti-bacterial functions. As a naphthoquinone, shikonin acts by blocking the activation of two major targets, NF-κB and STAT-3. Study showed that shikonin can reduce the activation of NF-κB, the expression of cyclooxygenase-2, inducible nitric oxide synthase, and myeloperoxidase activity, as well as pSTAT-3, TNF-α and IL-1β while promoting the production of IL-6 and present the cytotoxic in DSS-induced UC mice *in vitro* and *in vivo* [94-95]. Besides, *in vitro*, shikonin significantly enhanced intestinal epithelial cell (IEC)-18 restitution by enhancing the migration of intestinal epithelial cells *via* involves transforming growth factor (TGF)-β_1 induction, without interfering with IEC-18 cell proliferation [96].

Rhubarb-type anthraquinones

Rhubarb-type anthraquinones are from *Rheum palmatum* L., *Rheum tanguticum* Maxim. ex Balf., or the dried roots and rhizomes of *Rheum officinale* Baill., including rhein, emodin, chrysophanol, and aloe emodin. The activities of β-glucosidase and microbial β-glucosidase are significantly reduced which leads to the abrogation of enterohepatic recirculation due to under the action of aglycone of rhubarb-type anthraxquinones to improve microbial disturbance in the intestinal tract [97].

As an important component of the rhubarb-type anthraxquinones, rhein can significantly reduce the inflammation-associated migration of immune cells. *In vitro*, rhein decrease the levels of IL-6, IL-1β, and TNF-α. Rhein reduces NO production by suppressing the protein expressions of iNOS and COX-2, thereby showing that the anti-inflammatory action of rhein is partially associated with reducing the phosphorylation levels of NF-κB p65 and the suppression of NLRP3 expression in RAW264.7 macrophages [98].

Another important component of the rhubarb-type anthraquinone, emodin, decreased the DAI, intestinal damages and the count of white blood cells (WBC) in peripheral blood, and presented the prevention of the loss of body weight and colon shortening. It is reported that emodin decreased the level of anti-flagellin antibody in serum and significantly suppressed the expression of antibody toll like receptor 5 (TLR5) and NF-κB p65. *In vitro*, emodin showed that down-regulation of the expression of antibody TLR5 and MyD88, up-regulation of the expression of antibody IκB, and decreased the release of IL-8 in inflagellin-stimulated HT-29 cells [99].

Chrysophanol decreased DAI and attenuated the body weight loss by inhibiting the production of IL-6, PGE_2 and the expression of COX-2 levels in DSS-induced colitis *in vivo,* and decreasing NF-κB (p65) and caspase-1 activation in LPS-stimulated mouse *in vitro* [100].

Bile acids

Taurocholate

Taurocholate (TC) is a natural conjugated bile acid, which not only found in ox gall, but also in snakes bile, such as *Zaocys dhumnades* (Cantor) and *Agkisrrodon acutus* (Guenther) [101]. It has been reported that TC has the anti-inflammatory effect against TNBS-induced colitis [102].

TC could decrease MPO activity, TNF-α, IFN-γ and IL-1β levels from colonic tissue. Oral TC significantly decreased MPO activity. These findings suggested that TC could inhibit neutrophils infiltrations in the inflamed colonic tissue and inhibit the development of inflammation and damage of epithelial cells. TC suppressed TNBS-induced colitis in mice and this suppression effect at least associated with the expression of some cytokines, including TNF-α, IL-1β, IFN-γ and MPO [103].

Tauroursodeoxycholate

Tauroursodeoxycholate (TUDC), taurine-conjugated ursodeoxycholic bile acid, is endogenous bile acid and found in biles of *Selenarctos thibetanus* (G. Cuvier) and *Ursus arctos* L. [101]. TUDC was proven to be potent anti-aggregation inhibitors via restraining the unfolded protein response and decreasing ER stress in intestinal epithelial cells to consider as a potential function for treatment of inflammatory bowel diseases *in vitro* [104-105].

It is reported that TUDC can reduce the number of MPO, and significantly suppress the secretion of TNF-α, IL-1β, and IFN-γ in TNBS-induced colitis, which was estimated that this effect might be associated with the expression of these cytokines, including TNF-α, IL-1β, IFN-γ and MPO [106].

Else

Indirubin and isatin

Indirubin and isatin, the active compounds are isolated from *Indigofera tinctoria* L., is an indole antitumor drug and used for treating chronic myeloid leukemia.

Indirubin is an effective component of Chinese medicinal herb recipe Qingre Zaoshi Liangxue Fang (QRZSLXF) for the treatment of UC [107], wherein the role of indirubin during the mucosal healing process through the signaling pathway involved stimulating the mucosal type 3 innate lymphoid cells to produce IL-22, consequently inducing antimicrobial peptide and tight junction molecule production [108]. Indirubin and isatin reversed the elevation of DAI, thus ameliorating DSS-induced UC by reducing inflammatory cell infiltration in the colon mucosa, which in turn alleviated crypt distortion and mucosal injury. The levels of TNF-α, interferon (IFN)-γ, and IL-2, as well as MPO activity in colon tissues were significantly decreased, whereas the levels of IL-4 and IL-10 were distinctly increased. Moreover, indirubin remarkably suppressed $CD4^+$ T cell infiltration in the colon of DSS-induced mice, and promoted the generation of Foxp3-expressing regulatory T cells, as well as inhibited DSS- induced activation of NF-κB signaling. The protective effect of indirubin/isatin combination therapy was superior to that of single-agent treatment [109-110]. Besides, isatin inhibited the increase of PGE_2 levels, prevented the decrease of SOD activity and increase of glutathione reductase (GSH-Rd) activity, glutathione peroxidase (GSH-Px) as well as the depletion of glutathione (GSH) levels [111].

Brusatol

Brusatol (BR) is one of the main bioactive components derived from *Brucea javanica* (L.) Merr., a medicinal herb historically used in the treatment of dysenteric disorders (also known as ulcerative colitis). BR was found to exhibit diverse bioactivities including antimalarial, antineoplastic, anthelmintic and hypoglycemic activities [112-114]. In addition, BR was reported to be a potent anti-inflammatory agent by inhibition of protein synthesis [115].

BR treatment inhibited the levels of pro-inflammatory cytokines and PGE2, and promoted the production of the immunoregulatory mediators IL-4 and IL-10. The beneficial effect of BR might be intimately associated with the enhancement of antioxidant enzymes including SOD and GSH-Px, as well as dose-dependent amelioration of MPO and MDA levels. In addition, treatment with BR aqueous solution caused significant attenuation of TLR4, MyD88 and NF-κB p65 expression in the colon tissue. Oral administration of BR could effectively attenuate colonic inflammation in mice, at least partially, *via* favorable regulation of anti-oxidative and anti-inflammatory status and inhibition of the TLR4-linked NF-κB signaling pathway [116].

Allicin

Allicin, a sulfur-containing natural compound which extract from *Allium sativum* L., with many different biological properties, is responsible for the typical smell and taste of freshly cut or crushed garlic. Allicin has many beneficial effects, including antioxidant, anti-inflammatory, anti-proliferative, and proapoptotic effects.

Allicin treatment significantly decreased CD68, MPO, MDA and pro-inflammatory cytokines, and increased the enzymic antioxidants significantly. In addition, allicin was capable of reducing the activation and nuclear accumulation of signal transducer, and activator of transcription 3 (STAT3), thereby it prevented the degradation of the inhibitory protein IκB and induced inhibition of the nuclear translocation of nuclear factor (NF)-κB-p65 in the colonic mucosa. These findings suggested that allicin exerted clinically useful anti-inflammatory effects through the suppression of the NF-κB and IL-6/p-$STAT3^{Y705}$ pathways [117].

Resveratrol

Resveratrol is a naturally occurring and biologically active polyphenol ingredient that is present in grapes (*Vitis vinifera* L.), peanuts, and other plants. Resveratrol presents a variety of biologic activities, including immune regulation, anti-inflammation, anti-oxidation, anti-angiogenesis, and reduction of tissue damage [118-119].

Table 1 Compounds from Chinese medicines effective on ulcerative colitis (*in vivo* studies)

