Progress in active compounds effective on ulcerative colitis from Chinese medicines

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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


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.
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.
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., Ghrystanthemum 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].

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 Foxp3 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 (MIF), 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 japonica 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 H2O2-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. 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.

**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 reducing 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. 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, p85α), HIF-1α, p70 ribosomal protein S6 kinase (p70S6K1), and RPS6 protein in LPS-treated CCD-18Co cells in vitro. Another study showed that Mango extract suppressed the ratio of phosphorylated/total protein expression of the insulin-like growth factor-1 receptor (IGF)-1R-mTOR axis and down-regulates the mRNA expression of gene Insr, Igf1 and pik3cv.

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. 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.

**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-alsgesic 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.

**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.

**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.) Brit.

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. 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.

**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 inhibited Ral1 protein (Rho GTP-bound) activity and blocked cyclin D1 and CDK4 expression, thereby leading to G1 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 IL-17A in patients’ serum and in the colon tissues, and the tract infections and dysentery.

β levels of proinflammatory factors IL-1 and ROR-γ, and the levels of IL-17A, IL-23, ROR-γ in the colon tissues [37-38]. Moreover, an andrographolide derivative AL-1 (the andrographolide-lipoic acid conjugate), presented a significant reduction in DAI, and the activity of MPO in colonic tissues, and the overexpression of COX-2 and iNOS proteins, while in-...
loperoxidase activity in the colon tissue, and markedly reduce the content of TNF-α and IL-1β in the serum [29].

6-shogaol, which can be extracted from Zingiber officinale Ros., 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].

**Paecanol**

Paecanol, 20-hydroxy-4-methoxyacetophenone, is the main active component isolated from Cynanchum paniculatum and Aaeoina suffruticosa [62-63]. Paecanol has shown significant anti-inflammation [64-66], anti-tumor [67-68], and anti-oxidant properties [69].

Paecanol 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-xB 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 paecanol, the anti-inflammatory and anti-oxidative activities of paecanol and its metabolite were related to the blocking of the MAPK/ERK/p38 signaling pathway [70]. Moreover, paecanol 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 UC of epicatechin is mainly related to its antioxidant properties and the inhibition of inflammatory molecules via the NF-xB pathway [72].

**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 [73].

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 [74]. As for therapeutic effects in TNBS-induced UC rats, GSPs was effective on either acute or recurrent colitis.

**Alkaloids**

**Berberine**

Berberine is an isouquinoline alkaloid and mainly originates from the roots and stems of *Berberis juliana* 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 cytokinin and H2O2. 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) [75-79]. 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-xB 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-adrenoceptor (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 cassisculum [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 [93]. Moreover, tanshinone IIA improved intestinal permeability, decreases the neutrophil (PMN) infiltration and activation of intestinal mucosa by the decreased production of PMO, 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 *Lithospermum 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)-β1 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 anthraquinones to improve microbial disturbance in the intestinal tract [97].

As an important component of the rhubarb-type anthraquinones, 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 anthraquinones, 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, PGE2 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 *Zaoxys dhunnades* (Cantor) and *Agkistrodon 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-\(\alpha\), IFN-\(\gamma\) and IL-1\(\beta\) levels from colonic tissue. Oral TC significantly decreased MPO activity. These findings suggested that TC could inhibit neutrophil 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-\(\alpha\), IL-1\(\beta\), IFN-\(\gamma\) and MPO\(^{[103]}\).

**Tauroursodeoxycholate**

Tauroursodeoxycholate (TUDC), taurine-conjugated ursodeoxycholic 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 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-\(\alpha\), IL-1\(\beta\), IFN-\(\gamma\) and MPO\(^{[103]}\).

**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-\(\alpha\), interferon (IFN)-\(\gamma\), 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-\(\kappa\)B 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-\(\kappa\)B, 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-\(\kappa\)B, as well as dose-dependent amelioration of MPO and MDA levels.