Compound	Source from Chinese medicine	Animal and model	Dose (duration of treatment)	Dose and duration of inducer	Reported activity	Mechanism	Ref.
Luteolin	*Reseda odorata* L.	AOM -induced male BALB/c mice	1.2 mg·kg^{-1}	AOM (15 mg·kg^{-1}) for 3 weeks	Reduce the expressions of iNOS and COX-2 Inhibit NF-*k*B-dependent enterocyte COX-2 expression; Inhibit NF-*k*B by enhancing green fluorescent protein (EGFP) expression	Targeting oxidative stress Targeting protein	[5]
		DSS-induced colitis mice	0.5%, 2% and 5% luteolin for 3 days, followed by 32 mg/mouse for 6 days	3% DSS in drinking water for 6 days			[6]
Baicalin	*Scutellaria baicalensis* Georgi	DSS-induced male C57BL/6 mice	Baicalin (50, 100, or 150 mg·kg^{-1}) for 30 days	2% DSS in drinking water (three cycles of 5-day)	Reduce MPO and NO Increase TNF-α, IL-1β, and IL-6 Elevate IL-33 and NF-κB p65 Down-regulate the migration inhibitory factor (MIF) and the quantity of MΦs Down-regulate the amount of MΦ-related cytokines, including macrophage chemotactic factor-1 Down-regulate the macrophage inflammatory protein-3a	Targeting oxidative stress Targeting cytokines Targeting signal transduction pathway Targeting immune cells Targeting proteins	[7]
		TNBS-induced SD rats	1% (*W/V*) baicalin powder (purity 98.8%, 10 mL·kg^{-1}) twice a day for one week	5% TNBS in 50% alcohol (100 mg·kg^{-1}, 0.25 mL per rat)			[9]
Cardamonin	*Alpinia katsumadai* Hayata	Acetic acid-induced male SD rats	Cardamonin (10 or 30 mg·kg^{-1}) for 2 weeks	Intrarectal instillation of 2 ml 3% acetic acid for 1 min	Reveal down COX-2 and caspase-3 Reduce MPO, iNOS Reduce NF-κB, TNF-α, and MDA	Targeting oxidative stress Targeting inflammation Targeting protein (anti-apoptosis)	[13]
Myricetin	*Allium cepa* L. *Vitis vinifera* L.	DSS-induced female BALB/c mice	Myricetin (200, 100, 50 mg·kg^{-1}) for 10 days	5% (*W/V*) DSS for 10 days	Decrease the MPO levels Increase the GSH-Px and the SOD activity Decrease the MDA and the NO content Decreased the levels of IL-1β and IL-6	Targeting oxidative stress Targeting inflammation	[18]
Chlorogenic acid (CGA)	*Lonicera japora'ca* Thunb. *Lonicera japonica* Thunb. *Crataegus pinnatifida* Bge. *Eucommia almodies* Oliv.	TNBS-induced male BALB/c mice	CGA [20 mg·kg^{-1} (p.o., 150 μL) and i.c. (100 μL)] two times daily	TNBS (4 mg in 0.1 mL of 30 % ethanol in saline)	Reduce MPO, H_2O_2 and NF-κB level in the colon tissue, Suppress the secretions of IFNγ, TNFα, and IL-6 and colonic infiltration of F4/80$^+$ macrophages, CD177$^+$ neutrophils, and CD3$^+$ T-cells Enhance a reduction in fecal microbiota diversity	Targeting oxidative stress Targeting inflammation Inhibiting the active NF-κB signaling pathway Targeting intestinal microflora	[20]
		DSS-induced female C57BL/6 mice	CGA (1 mmol·L^{-1}) for 15 days	2.5% DSS for eight days			[19]

Continued

Compound	Source from Chinese medicine	Animal and model	Dose (duration of treatment)	Dose and duration of inducer	Reported activity	Mechanism	Ref.
Gallic Acid	*Rheum palmatum* L. *Eucalyptus robusta* Smith *Cornus officinalis* Sieb. et Zucc.	DSS-induced male BALB/c mice	Gallic Acid (10mg·kg^{-1}, orally) for 7 days	2.5% (*W/V*) DSS in the drinking water for 7 days	Decrease the expression of the pro-inflammatory proteins iNOS and COX-2 Prevent the expressions of p-STAT3^{Y705} Attenuate the expression of TNF-*α*, IL-1*β*, and iNOS Reduce PI3K, AKT, and Mtor, while increase miR-126 Decrease the Ki-67 labeling index Suppress the activity of the enzyme via the catalytic domain of IGF-1R	Inhibiting p65-NF-*κ*B-mediated transcriptional activation Targeting oxidative stress Targeting proteins Regulating gene expression Targeting inflammation	[23]
		DSS-induced male SD rats	mango extract	3% (*W/V*) DSS (over three cycles, with a 14 d separation)			[24]
		DSS-induced male SD rats	mango extract	3% (*W/V*) DSS (over three cycles, with a 14 d separation)			[25]
3,4-Oxo-isopropylidene-shikimic acid	*Illicium verum* Hook.f.	TNBS-induced male SD rats	ISA (50, 100, 200 mg·kg^{-1}) twice daily for 14 days	TNBS (30 mg) dissolved in 0.9 ml of 30% (*V/V*) ethanol	Decrease the activity of MPO Reduce MDA level Increase SOD and GSH-Px activities Reduce NO level	Targeting oxidative stress	[27]
Vanillic acid	*Angelica sinensis* (Oliv.) Diels.	DSS-induced female C57BL/6 mice	Vanillic acid (200 mg·kg^{-1}) for 7 days	5% (*W/V*) DSS for seven days	Reduce IL-6 level and COX-2 levels Suppressed the activation of transcription NF-*κ*B p65	Targeting cytokine Targeting signal transduction pathway Targeting oxidative stress	[28]
Ursolic Acid	*Cornus officinalis* Sieb.et Zucc.	TNBS-induced C57BL/6J mice	Ursolic Acid (10、20 mg·kg^{-1}) once a day for 3 days	2.5% (*W/V*) TNBS: 100 μL	Inhibit the MPO activity; Inhibit the expression of pro- inflammatory cytokines TNF-*α*, IL-1*β*, IL-6 Inhibited the degradation of IRAK1 and IRAK4	Targeting oxidative stress Targeting inflammation	[29]
Menthol	*Mentha haplocalyx* Briq. *Lysimachia christinae* Hance *Perilla frutescens* (L.) Britt.	Acetic acid-induced male Wistar rats	Menthol (20, 50 and 80 mg·kg^{-1}) for 3 days	2 ml of 3% acetic acid into the anus for 30 seconds	Reduce TNF-*α*, IL-1*β*, IL-6 Reduce the MPO activity	Targeting inflammation Targeting oxidative stress	[32]
Triptolide	*Tripterygium wilfordii* Hook. f.	DSS-induced female BALB/c mice	Triptolide (0.20, 0.4, 0.60 mg·kg^{-1} dissolved in 20% propylene glycol) for 8 days	2.5% and 5% DSS in the drinking water for 8 days	Inhibit the expression of IL-6, IL-1*β* Interrupt the IL6R-JAK/STAT pathway Prohibit Rac1 activity Block cyclin D1 and CDK4 expression Decrease extracellular matrix (ECM) deposition and collagen production Inhibit the expression of collagen Iα1 transcripts and collagen I protein	Targeting inflammation Targeting proteins Targeting signal transduction pathway	[34] [35]
		DMH/DSS-induced CD-1 (ICR) mice	Triptolide (0.1, 0.3, 1 mg·kg^{-1}·d^{-1}, dissolved with 0.9% saline) for 20 weeks	DMH (15 mg·kg^{-1}, injection) followed by 2% DSS in drinking water for 2 weeks			[123]
		TNBS-induced male SDrats	Triptolide (45 mg·kg^{-1} per day)	TNBS (60, 60, 67.5, 67.5, 75, 75 mg·kg^{-1} per week in 45% EtOH) for 6 weeks			[33]

Continued

Compound	Source from Chinese medicine	Animal and model	Dose (duration of treatment)	Dose and duration of inducer	Reported activity	Mechanism	Ref.
AL-1	*Andrographis paniculata* (Burm.f.) Nees.	TNBS-induced C57BL/6 mice	AL-1 twice a day (5, 15 and 45 mg·kg^{-1} suspended in 5% polyvinyl alcohol solution which contain 1% 1, 3-Propanediol, 1% Tween 80 and 1% ethanol) twice a day	TNBS (100 mg·kg^{-1}) in 50% ethanol solution	Decrease the level of inflammatory cytokines and MPO activity Attenuate the expression levels of p-IκBα, p-p65, COX-2 and NF-κB Increased the expression of PPAR-γ	Targeting cytokines Targeting oxidative stress Targeting proteins Targeting signal transduction pathway	[39]
CO-X	*Andrographis paniculata* (Burm.f.) Nees.	DSS-induced male BALB/c mice	DSS+CX-10 (50, 100, or 200 mg·kg^{-1}) for 8 days	3.5% DSS in water	Decrease the level of IL-6 and TNF-α and MPO activity Attenuate the expression levels of p-IκBα, p-p65, COX-2 and NF-κB	Targeting inflammation Targeting oxidative stress Targeting proteins Targeting signal transduction pathway	[40]
Gentiopicroside	*Gentiana lutea* L.	DSS-induced male ICR mice	Gentiopicroside (50, 100, 200 mg·kg^{-1}) for 7 days	5% DSS for 7days	Decrease the activity of MPO Down-regulate the mRNA expression of pro- inflammatory mediators Block the expression of COX-2 and iNOS at the protein level Attenuate the expression levels of TNF-α, IL-1β, IL-6	Targeting inflammation Targeting oxidative stress	[41]
Curcumin	*Curcuma Longa* L.	DSS-induced Kunming female mice	5 mg CUR/kg	3.5% (*W/V*) DSS in drinking water for 9 days	Alleviate visceral hyperalgesia Reverse increasing expression of TRPV1 and pTRPV1 Reduce TNF-α and MPO Reduce the expression of p-p38 MAPK-positive	Downregulate the colonic expression and phosphorylation of TRPV1 Targeting inflammation Targeting oxidative stress Targeting signal pathway	[49]
		DSS-induced male SD rats	Curcumin (20, 60 mg·kg^{-1}) for 10 days	5% DDS in drinking water for seven days			[50]
		DSS-induced BALB/c mice	Curcumin (15, 30, 60 mg·kg^{-1}) for 10 days	5% DDS in drinking water for seven days			[124]
6-gingerol	*Zingiber officinale* Rosc.	DSS-induced male SD rats	6-gingerol, 8-gingerol, and 10-gingerol (30 mg·kg^{-1} once a day for 7 days)	5% (*W/V*) DSS in drinking water for 7 consecutive days	Lower Lcn-2 level Lower the ulceration of the intestinal mucosa and the extent of neutrophil infiltration Elevated superoxide dismutase activity Decrease malondialdehyde levels and myeloperoxidase activity Decrease TNF-α, IL-6, IL-1β Decrease iNOS, Nrf-2 and HO-1	Heal the inflamed mucosa Regulating gene expression. Attenuated colitic symptoms Targeting inflammation Targeting oxidative stress Targeting immune cells	[61]
6-shogaol		DSS-induced FVB/NJ mice	6-shogaol (15 mg·kg^{-1}) for 7 days	2.5% (*W/V*) DSS in drinking water for 7 days			[53]
Paeonol	*Cynanchum paniculatum* (Bge.) Kitag.	TNBS-induced male SD rats	Paeonol (10 mL·kg^{-1}) for 7days	5% TNBS: 80 mg·kg^{-1}	Reduce the levels of IL-17 and IL-6 Increase the levels of TGF-β1	Targeting inflammation	[71]
Epicatechin	*Acacia catechu* (L.f.) Willd.	DSS-induced male C57BL/6J mice	Epicatechin (100, 200, or 300 mg·kg^{-1}) for seven days	2.3% DSS in drinking water for seven days.	Reduce TNF-α, IL-6, and NF-κB activation Inhibition of NO, MPO and MDA Increase activity of antioxidant enzymes	Targeting inflammation Targeting proteins	[73]

Continued

Compound	Source from Chinese medicine	Animal and model	Dose (duration of treatment)	Dose and duration of inducer	Reported activity	Mechanism	Ref.
Proanthocyanidins	*Cynanchum paniculatum*(Bge.)Kitag.	TNBS-induced male Wistar rats	Proanthocyanidins (200 mg·kg^{-1}) for 7days	5% TNBS: 80 mg·kg^{-1} 30mg·kg^{-1}	Decrease the MPO activity Reduce the levels of MDA Increase the SOD activity Increase GSH-Px activity and GSH levels Decrease the NO levels and iNOS activity	Targeting oxidative stress	[75]
Berberine	*Coptidis rhizoma* (Coptis chinensis Franch, Var. asperma Don, Ranunculaceae)	DSS-induced C57BL/6 J male mice	Berberine (100 mg·kg^{-1}, dissolved in distilled water) once a day for five days	3% (*W/V*) DSS in drinking water for six days	Inhibit the downregulation of TJ proteins ZO-1, E-cadherin Decrease MPO activity and stimulate the activity of CAT and SOD Decrease the mRNA expression of IL-1β, IL-6, IL-23, TNF-α, NF-κB and JAK2 phosphorylation Inhibite macrophage infiltration Decrease the phosphorylation of colonic STAT3 Reduce Th17-related cytokine (IL-17 and ROR-γt) mRNAs	Targeting proteins Targeting oxidative stress Targeting inflammation Regulating gene expression Targeting signal transduction pathway	[77]
		DSS-induced C57BL/6 male mice	Berberine hydrochloride (20 mg·kg^{-1}, dissolved in distilled water) treated daily	2% (*W/V*) DSS in drinking water (two cycles for five days followed by 14 days of drinking water plus a third cycle only for five days)			[76]
		DSS-induced C57BL/6 male mice	5-ASA (200 mg·kg^{-1}) alone and 5-ASA (200 mg·kg^{-1}) plus berberine (20mg·kg^{-1}) orally once daily for 30 days	2% (*W/V*) DSS in drinking water (two cycles for five days followed by 14 days of drinking water plus a third cycle only for five days)			[79]
Matrine	*Sophora flavescens* Ait.	TNBS-induced male SD rats	Matrine (180 mg·kg^{-1})	2% TNBS (20 mg·kg^{-1})	Decrease the level of SOD and MDA Inhibited LPS-induced release of NO Decrease TNF-α, IL-1β, IL-4, IL-6 and IL-10 levels Heal ulcer cells and reduced the lesion areas Inhibit expression levels of NOD2 and NF-κB p65 proteins	Targeting oxidative stress Targeting inflammation Targeting proteins	[81]
		TNBS-induced male SD rats	Matrine (63 mg·kg^{-1}) for 16 days	TNBS (0.6mL 5%, dissolved in ethanol)			[82]
Oxymatrine	*Sophora flavescens* Ait.	TNBS-induced male SD rats	Oxymatrine (63 mg·kg^{-1}) for 15 days	TNBS (0.6mL 5%, dissolved in 500 ml·L ethanol)	Decrease the expression of NF-κB p65 Increase the expressions of β2AR and β-arrestin2 Decrease the expression of DOR, β-arrestin1, Bcl-2 protein and mRNA Down-regulate the differentiation of Th1 and Th17 cells via PI3K/AKT pathway	Targeting signal transduction pathway Targeting proteins	[83]
		TNBS-induced male SD rats	Oxymatrine (63 mg·kg^{-1}) for 15 days	TNBS (0.6 mL 5%, dissolved in 0.25 ml 50% ethanol)			[84]
		DSS-induced male BALB/c mice	Oxymatrine (25, 50 or 100 mg·kg^{-1}) for 7 days	3.0% DSS for 7 days			[85]

Continued

Compound	Source from Chinese medicine	Animal and model	Dose (duration of treatment)	Dose and duration of inducer	Reported activity	Mechanism	Ref.
Theophylline	Viridis tea Camellia crassicolumna	Acetic acid solution in adult male Wistar rats	Theophylline (10, 20 or 50 mg·kg^{-1}) for 3 days	2 ml 3% acid acetic solution into the anus for 30 seconds	Reduce MPO activity Reduce TNF-α, IL-1β and IL-6 concentrations	Targeting oxidative stress Targeting inflammation	[125]
Tanshinone IIa	*Salvia miltiorrhiza* Bge. *Salvia sclarea* L.	DSS-induced male BALB/c mice	Tanshinone IIa (200 mg·kg^{-1}) for 7 days	3% DSS in drinking water	Alleviate inflammatory colitis possibly mediated Decrease production of MPO and ROS	Targeting immunocyte (neutrophils) Targeting oxidative stress	[92]
		DSS-induced male BALB/c mice	Tanshinone IIa (5, 10, or 20 mg·kg^{-1}·d^{-1}) for 10 days	4% (*W/V*) DSS in sterile, distilled water for 7 days	Induce *CYP3A4* mRNA Protein expression was mediated by the transactivation of *PXR*	Targeting proteins Regulating gene expression	[93]
Shikonin	*Lithosperraum erythrorhizon* Sieb. et Zucc. *Arnebia euchroma* (Royle) I.M. Johnst.	DSS-induced female BALB/c mice	Shikonin (6.25, 12.5, and 25 mg·kg^{-1}) on day 1 and on day 5	5% DSS in drinking water	Reduce the expression of cyclooxygenase-2, pSTAT-3, TNF-α and IL-1β, myeloperoxidase activity and the activation of NF-κB	Targeting proteins Targeting inflammation Targeting oxidative stress	[94]
		AOM/DSS-induced female BALB/c mice	Shikonin (3.5 and 7.0 mg·kg^{-1})	1.5% (*W/V*) DSS for 7 days, followed by AOM (7.5 mg·kg^{-1}, i.p.) for 3 weeks	Reduce the activation of NF-κB, IL-6 and NOS		[95]
Rhubarb-type anthraquinones	*Rheum palmatum* L. *Rheum tanguticum* Maxim. ex Balf. *Rheum officinale* Baill.	DSS-induced male SD rats	Rhubarb extract (10.0 ml·kg^{-1}, with 0.5% CMC sodium solution)	5% (*W/V*) DSS in autoclaved drinking water for 7 days followed 3% DSS for 14 days	Reduce the activities of β-glucosidase and microbial β-glucosidase Abrogate the enterohepatic recirculation	Targeting intestinal microflora	[97]
Rhein	*Rheum palmatum* L. *Rheum tanguticum* Maxim. ex Balf. *Rheum officinale* Baill.	Transgenic zebrafish line (TG)	Rhein (different concentrations)	/	Reduce the inflammation-associated migration of immune cells	Targeting migration of immune cells	[98]
Emodin	*Rheum palmatum* L. *Rheum tanguticum* Maxim. ex Balf. *Rheum officinale* Baill.	DSS-induced male C57BL/6 mice	Emodin (5, 10 and 20 mg·kg^{-1} bw) for 14 days	3% DSS	Decrease the count of white blood cells in peripheral blood Decrease the level of anti-flagellin antibody in serum and suppress the expression of antibody TLR5 and NF-κB p65	Targeting immune cell Targeting proteins	[99]
Crysophanol	*Rheum palmatum* L. *Rheum tanguticum* Maxim.ex Balf., *Rheum officinale* Baill	DSS-induced male and female C57BL/6 mice	Chrysophanol (5 mg·kg^{-1}) for 7 days	5% (*W/V*) DSS for 7 days	Inhibit the production of IL-6, PGE2 and the expression of COX-2 levels	Targeting inflammation Targeting oxidative stress	[100]
Taurocholate	*Zaocys dhumnades* (Cantor) *Agkisrrodon acutus* (Guenther)	TNBS-induced male Balb/c mice	Taurocholate (20, 40, 60 mg·kg^{-1}) for 7 consecutive days	TNBS (1mg dissolves in 0.1ml of 50% ethanol)	Reduce the level of MPO Decrease TNF-α, IFN-γ, IL-1β tissue levels	Targeting inflammation Targeting oxidative stress	[103]