**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 IxB and induced inhibition of the nuclear translocation of nuclear factor (NF)-xB-p65 in the colonic mucosa. These findings suggested that allicin exerted clinically useful anti-inflammatory effects through the suppression of the NF-\(\kappa\)B 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-inflammatory, anti-oxidation, anti-angiogenesis, and reduction of tissue damage\(^{[118-119]}\).
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<tr>
<td>Baicalin</td>
<td>Scutellaria baicalensis Georgi</td>
<td>DSS-induced male C57BL/6 mice</td>
<td>Baicalin (50, 100, or 150 mg·kg⁻¹) for 30 days</td>
<td>2% DSS in drinking water (three cycles of 5-day)</td>
<td>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 MØs Down-regulate the amount of MΦ-related cytokines, including macrophage chemotactic factor-1 Down-regulate the macrophage inflammatory protein-3a</td>
<td>Targeting oxidative stress Targeting cytokines Targeting signal transduction pathway Targeting immune cells Targeting proteins</td>
<td>[7]</td>
</tr>
<tr>
<td>Scutellaria baicalensis Georgi</td>
<td></td>
<td>TNBS-induced SD rats</td>
<td>1% (W/F) baicalin powder (purity 98.8%, 10 mL·kg⁻¹) twice a day for one week</td>
<td>5% TNBS in 50% alcohol (100 mg·kg⁻¹, 0.25 mL per rat)</td>
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</tr>
<tr>
<td>Cardamonin</td>
<td>Alpinia katsumadai Hayata</td>
<td>Acetic acid-induced male SD rats</td>
<td>Cardamonin (10 or 30 mg·kg⁻¹) for 2 weeks</td>
<td>Intrarectal instillation of 2 ml 3% acetic acid for 1 min</td>
<td>Reveal down COX-2 and caspase-3 Reduce MPO, iNOS Reduce NF-κB, TNF-α, and MDA</td>
<td>Targeting oxidative stress Targeting inflammation Targeting protein (anti-apoptosis)</td>
<td>[13]</td>
</tr>
<tr>
<td>Myricetin</td>
<td>Allium cepa L. Vitis vinifera L.</td>
<td>DSS-induced female BALB/c mice</td>
<td>Myricetin (200, 100, 50 mg·kg⁻¹) for 10 days</td>
<td>5% (W/F) DSS for 10 days</td>
<td>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</td>
<td>Targeting oxidative stress Targeting inflammation</td>
<td>[18]</td>
</tr>
<tr>
<td>Chlorogenic acid (CGA)</td>
<td>Lonicer japoraca Thunb. Lonicer japonica Thunb. Crataegus pinnatfolia Bge. Eucommia alnoides Oliv.</td>
<td>TNBS-induced male BALB/c mice</td>
<td>CGA [20 mg·kg⁻¹ (p.o., 150 μL) and i.c. (100 μL)] two times daily</td>
<td>TNBS (4 mg in 0.1 mL of 30 % ethanol in saline)</td>
<td>Reduce MPO, H₂O₂ 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</td>
<td>Targeting oxidative stress Targeting inflammation Inhibiting the active NF-κB signaling pathway Targeting intestinal microflora</td>
<td>[20]</td>
</tr>
<tr>
<td>Compound</td>
<td>Source from Chinese medicine</td>
<td>Animal and model</td>
<td>Dose (duration of treatment)</td>
<td>Dose and duration of inducer</td>
<td>Reported activity</td>
<td>Mechanism</td>
<td>Ref.</td>
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<tr>
<td>Gallic Acid</td>
<td><em>Rheum palmatum</em> L.</td>
<td>DSS-induced male BALB/c mice</td>
<td>Gallic Acid (10mg·kg⁻¹, orally) for 7 days</td>
<td>2.5% (<em>W/W</em>) DSS in the drinking water for 7 days</td>
<td>Decrease the expression of the pro-inflammatory proteins iNOS and COX-2</td>
<td>Inhibiting p65-NF-κB-mediated transcriptional activation</td>
<td>[23]</td>
</tr>
<tr>
<td></td>
<td><em>Eucalyptus robusta</em> Smith</td>
<td>DSS-induced male SD rats</td>
<td>mango extract</td>
<td>3% (<em>W/W</em>) DSS (over three cycles, with a 14 d separation)</td>
<td>Prevent the expressions of p-STAT3 and iNOS</td>
<td>Targeting oxidative stress</td>
<td>[24]</td>
</tr>
<tr>
<td></td>
<td><em>Cornus officinalis</em> Sieb. et Zucc.</td>
<td>DSS-induced male SD rats</td>
<td>mango extract</td>
<td>3% (<em>W/W</em>) DSS (over three cycles, with a 14 d separation)</td>
<td>Increase the expression of TNF-α, IL-1β, and iNOS, as well as miR-126, and decrease the Ki-67 labeling index</td>
<td>Targeting inflammation</td>
<td>[25]</td>
</tr>
<tr>
<td>3,4-Oxo-isopropylideneshikimic acid</td>
<td><em>Illicium verum</em> Hook.f.</td>
<td>TNBS-induced male SD rats</td>
<td>ISA (50, 100, 200 mg·kg⁻¹) twice daily for 14 days</td>
<td>TNBS (30 mg) dissolved in 0.9 ml of 30% (<em>V/V</em>) ethanol</td>