Continued

Compound	Source from Chinese medicine	Animal and model	Dose (duration of treatment)	Dose and duration of inducer	Reported activity	Mechanism	Ref.
Tauroursodeoxycholate	*Selenarctos thibetanus* (G. Cuvier) *Ursus arctos* L.	TNBS-induced male Balb/c mice	Tauroursodeoxycholate (20, 40, 60 mg·kg^{-1}) for 7 days	2.5% (*W/V*) TNBS: 100 μL	Decrease levels of TNF-α, IL-1β, IFN-γ, MPO	Targeting inflammation Targeting oxidative stress	[106]
Indirubin and isatin	*Indigofera tinctoria* L.	DSS-induced male C57BL/6 mice	Indirubin/isatin (10 mg·kg^{-1}) for 7 days	3% DSS in drinking water for 7 days	Decrease the MPO activity, and levels of TNF-α, interferon (IFN)-γ and IL-2 Inhibit NF-κB signaling Increase the levels of IL-4 and IL-10 Promote the generation of Foxp3-expressing regulatory T cells Suppresse $CD4^+$ T cell infiltration	Targeting oxidative stress Targeting inflammation Targeting immunocyte	[109] [110]
		DSS-induced male C57BL/6 mice	Indirubin (200, 400 mg·kg^{-1}) for 7 days	5% DSS in drinking water for 7 days			[126]
		TNBS-induced WH rats	Isatin (3, 6, 12.5, 18.75 and 25 mg·kg^{-1} orally) at 72, 48, 24 and 2 h before colitis induction	TNBS, 10 mg dissolved in 0.25 ml 50% ethanol (*V/V*)	Inhibit the increase of PGE_2 levels Prevent the decrease of SOD activity Increase GSH-Rd, GSH-Px activity as well as the depletion of GSH levels		[111]
Brusatol	*Brucea javanica*(L.)Merr.	DSS-induced male BALB/c mice	Brusatol (0.25, 0.5, 1 mg·kg^{-1}) once a day for seven consecutive days	3% (*W/V*) DSS for seven consecutive days	Attenuate the levels of TNF-α, IFN-γ, IL-1β and IL-6 Increase the productions of IL-4 and IL-10 Ameliorate PGE2 production Reduce MPO and MDA contents Enhance SOD and GSH-Px levels Inhibit the TLR4-linked NF-κB signaling pathway	Targeting inflammation Targeting oxidative stress Targeting signaling pathway	[116]
Allicin	*Allium sativum* L.	DSS-induced BALB/c mice	Allicin (10 mg·kg^{-1}) for 7 days	2.5% DSS in drinking water for seven days	Reduce the expression/activity of CD68 and MPO Reduce the mRNA levels of pro-inflammatory cytokines Attenuate level of MDA in AOM/DSS-Induced CAC Elevate the SOD, CAT, GPx, and GR activities Reduce the expression of NF-κB Inhibit the DSS-Induced activation of STAT3	Targeting oxidative stress Targeting inflammation Targeting signaling pathway	[117]
Resveratrol	Vitis vinifera L.	DSS-induced Specific pathogen-free BALB/c mice	Resveratrol (50, 100 mg·kg^{-1}) per day for 14 days	5% DSS for 7 days	Decrease levels of IL-6, IL-17, HIF-1α, mTOR and STAT3 Increase anti-inflammatory cytokine Decrease proinflammatory cytokines Regulate the balance of Treg/Th17	Targeting inflammation Inhibition of the HIF-1α-Th17 pathway (Targeting signaling pathway)	[122]

Table 2 Compounds from Chinese medicines effective on ulcerative colitis (*in vitro/ ex vivo* studies)

Name	Source	Cell/specimen	Dose/concentration	Reported activity	Mechanism	Ref.
Baicalin	*Scutellaria baicalensis* Georgi	CD4+CD29+T cells IL23R gene	5, 10, 20, 40 μmol·L^{-1} 5, 10, 20, 40 μmol·L^{-1}	Upregulate expression of IFN-γ, IL-4, TGF-β1 and IL-10 Downregulate expression of IFN-γ, IL-5, IL-6, RORC, Foxp3 and T-bet Decrease ratios of T-bet/GATA-3, p-STAT4/STAT4 and p-NF-κB/NF-κB Increase p-STAT6/STAT6 ratio Inhibit p-STAT4/STAT4 ratios	Activating transcription factor expression Targeting inflammation Targeting signal transduction Targeting receptor	[8] [127]
Cardamonin	*Alpinia katsumadai* Hayata	THP-1 human monocytes RAW264.7 murine macrophages	Cardamonin lipopolysaccharide (1 μg·mL^{-1})	Inhibit NO release and iNOS expression Inhibited NF-κB DNA-binding in LPS-stimulated cells and nuclear extracts Inhibited IFNg-stimulated iNOS induction and GAS/GAF-DNA binding	Targeting transcription factor binding to DNA Targeting oxidative stress	[12]
Dimethyl cardamonin	*Alpinia katsumadai* Hayata	RAW264.7 cell	Dimethyl cardamonin lipopolysaccharide (1 μg·mL^{-1})	Inhibit production of NO and PGE2 Attenuate TNF-α, IL-6, IL-1β, iNOS and COX-2 Reduce I-κBα phosphorylation and degradation Decrease TNF-α, IL-6 and IL-1β	Blocking NF-κB activation (Targeting signal transduction pathway) Targeting inflammation	[11]
Chlorogenic acid	*Lonicera japora'ca* Thunb., *Lonicera japonica* Thunb. *Crataegus pinnatifida* Bge. *Eucommia almodies* Oliv.	Caco-2 cells Intestinal epithelial cell line (IPEC)-J2	1 mmol·L^{-1}and H_2O_2 for 24h 25, 50 and 100 μmol·L^{-1}	Inhibit H_2O_2-induced IL-8 production (*via* suppression of PKD- NF-κB signaling) Reduce the level of reactive oxygen species *via* decreasing gene expression and concentration of IL-6 and IL-8, as well as COX-2 and TNF-α mRNA levels;	Targeting oxidative stress Targeting signal transduction pathway Targeting inflammation	[128] [129]
Gallic acid	*Rheum palmatum* L. *Eucalyptus robusta* Smith *Cornus officinalis* Sieb. et Zucc.	RAW264.7 macrophages Human colon CCD-18Co myofibroblastic HT-29 cell lines Human CCD-18Co colon myofibroblast cells	0–200 μg·mL^{-1} for 24 h Mango extract 1–4 mg·L^{-1} GA extracts	Decrease the expression of p65-NF-κB Suppress the protein expression levels of p-NF-κB, NF-κB, 3-kinase (PI3K, p85β), HIF-1α, p70 ribosomal protein S6 kinase (p70S6K1), and RPS6 protein Inhibit the IGF-1R- AKT/mTOR axis	Targeting signal transduction pathway Targeting protein	[23] [24] [25]
Ursolic Acid	*Cornus officinalis* Sieb.et Zucc.	Peritoneal Macrophages	5, 10, 20 μmol·L^{-1}	Inhibit the expression of TNF-α, IL-1β, IL-6 Inhibit the phosphorylation of TAK1, IKKβ, IκBα, ERK, JNK, p38 Regulate NF-κB and MAPK signaling pathways Decrease PGE2 and NO production Suppress COX-2 and iNOS expression	Targeting inflammation Inhibition of LPS binding to TLR4 (Targeting signaling pathways) Targeting oxidative stress Targeting proteins	[29]
Triptolide	*Tripterygium wilfordii* Hook. f.	SW480 and Caco 2 cells	0, 10, 30, 100 or 300 nmol·L^{-1} for 24 h, 48 h or 72 h	Reduce the secretion of IL-6, IL-6R, IL-1β, the levels of JAK1, and phosphorylated STAT3; Prohibit Rac1 protein activity and blocked cyclin D1 and CDK4 expression	Targeting inflammation Targeting signal transduction pathway Targeting proteins	[123]
Andrographolide	*Andrographis paniculata* (Burm.f.) Nees.	Peripheral blood mononuclear cells (PBMCs)	10, 20 and 30 μg·mL^{-1} in pre-treated followed 10, 20 and 30 μg·mL^{-1}	Up-regulate expression of Th17 cells Increase expression of IL-23, IL-17A, ROR-γt and p-STAT3	Targeting inflammation Targeting oxidative stress Targeting gene transcription and ptotein	[37]

Continued

Name	Source	Cell/specimen	Dose/concentration	Reported activity	Mechanism	Ref.
Curcumin	*Curcuma Longa* L.	HEK293 cells	1, 3, 10 mmol·L^{-1}	Inhibit membrane TRPV1	Targeting anti-nociceptive action	[50]
6-shogaol	*Zingiber officinale* Rosc.	264.7 macrophage and colon-26 cells	50, 100, 200, 500, 1000 μg·mL^{-1}	Decrease TNF-α, IL-6, IL-1β Decrease iNOS	Remain the cell viability Enhance the expression of folate receptor Targeting inflammation	[61]
Epicatechin	*Acacia catechu* (L.f.) Willd.	Murine macrophage cell line RAW264.7 Murine intestinal epithelial cell line IEC6	0.1, 1, 10 mmol·L^{-1}	Inhibit effect on NF-κB activation Increase SOD, GSH-Px and CAT activity Decreased the concentration of MDA	Targeting inflammation Targeting oxidative stress	[73]
Berberine	*Coptidis rhizoma* (species: Coptis chinensis Franch, genus: Var. asperma Don, family: Ranunculaceae)	lymphocyte	0.3, 1, 3, 10, 30, 100 mg·mL^{-1}	Inhibit the lymphocyte proliferation Reduce and occlude the tight junction (TJ) protein ZO-1	Targeting immune cell Targeting protein	[80]
		CACO-2 cell culture (an epithelial cell line derived from human colon adenocarcinoma)	Berberine chloride solution (2.7mmol·L^{-1}) for 24h			[78]
Tanshinone IIa	*Salvia miltiorrhiza* Bge. *Salvia sclarea* L.	Neutrophils	10 mg·mL^{-1}, dissolved in DMSO	Suppress the levels of ROS and the inflammatory cytokines (IL-1β, IL-6, IL-10, and TNF-α)	Targeting oxidative stress Targeting immunocyte (neutrophil)	[92]
		HepG2 cells and LS174T cells	2.5, 5, 10, 20, or 40 μmol·L^{-1} for HepG2 cells, 2.5, 5, 10, 20 μmol·L^{-1} for LS174T cells	Inhibit the mRNA expression of inflammatory mediators iNOS, and MCP	Targeting inflammation Targeting of *PXR*	[130]
Shikonin	*Lithosperraum erythrorhizon* Sieb. et Zucc. *Arnebia euchroma* (Royle) I.M. Johnst.	Human epithelial colorectal adenocarcinoma Caco-2 cells	50–1.56 μmol·L^{-1}	Induce the proapoptotic Bcl-2 Inhibit the antiapoptotic caspase 3 Enhance the migration of intestinal epithelial cells	Targeting gene expression Targeting inflammation factor (TGF-β1) Targeting protein (enzyme) Targeting intestinal epithelial cells	[95]
		The intestinal epithelial cell line (IEC)-18	1.0–0.1 μmol·L^{-1}			[96]
Rhein	*Rheum palmatum* L. *Rheum tanguticum* Maxim. ex Balf. *Rheum officinale* Baill.	RAW264.7 mouse macrophage cells	1, 5, and 20 μmol·L^{-1}	Decrease IL-6, IL-1β, and TNF-α Reduce the phosphorylation levels of NF-κB p65 and the suppression of NLRP3 expression Reduce NO production and suppress the protein expressions of iNOS and COX-2	Targeting inflammation Targeting oxidative stress Targeting protein	[98]
Emodin	*Rheum palmatum* L. *Rheum tanguticum* Maxim. ex Balf. *Rheum officinale* Baill.	Human transformed colonic epithelial (HT29) cells	2.5, 5, 10, 20, 40, 80 μmol·L^{-1}	Down-regulate the expression of antibody TLR5 and MyD88 Up-regulate the expression of antibody IκB Decrease the release of IL-8	Targeting protein Targeting inflammation	[99]
Crysophanol	*Rheum palmatum* L. *Rheum tanguticum* Maxim. ex Balf. *Rheum officinale* Baill.	TG-elicited macrophages	2, 20 μmol·L^{-1}	Inhibit the production of IL-6, PGE2 and the expression of COX-2 levels Decrease NF-κB (p65) and caspase-1 activation	Targeting inflammation Targeting oxidative stress Targeting protein	[100]

Previous studies demonstrated that resveratrol exhibited anti-inflammatory effects on colitis in mice *via* antioxidant activities [118]. Recently, two reports shown that resveratrol has excellent therapeutic efficacy on UC by reducing neutrophilic exudate, inhibiting adhesion molecules, and regulating cytokine levels [120-121]. It was found that resveratrol can regulate the rebalancing of Treg/Th17, increase TGF-β1 and IL-10 levels, decrease IL-6 and IL-17 levels, and inhibit hypoxia-mTOR-HIF-1α-Th17 and IL-6-STAT3-HIF-1α-Th17 pathways. The therapeutic efficacy of resveratrol in UC was dose-dependent and closely associated with the regulation of Treg/Th17 balance and the HIF-1α/ mTOR signaling pathway [122].

Discussion and Future Prospects

The detailed information on the above-mentioned compounds from TCM effective on UC, both *in vivo* and *in vitro/ex vivo* studies, are shown in Tables 1 and 2. The anti-UC activities are mainly focus on targeting inflammation or oxidative stress, which is associated with increasing the levels of anti-inflammatory cytokine (IL-4, IL-10, SOD), suppressing the levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8, IL-23, NF-κB, NO), reducing the activity of MPO, MDA, IFN-γ, and iNOS. In additional to regular anti-inflammatory mechanism, some compounds may lower the ulceration of the intestinal mucosa and extent of neutrophil infiltration, or inhibit the downregulation of TJ protein ZO-1 and E-cadherin, which also present their anti-inflammation activities in inflammatory colons of ulcerative colitis.

In conclusion, these natural active compounds in various Chinese medicines present favorable effects on experimental UC models, most of which are found to be active in anti-inflammation or anti-oxidation with oral administration to avoid severe toxic or side effects. TCM, with their unique, mild, and long-term effectiveness on UC, might benefit this inflammatory bowel disease, with further efforts on the investigations on their drugability. However, the majority of the compounds are used in the acute experimental colitis (from 3 to 15 days), except triptolide (20 weeks). Since the clinical UC has been found to be a long-term recurrent disease, the applicability of these compounds still needs further investigation and evaluation, before they are practically employed with medication purpose.

References

[1] Wan P, Chen H, Guo Y, *et al.* Advances in treatment of ulcerative colitis with herbs: from bench to bedside [J]. *World J Gastroenterol*, 2014, **20**(39): 14099-14104.

[2] Pastorelli L, Pizarro TT, Cominelli F, *et al.* Emerging drugs for the treatment of ulcerative colitis [J]. *Expert Opin Emerg Drugs*, 2009, **14**(3): 505-521.

[3] Zhang C, Jiang M, Lu A. Considerations of traditional Chinese medicine as adjunct therapy in the management of ulcerative colitis [J]. *Clin Rev Allergy Immunol*, 2013, **44**(3): 274-283.

[4] Salaga M, Zatorski H, Sobczak M, *et al.* Chinese herbal medicines in the treatment of IBD and colorectal cancer: a review [J]. *Curr Treat Options Oncol*, 2014, **15**(3): 405-420.

[5] Pandurangan AK, Kumar SA, Dharmalingam P, *et al.* Luteolin, a bioflavonoid inhibits azoxymethane-induced colon carcinogenesis: involvement of iNOS and COX-2 [J]. *Pharmacogn Mag*, 2014, **10**(Suppl 2): S306-310.

[6] Karrasch T, Kim JS, Jang BI, *et al.* The flavonoid luteolin worsens chemical-induced colitis in NF-kappaB (EGFP) transgenic mice through blockade of NF-kappaB-dependent protective molecules [J]. *PLos One*, 2007, **2**(7): e596.

[7] Zhang CL, Zhang S, He WX, *et al.* Baicalin may alleviate inflammatory infiltration in dextran sodium sulfate-induced chronic ulcerative colitis *via* inhibiting IL-33 expression [J]. *Life Sci*, 2017, **186**: 125-132.

[8] Yu FY, Huang SG, Zhang HY, *et al.* Effects of baicalin in CD4 + CD29 + T cell subsets of ulcerative colitis patients [J]. *World J Gastroenterol*, 2014, **20**(41): 15299-15309.

[9] Dai SX, Zou Y, Feng YL, *et al.* Baicalin down-regulates the expression of macrophage migration inhibitory factor (MIF) effectively for rats with ulcerative colitis [J]. *Phytother Res*, 2012, **26**(4): 498-504.

[10] Goncalves LM, Valente IM, Rodrigues JA. An overview on cardamonin [J]. *J Med Food*, 2014, **17**(6): 633-640.

[11] Kim YJ, Ko H, Park JS, *et al.* Dimethyl cardamonin inhibits lipopolysaccharide-induced inflammatory factors through blocking NF-kappaB p65 activation [J]. *Int Immunopharmacol*, 2010, **10**(9): 1127-1134.

[12] Hatziieremia S, Gray AI, Ferro VA, *et al.* The effects of cardamonin on lipopolysaccharide-induced inflammatory protein production and MAP kinase and NF-kappaB signalling pathways in monocytes/macrophages [J]. *Br J Pharmacol*, 2006, **149**(2): 188-198.

[13] Ali AA, Abd Al Haleem EN, Khaleel SA, *et al.* Protective effect of cardamonin against acetic acid-induced ulcerative colitis in rats [J]. *Pharmacol Rep*, 2017, **69**(2): 268-275.

[14] Lee YS, Choi EM. Myricetin inhibits IL-1beta-induced inflammatory mediators in SW982 human synovial sarcoma cells [J]. *Int Immunopharmacol*, 2010, **10**(7): 812-814.

[15] Chen W, Li Y, Li J, *et al.* Myricetin affords protection against peroxynitrite-mediated DNA damage and hydroxyl radical formation [J]. *Food Chem Toxicol*, 2011, **49**(9): 2439-2444.

[16] Nirmala P, Ramanathan M. Effect of myricetin on 1, 2 dimethylhydrazine induced rat colon carcinogenesis [J]. *J Exp Ther Oncol*, 2011, **9**(2): 101-108.

[17] Kang NJ, Jung SK, Lee KW, *et al.* Myricetin is a potent chemopreventive phytochemical in skin carcinogenesis [J]. *Ann N Y Acad Sci*, 2011, **1229**: 124-132.

[18] Zhao J, Hong T, Dong M, *et al.* Protective effect of myricetin in dextran sulphate sodium-induced murine ulcerative colitis [J]. *Mol Med Rep*, 2013, **7**(2): 565-570.

[19] Zhang Z, Wu X, Cao S, *et al.* Chlorogenic acid ameliorates experimental colitis by promoting growth of akkermansia in mice [J]. *Nutrients*, 2017, **9**(7): 677.

[20] Zatorski H, Salaga M, Zielinska M, *et al.* Experimental colitis in mice is attenuated by topical administration of chlorogenic acid [J]. *Naunyn Schmiedebergs Arch Pharmacol*, 2015, **388**(6): 643-651.

[21] Shin HS, Satsu H, Bae MJ, *et al.* Catechol groups enable reactive oxygen species scavenging-mediated suppression of PKD-NFkappaB-IL-8 signaling pathway by chlorogenic and caffeic acids in human intestinal cells [J]. *Nutrients*, 2017, **9**(2): 165.

[22] Palócz O, Pászti-Gere E, Gálfi P, *et al.* Chlorogenic acid combined with lactobacillus plantarum 2142 reduced LPS- induced intestinal inflammation and oxidative stress in IPEC-J2 Cells [J]. *PLoS One*, 2016, **11**(11): e0166642.

[23] Pandurangan AK, Mohebali N, Esa NM, *et al.* Gallic acid suppresses inflammation in dextran sodium sulfate-induced colitis in mice: possible mechanisms [J]. *Int Immunopharmacol*, 2015, **28**(2): 1034-1043.

[24] Kim H, Banerjee N, Barnes RC, *et al.* Mango polyphenolics reduce inflammation in intestinal colitis-involvement of the miR-126/PI3K/AKT/mTOR axis *in vitro* and *in vivo* [J]. *Mol Carcinog*, 2017, **56**(1): 197-207.

[25] Kim H, Banerjee N, Ivanov I, *et al.* Comparison of anti-inflammatory mechanisms of mango (*Mangifera Indica* L.) and pomegranate (*Punica Granatum* L.) in a preclinical model of colitis [J]. *Mol Nutr Food Res*, 2016, **60**(9): 1912-1923.

[26] Xing JF, Sun JN, Sun JY, *et al.* Protective effects of 3, 4-oxo-isopropylidene-shikimic acid on experimental colitis induced by trinitrobenzenesulfonic acid in rats [J]. *Dig Dis Sci*, 2012, **57**(8): 2045-2054.

[27] Xing J, You C, Dong K, *et al.* Ameliorative effects of 3, 4-oxo-isopropylidene-shikimic acid on experimental colitis and their mechanisms in rats [J]. *Int Immunopharmacol*, 2013, **15**(3): 524-531.

[28] Kim SJ, Kim MC, Um JY, *et al.* The beneficial effect of vanillic acid on ulcerative colitis [J]. *Molecules*, 2010, **15**(10): 7208-7217.

[29] Jang SE, Jeong JJ, Hyam SR, *et al.* Ursolic acid isolated from the seed of Cornus officinalis ameliorates colitis in mice by inhibiting the binding of lipopolysaccharide to Toll-like receptor 4 on macrophages [J]. *J Agric Food Chem*, 2014, **62**(40): 9711-9721.

[30] Li Q, Wang X, Yang Z, *et al.* Menthol induces cell death *via* the TRPM8 channel in the human bladder cancer cell line T24 [J]. *Oncology*, 2009, **77**(6): 335-341.

[31] Wang Y, Wang X, Yang Z, *et al.* Menthol inhibits the proliferation and motility of prostate cancer DU145 cells [J]. *Pathol Oncol Res*, 2012, **18**(4): 903-910.

[32] Ghasemi-Pirbaluti M, Motaghi E, Bozorgi H. The effect of menthol on acute experimental colitis in rats [J]. *Eur J Pharmacol*, 2017, **805**: 101-107.

[33] Tao Q, Wang B, Zheng Y, *et al.* Triptolide ameliorates colonic fibrosis in an experimental rat model [J]. *Mol Med Rep*, 2015, **12**(2): 1891-1897.

[34] Zhang H, Gong C, Qu L, *et al.* Therapeutic effects of triptolide *via* the inhibition of IL-1beta expression in a mouse model of ulcerative colitis [J]. *Exp Ther Med*, 2016, **12**(3): 1279-1286.

[35] Zhang H, Chen W. Interleukin 6 inhibition by triptolide prevents inflammation in a mouse model of ulcerative colitis [J]. *Exp Ther Med*, 2017, **14**(3): 2271-2276.

[36] Wang Z, Jin H, Xu R, *et al.* Triptolide downregulates Rac1 and the JAK/STAT3 pathway and inhibits colitis-related colon cancer progression [J]. *Exp Mol Med*, 2009, **41**(10): 717-727.

[37] Zhu Q, Zheng P, Chen X, *et al.* Andrographolide presents therapeutic effect on ulcerative colitis through the inhibition of IL-23/IL-17 axis [J]. *Am J Transl Res*, 2018, **10**(2): 465-473.

[38] Zhu Q, Zheng P, Zhou J, *et al.* Andrographolide affects Th1/Th2/Th17 responses of peripheral blood mononuclear cells from ulcerative colitis patients [J]. *Mol Med Rep*, 2018, **18**(1): 622-626.

[39] Yang Y, Yan H, Jing M, *et al.* Andrographolide derivative AL-1 ameliorates TNBS-induced colitis in mice: involvement of NF-small ka, CyrillicB and PPAR-gamma signaling pathways [J]. *Sci Rep*, 2016, **6**: 29716.

[40] Gao Z, Yu C, Liang H, *et al.* Andrographolide derivative CX-10 ameliorates dextran sulphate sodium-induced ulcerative colitis in mice: Involvement of NF-kappaB and MAPK signalling pathways [J]. *Int Immunopharmacol*, 2018, **57**: 82-90.

[41] Niu YT, Zhao YP, Jiao YF, *et al.* Protective effect of gentiopicroside against dextran sodium sulfate induced colitis in mice [J]. *Int Immunopharmacol*, 2016, **39**: 16-22.

[42] Asher GN, Spelman K. Clinical utility of curcumin extract [J]. *Altern Ther Health Med*, 2013, **19**(2): 20-22.

[43] Salomon N, Lang A, Gamus D. Curcumin add-on therapy for ulcerative colitis [J]. *Harefuah*, 2015, **154**(1): 56-58, 66.

[44] Vecchi Brumatti L, Marcuzzi A, Tricarico PM, *et al.* Curcumin and inflammatory bowel disease: potential and limits of innovative treatments [J]. *Molecules*, 2014, **19**(12): 21127-21153.

[45] Sreedhar R, Arumugam S, Thandavarayan RA, *et al.* Curcumin as a therapeutic agent in the chemoprevention of inflammatory bowel disease [J]. *Drug Discov Today*, 2016,

21(5): 843-849.

[46] Baliga MS, Joseph N, Venkataranganna MV, *et al.* Curcumin, an active component of turmeric in the prevention and treatment of ulcerative colitis: preclinical and clinical observations [J]. *Food Funct*, 2012, **3**(11): 1109-1117.

[47] Viljakainen HT, Pekkinen M, Saarnio E, *et al.* Dual effect of adipose tissue on bone health during growth [J]. *Bone*, 2011, **48**(2): 212-217.

[48] Deguchi Y, Andoh A, Inatomi O, *et al.* Curcumin prevents the development of dextran sulfate Sodium (DSS)-induced experimental colitis [J]. *Dig Dis Sci*, 2007, **52**(11): 2993-2998.

[49] Wang Y, Tang Q, Duan P, *et al.* Curcumin as a therapeutic agent for blocking NF-kappaB activation in ulcerative colitis [J]. *Immunopharmacol Immunotoxicol*, 2018, doi: 10.1080/08923973.2018.1469145.

[50] Yang M, Wang J, Yang C, *et al.* Oral administration of curcumin attenuates visceral hyperalgesia through inhibiting phosphorylation of TRPV1 in rat model of ulcerative colitis [J]. *Mol Pain*, 2017, **13**: 1744806917726416.

[51] Xin KB, Zhang JL, Yang J, *et al.* A Study on the effect of Tanshinone IIA sulfonate injection on the clinical efficacy of ulcerative colitis [J]. *Prog Modern Biomed*, 2015, **15**(34): 6701-6703, 6623.

[52] Huang G, Ye L, Du G, *et al.* Effects of curcumin plus Soy oligosaccharides on intestinal flora of rats with ulcerative colitis [J]. *Cell Mol Biol (Noisy-le-grand)*, 2017, **63**(7): 20-25.

[53] Zhang F, Ma N, Gao YF, *et al.* Therapeutic effects of 6-gingerol, 8-gingerol, and 10-gingerol on dextran sulfate sodium-nduced acute ulcerative colitis in rats [J]. *Phytother Res*, 2017, **31**(9): 1427-1432.

[54] Ajayi BO, Adedara IA, Farombi EO. Pharmacological activity of 6-gingerol in dextran sulphate sodium-induced ulcerative colitis in BALB/c mice [J]. *Phytother Res*, 2015, **29**(4): 566-572.

[55] Dugasani S, Pichika MR, Nadarajah VD, *et al.* Comparative antioxidant and anti-inflammatory effects of 6-gingerol, 8-gingerol, 10-gingerol and 6-shogaol [J]. *J Ethnopharmacol*, 2010, **127**(2): 515-520.

[56] Shim S, Kim S, Choi DS, *et al.* Anti-inflammatory effects of 6-shogaol: potential roles of HDAC inhibition and HSP70 induction [J]. *Food Chem Toxicol*, 2011, **49**(11): 2734-2740.

[57] Sun X, Li Q, Gong Y, *et al.* Low-dose theophylline restores corticosteroid responsiveness in rats with smoke-induced airway inflammation [J]. *Can J Physiol Pharmacol*, 2012, **90**(7): 895-902.

[58] Zhang M, Viennois E, Prasad M, *et al.* Edible ginger-derived nanoparticles: a novel therapeutic approach for the prevention and treatment of inflammatory bowel disease and colitis- associated cancer [J]. *Biomaterials*, 2016, **101**: 321-340.

[59] Zhang M, Xiao B, Wang H, *et al.* Edible ginger-derived nanolipids loaded with doxorubicin as a novel drug-delivery approach for colon cancer therapy [J]. *Mol Ther*, 2016, **24**(10): 1783-1796.

[60] Zhang M, Collins JF, Merlin D. Do ginger-derived nanoparticles represent an attractive treatment strategy for inflammatory bowel diseases? [J]. *Nanomedicine (Lond)*, 2016, **11**(23): 3035-3037.

[61] Zhang M, Xu C, Liu D, *et al.* Oral delivery of nanoparticles loaded with ginger active compound, 6-shogaol, attenuates Ulcerative Colitis and Promotes Wound Healing in a Murine Model of Ulcerative Colitis [J]. *J Crohns Colitis*, 2018, **12**(2): 217-229.

[62] Yun CS, Choi YG, Jeong MY, *et al.* Moutan cortex radicis inhibits inflammatory changes of gene expression in lipopolysaccharide-stimulated gingival fibroblasts [J]. *J Nat Med*, 2013, **67**(3): 576-589.

[63] Jamal J, Mustafa MR, Wong PF. Paeonol protects against premature senescence in endothelial cells by modulating Sirtuin 1 pathway [J]. *J Ethnopharmacol*, 2014, **154**(2): 428-436.

[64] Gong X, Yang Y, Huang L, *et al.* Antioxidation, anti-inflammation and anti-apoptosis by paeonol in LPS/d-GalN-induced acute liver failure in mice [J]. *Int Immunopharmacol*, 2017, **46**: 124-132.

[65] Fu PK, Yang CY, Huang SC, *et al.* Evaluation of LPS-induced acute lung injury attenuation in rats by aminothiazole-paeonol derivatives [J]. *Molecules*, 2017, **22**(10): 1605.

[66] Meng Y, Wang M, Xie X, *et al.* Paeonol ameliorates imiquimod-induced psoriasis-like skin lesions in BALB/c mice by inhibiting the maturation and activation of dendritic cells [J]. *Int J Mol Med*, 2017, **39**(5): 1101-1110.

[67] Zhang L, Tao L, Shi T, *et al.* Paeonol inhibits B16F10 melanoma metastasis *in vitro* and *in vivo via* disrupting proinflammatory cytokines-mediated NF-kappaB and STAT3 pathways [J]. *IUBMB Life*, 2015, **67**(10): 778-788.

[68] Li M, Tan SY, Wang XF. Paeonol exerts an anticancer effect on human colorectal cancer cells through inhibition of PGE(2) synthesis and COX-2 expression [J]. *Oncol Rep*, 2014, **32**(6): 2845-2853.

[69] Liu J, Wang S, Feng L, *et al.* Hypoglycemic and antioxidant activities of paeonol and its beneficial effect on diabetic encephalopathy in streptozotocin-induced diabetic rats [J]. *J Med Food*, 2013, **16**(7): 577-586.

[70] Jin X, Wang J, Xia ZM, *et al.* Anti-inflammatory and antioxidative activities of paeonol and its metabolites through blocking MAPK/ERK/p38 signaling pathway [J]. *Inflammation*, 2016, **39**(1): 434-446.

[71] Zong S, Pu Y, Li S, *et al.* Beneficial anti-inflammatory effect of paeonol self-microemulsion-loaded colon-specific capsules

on experimental ulcerative colitis rats [J]. *Artif Cells Nanomed Biotechnol*, *2018,* doi:10.1080/21691401.2017.1423497.

[72] Rtibi K, Grami D, Wannes D, *et al.* Ficus carica aqueous extract alleviates delayed gastric emptying and recovers ulcerative colitis-enhanced acute functional gastrointestinal disorders in rats [J]. *J Ethnopharmacol*, 2018, **224**: 242-249.

[73] Zhang H, Deng A, Zhang Z, *et al.* The protective effect of epicatechin on experimental ulcerative colitis in mice is mediated by increasing antioxidation and by the inhibition of NF-kappaB pathway [J]. *Pharmacol Rep*, 2016, **68**(3): 514-520.

[74] De Rezende AA, Graf U, Guterres Zda R, *et al.* Protective effects of proanthocyanidins of grape (*Vitis vinifera* L.) seeds on DNA damage induced by doxorubicin in somatic cells of drosophila melanogaster [J]. *Food Chem Toxicol*, 2009, **47**(7): 1466-1472.

[75] Wang YH, Yang XL, Wang L, *et al.* Effects of proanthocyanidins from grape seed on treatment of recurrent ulcerative colitis in rats [J]. *Can J Physiol Pharmacol*, 2010, **88**(9): 888-898.

[76] Li YH, Xiao HT, Hu DD, *et al.* Berberine ameliorates chronic relapsing dextran sulfate sodium-induced colitis in C57BL/6 mice by suppressing Th17 responses [J]. *Pharmacol Res*, 2016, **110**: 227-239.

[77] Zhang LC, Wang Y, Tong LC, *et al.* Berberine alleviates dextran sodium sulfate-induced colitis by improving intestinal barrier function and reducing inflammation and oxidative stress [J]. *Exp Ther Med*, 2017, **13**(6): 3374-3382.

[78] DiGuilio KM, Mercogliano CM, Born J, *et al.* Sieving characteristics of cytokine- and peroxide-induced epithelial barrier leak: inhibition by berberine [J]. *World J Gastrointest Pathophysiol*, 2016, **7**(2): 223-234.

[79] Li YH, Zhang M, Xiao HT, *et al.* Addition of berberine to 5-aminosalicylic acid for treatment of dextran sulfate sodium-induced chronic colitis in C57BL/6 mice [J]. *PLoS One*, 2015, **10**(12): e0144101.

[80] Li YH, Zhang M, Fu HB, *et al.* Pre-clinical toxicity of a combination of berberine and 5-aminosalicylic acid in mice [J]. *Food Chem Toxicol*, 2016, **97**: 150-158.

[81] Zhong Z, Xiong Y, Yang L. Effect of matrine on the expression of cytokines and free radicals of intestinal mucosa in rats with TNBS-induced ulcerative colitis [J]. *Chin Med Biotechnol*, 2011, **6**(4): 251-254.

[82] Tang Q, Fan H, Shou Z, *et al*. Study on protective mechanism of kushenin injection on colonic mucosa of experimental colitis rats [J]. *China J Chin Mater Med*, 2012, **37**(12): 1814-1817.

[83] Fan H, Liao Y, Tang Q, *et al.* Role of beta2-adrenoceptor-beta-arrestin2-nuclear factor-kappaB signal transduction pathway and intervention effects of oxymatrine in ulcerative colitis [J]. *Chin J Integr Med*, 2012, **18**(7): 514-521.

[84] Zhou PQ, Fan H, Hu H, *et al.* Role of DOR-beta-arrestin1-Bcl2 signal transduction pathway and intervention effects of oxymatrine in ulcerative colitis [J]. *J Huazhong Univ Sci Technolog Med Sci*, 2014, **34**(6): 815-820.

[85] Chen Q, Duan X, Fan H, *et al.* Oxymatrine protects against DSS-induced colitis *via* inhibiting the PI3K/AKT signaling pathway [J]. *Int Immunopharmacol*, 2017, **53**: 149-157.

[86] Liu Q, Zhang YJ, Yang CR, *et al.* Phenolic antioxidants from green tea produced from Camellia crassicolumna Var. multiplex [J]. *J Agric Food Chem*, 2009, **57**(2): 586-590.

[87] Pal R, Chaudhary MJ, Tiwari PC, *et al.* Protective role of theophylline and their interaction with nitric oxide (NO) in adjuvant-induced rheumatoid arthritis in rats [J]. *Int Immunopharmacol*, 2015, **29**(2): 854-862.

[88] Lal D, Manocha S, Ray A, *et al.* Comparative study of the efficacy and safety of theophylline and doxofylline in patients with bronchial asthma and chronic obstructive pulmonary disease [J]. *J Basic Clin Physiol Pharmacol*, 2015, **26**(5): 443-451.

[89] Urbanova A, Kertys M, Simekova M, *et al.* Bronchodilator and anti-inflammatory action of theophylline in a model of ovalbumin-induced allergic inflammation [J]. *Adv Exp Med Biol*, 2016, **935**: 53-62.

[90] Barnes PJ. Theophylline: new perspectives for an old drug [J]. *Am J Respir Crit Care Med*, 2003, **167**(6): 813-818.

[91] Ghasemi-Pirbaluti M, Motaghi E, Najafi A, *et al.* The effect of theophylline on acetic acid induced ulcerative colitis in rats [J]. *Biomed Pharmacother*, 2017, **90**: 153-159.

[92] Liu X, He H, Huang T, *et al.* Tanshinone IIA protects against dextran sulfate sodium- (DSS-) induced colitis in mice by modulation of neutrophil infiltration and activation [J]. *Oxid Med Cell Longev*, 2016, **2016**: 7916763.

[93] Zhang X, Wang Y, Ma Z, *et al.* Tanshinone IIA ameliorates dextran sulfate sodium-induced inflammatory bowel disease *via* the pregnane X receptor [J]. *Drug Des Devel Ther*, 2015, **9**: 6343-6362.

[94] Andujar I, Rios JL, Giner RM, *et al.* Beneficial effect of shikonin on experimental colitis induced by dextran sulfate sodium in BALB/c mice [J]. *Evid Based Complement Alternat Med*, 2012, **2012**: 271606.

[95] Andujar I, Marti-Rodrigo A, Giner RM, *et al.* Shikonin prevents early phase inflammation associated with azoxymethane/dextran sulfate sodium-induced colon cancer and induces apoptosis in human colon cancer cells [J]. *Planta Med*, 2018, **84**(9-10): 674-683.

[96] Andujar I, Rios JL, Giner RM, *et al.* Shikonin promotes intestinal wound healing *in vitro via* induction of TGF-beta release in IEC-18 cells [J]. *Eur J Pharm Sci*, 2013, **49**(4): 637- 641.

[97] Wu WJ, Yan R, Li T, *et al.* Pharmacokinetic alterations of

rhubarb anthraquinones in experimental colitis induced by dextran sulfate sodium in the rat [J]. *J Ethnopharmacol*, 2017, **198**: 600-607.

[98] Ge H, Tang H, Liang Y, *et al.* Rhein attenuates inflammation through inhibition of NF-kappaB and NALP3 inflammasome *in vivo* and *in vitro* [J]. *Drug Des Devel Ther*, 2017, **11**: 1663-1671.

[99] Luo S, Deng X, Liu Q, *et al.* Emodin ameliorates ulcerative colitis by the flagellin-TLR5 dependent pathway in mice [J]. *Int Immunopharmacol*, 2018, **59**: 269-275.

[100] Kim SJ, Kim MC, Lee BJ, *et al.* Anti-inflammatory activity of chrysophanol through the suppression of NF-kappaB/caspase-1 activation *in vitro* and *in vivo* [J]. *Molecules*, 2010, **15**(9): 6436-6451.

[101] Qiao X, Ye M, Pan DL, *et al.* Differentiation of various traditional Chinese medicines derived from animal bile and gallstone: simultaneous determination of bile acids by liquid chromatography coupled with triple quadrupole mass spectrometry [J]. *J Chromatogr A*, 2011, **1218**(1): 107-117.

[102] Arumugam S, Sreedhar R, Thandavarayan RA, *et al.* Telmisartan treatment targets inflammatory cytokines to suppress the pathogenesis of acute colitis induced by dextran sulphate sodium [J]. *Cytokine*, 2015, **74**(2): 305-312.

[103] Yang Y, He J, Suo Y, *et al.* Anti-inflammatory effect of taurocholate on TNBS-induced ulcerative colitis in mice [J]. *Biomed Pharmacother*, 2016, **81**: 424-430.

[104] Cao SS, Zimmermann EM, Chuang BM, *et al.* The unfolded protein response and chemical chaperones reduce protein misfolding and colitis in mice [J]. *Gastroenterology*, 2013, **144**(5): 989-1000.

[105] Berger E, Haller D. Structure-function analysis of the tertiary bile acid TUDCA for the resolution of endoplasmic reticulum stress in intestinal epithelial cells [J]. *Biochem Biophys Res Commun*, 2011, **409**(4): 610-615.

[106] Yang Y, He J, Suo Y, *et al.* Tauroursodeoxycholate improves 2, 4, 6-trinitrobenzenesulfonic acid-induced experimental acute ulcerative colitis in mice [J]. *Int Immunopharmacol*, 2016, **36**: 271-276.

[107] Fan H, Liu XX, Zhang LJ, *et al.* Intervention effects of QRZSLXF, a Chinese medicinal herb recipe, on the DOR-beta-arrestin1-Bcl2 signal transduction pathway in a rat model of ulcerative colitis [J]. *J Ethnopharmacol*, 2014, **154**(1): 88-97.

[108] Sugimoto S, Naganuma M, Kanai T. Indole compounds may be promising medicines for ulcerative colitis [J]. *J Gastroenterol*, 2016, **51**(9): 853-861.

[109] Gao W, Guo Y, Wang C, *et al.* Indirubin ameliorates dextran sulfate sodium-induced ulcerative colitis in mice through the inhibition of inflammation and the induction of Foxp3- expressing regulatory T cells [J]. *Acta Histochem*, 2016, **118**(6): 606-614.

[110] Gao W, Zhang L, Wang X, *et al.* The combination of indirubin and isatin attenuates dextran sodium sulfate-induced ulcerative colitis in mice [J]. *Biochem Cell Biol*, 2018, **96**(5): 636-645.

[111] Socca EA, Luiz-Ferreira A, de Faria FM, *et al.* Inhibition of tumor necrosis factor-alpha and cyclooxigenase-2 by Isatin: a molecular mechanism of protection against TNBS-induced colitis in rats [J]. *Chem Biol Interact*, 2014, **209**: 48-55.

[112] NoorShahida A, Wong TW, Choo CY. Hypoglycemic effect of quassinoids from *Brucea javanica* (L.) Merr (Simaroubaceae) seeds [J]. *J Ethnopharmacol*, 2009, **124**(3): 586-591.

[113] Zhang L, Feng X, Ma D, *et al.* Brusatol isolated from *Brucea javanica* (L.) Merr. induces apoptotic death of insect cell lines [J]. *Pestic Biochem Physiol*, 2013, **107**(1): 18-24.

[114] Turpaev K, Welsh N. Brusatol inhibits the response of cultured beta-cells to pro-inflammatory cytokines *in vitro* [J]. *Biochem Biophys Res Commun*, 2015, **460**(3): 868-872.

[115] Tang W, Xie J, Xu S, *et al.* Novel nitric oxide-releasing derivatives of brusatol as anti-inflammatory agents: design, synthesis, biological evaluation, and nitric oxide release studies [J]. *J Med Chem*, 2014, **57**(18): 7600-7612.

[116] Zhou J, Tan L, Xie J, *et al.* Characterization of brusatol self-microemulsifying drug delivery system and its therapeutic effect against dextran sodium sulfate-induced ulcerative colitis in mice [J]. *Drug Deliv*, 2017, **24**(1): 1667-1679.

[117] Pandurangan AK, Ismail S, Saadatdoust Z, *et al.* Allicin alleviates dextran sodium sulfate- (DSS-) induced ulcerative colitis in BALB/c mice [J]. *Oxid Med Cell Longev*, 2015, **2015**: 605208.

[118] Yao J, Wang JY, Liu L, *et al.* Anti-oxidant effects of resveratrol on mice with DSS-induced ulcerative colitis [J]. *Arch Med Res*, 2010, **41**(4): 288-294.

[119] Trapp V, Parmakhtiar B, Papazian V, *et al.* Anti-angiogenic effects of resveratrol mediated by decreased VEGF and increased TSP1 expression in melanoma-endothelial cell co-culture [J]. *Angiogenesis*, 2010, **13**(4): 305-315.

[120] Singh UP, Singh NP, Singh B, *et al.* Role of resveratrol- induced $CD11b^{+}Gr\text{-}1^{+}$ myeloid derived suppressor cells (MDSCs) in the reduction of $CXCR3^{+}$ T cells and amelioration of chronic colitis in $IL\text{-}10^{-/-}$ mice [J]. *Brain Behav Immun*, 2012, **26**(1): 72-82.

[121] Abdallah DM, Ismael NR. Resveratrol abrogates adhesion molecules and protects against TNBS-induced ulcerative colitis in rats [J]. *Can J Physiol Pharmacol*, 2011, **89**(11): 811-818.

[122] Yao J, Wei C, Wang JY, *et al.* Effect of resveratrol on Treg/Th17 signaling and ulcerative colitis treatment in mice [J]. *World J Gastroenterol*, 2015, **21**(21): 6572-6581.

[123] Wang Z, Jin H, Xu R, *et al.* Triptolide downregulates Rac1 and the JAK/STAT3 pathway and inhibits colitis-related colon

cancer progression [J]. *Exp Mol Med*, 2009, **41**(10): 717-727.

[124] Li CP, Li JH, He SY, *et al.* Effect of curcumin on p38MAPK expression in DSS-induced murine ulcerative colitis [J]. *Genet Mol Res*, 2015, **14**(2): 3450-3458.

[125] Ghasemi-Pirbaluti M, Motaghi E, Najafi A, *et al.* The effect of theophylline on acetic acid induced ulcerative colitis in rats [J]. *Biomed Pharmacother*, 2017, **90**: 153-159.

[126] Zhu SM, Hao WW, Tang ZP, *et al*. Effect of indirubin on cytokinesin colonic mucosa of DSS-induced colitisin mice [J]. *Chin J Integr West Med Dig*, 2011, **19**(6): 370-372.

[127] Yu FY, Huang SG, Zhang HY, *et al.* Effect of baicalin on signal transduction and activating transcription factor expression in ulcerative colitis patients [J]. *Chin J Integr Tradit Chin West*, 2015, **35**(4): 419-424.

[128] Shin HS, Satsu H, Bae MJ, *et al.* Catechol groups enable reactive oxygen species scavenging-mediated suppression of PKD-NFkappaB-IL-8 signaling pathway by chlorogenic and caffeic acids in human intestinal cells [J]. *Nutrients*, 2017, **9**(2): 165.

[129] Palócz O, Pászti-Gere E, Gálfi P, *et al*. Chlorogenic acid combined with *Lactobacillus plantarum* 2142 reduced LPS- induced intestinal inflammation and oxidative stress in IPEC-J2 Cells [J]. *PLoS ONE*, 2016, **11**(11): e0166642.

[130] Bai A, Lu N, Guo Y, *et al.* Tanshinone IIA ameliorates trinitrobenzene sulfonic acid (TNBS)-induced murine colitis [J]. *Dig Dis Sci*, 2008, **53**(2): 421-428.

Cite this article as: CAO Si-Yu, YE Sheng-Jie, WANG Wei-Wei, WANG Bing, ZHANG Tong, PU Yi-Qiong. Progress in active compounds effective on ulcerative colitis from Chinese medicines [J]. *Chin J Nat Med*, 2019, **17**(2): 81-102.

PU Yiqiong, Ph.D, Associate Professor from Shanghai University of Traditional Chinese Medicine. Dr. Pu is mainly engaged in the pharmaceutical study and new drug development from traditional Chinese medicines. She has led or participated more than 20 scientific research projects at different levels (including 10 national projects). She has published more than 40 papers, among which there are 14 SCI papers, with 4 Chinese invention patents granted.

In the scientific research, Dr. Pu's basic research focuses on the research of oral preparations of TCM, such as solid dispersions, self-microemulsions, phospholipid complexes, and colon-targeted preparations. The application focus is the pharmaceutical research of new Chinese medicines, including the research and development of new Chinese medicines, including Fufang Qiancao Tablets, Tenglong Buzhong Granules, Linggui Zhugan Granules and Banxia Xiexin Granules. It involves the optimized preparation of the active compounds extracted from Chinese medicines, the selection of the indicator components, the establishment of the detection method, and the safety study of the components.

This review mainly focused on the active components extracted from TCM, which were found to be effective to ulcerative colitis, and summarized their possible mechanisms reported in the anti-UC experimental studies, which may offer valuable reference for UC-related studies on the compounds from natural medicines, or the potential developments of anti-UC drugs.