<td>Decrease the activity of MPO, reduce MDA level, and increase SOD and GSH-Px activities.</td>
<td>Targeting oxidative stress</td>
<td>[27]</td>
</tr>
<tr>
<td>Vanillic acid</td>
<td><em>Angelica sinensis</em> (Oliv.) Diels.</td>
<td>DSS-induced female C57BL/6 mice</td>
<td>Vanillic acid (200 mg·kg⁻¹) for 7 days</td>
<td>5% (<em>W/W</em>) DSS for seven days</td>
<td>Reduce IL-6 level and COX-2 levels, and suppress the activation of transcription factor p65.</td>
<td>Targeting cytokine</td>
<td>[28]</td>
</tr>
<tr>
<td>Ursolic Acid</td>
<td><em>Cornus officinalis</em> Sieb. et Zucc.</td>
<td>TNBS-induced C57BL/6J mice</td>
<td>Ursolic Acid (10, 20 mg·kg⁻¹) once a day for 3 days</td>
<td>2.5% (<em>W/W</em>) TNBS; 100 μL</td>
<td>Inhibit the MPO activity. Reduce the expression of pro-inflammatory cytokines TNF-α, IL-1β, IL-6. And inhibit the degradation of IRAK1 and IRAK4.</td>
<td>Targeting oxidative stress, targeting inflammation.</td>
<td>[29]</td>
</tr>
<tr>
<td>Menthol</td>
<td><em>Mentha haplocalyx</em> Briq.</td>
<td>Acetic acid-induced male Wistar rats</td>
<td>Menthol (20, 50 and 80 mg·kg⁻¹) for 3 days</td>
<td>2 ml of 3% acetic acid into the anus for 30 seconds</td>
<td>Reduce TNF-α, IL-1β, IL-6, and MPO activity.</td>
<td>Targeting inflammation</td>
<td>[32]</td>
</tr>
<tr>
<td>Triptolide</td>
<td><em>Tripterigynium wilfordii</em> Hook. f.</td>
<td>DSS-induced female BALB/c mice</td>
<td>Triptolide (0.2, 0.4, 0.60 mg·kg⁻¹ dissolved in 20% propylene glycol) for 8 days</td>
<td>2.5% and 5% DSS in the drinking water for 8 days</td>
<td>Inhibit the expression of IL-6, IL-1β, and IL-18. block the IL-6R-JAK/STAT pathway.</td>
<td>Targeting inflammation, targeting signal transduction pathway</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DMH/DSS-induced CD-1 (ICR) mice</td>
<td>Triptolide (0.1, 0.3, 1 mg·kg⁻¹·d⁻¹ dissolved with 0.9% saline) for 20 weeks</td>
<td>DMH (15 mg·kg⁻¹, injection) followed by 2% DSS in drinking water for 2 weeks</td>
<td>Block the cyclin D1 and CDK expression, inhibit the expression of collagen 1α1 transcript and collagen 1 protein.</td>
<td>Targeting inflammation, targeting signal transduction pathway</td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TNBS-induced male SD rats</td>
<td>Triptolide (45 mg·kg⁻¹ per day)</td>
<td>TNBS (60, 60, 67.5, 67.5, 75, 75 mg·kg⁻¹ per week in 45% EtOH) for 6 weeks</td>
<td>Inhibit the expression of collagen 1α1 transcript and collagen 1 protein.</td>
<td>Targeting inflammation</td>
<td>[123]</td>
</tr>
<tr>
<td>Compound</td>
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<td>Animal and model</td>
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<tr>
<td>AL-1</td>
<td>Andrographis paniculata (Burman) Nees.</td>
<td>TNBS-induced C57BL/6 mice</td>
<td>AL-1 twice a day (5, 15 and 45 mg kg⁻¹ suspended in 5% polyvinyl alcohol solution which contain 1% l, 3-Propanediol, 1% Tween 80 and 1% ethanol) twice a day</td>
<td>TNBS (100 mg kg⁻¹) in 50% ethanol solution</td>
<td>Decrease the level of inflammatory cytokines and MPO activity</td>
<td>Targeting cytokines, Targeting oxidative stress, Targeting proteins, Targeting signal transduction pathway</td>
<td>[39]</td>
</tr>
<tr>
<td>CO-X</td>
<td>Andrographis paniculata (Burman) Nees.</td>
<td>DSS-induced male BALB/c mice</td>
<td>DSS+CX-10 (50, 100, or 200 mg kg⁻¹) for 8 days</td>
<td>3.5% DSS in water</td>
<td>Decrease the level of IL-6 and TNF-α and MPO activity</td>
<td>Targeting inflammation, Targeting oxidative stress, Targeting proteins, Targeting signal transduction pathway</td>
<td>[40]</td>
</tr>
<tr>
<td>Gentiopicroside</td>
<td>Gentiana lutea L.</td>
<td>DSS-induced male ICR mice</td>
<td>Gentiopicroside (50, 100, 200 mg kg⁻¹) for 7 days</td>
<td>5% DSS for 7 days</td>
<td>Decrease the activity of MPO</td>
<td>Targeting inflammation, Targeting oxidative stress</td>
<td>[41]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Curcuma Longa L.</td>
<td>DSS-induced Kunming female mice</td>
<td>Curcumin (20, 60 mg kg⁻¹) for 10 days</td>
<td>3.5% (W/V) DSS in drinking water for 9 days</td>
<td>Alleviate visceral hyperalgesia</td>
<td>Downregulate the colonic expression and phosphorylation of IRE1</td>
<td>[49]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Curcuma Longa L.</td>
<td>DSS-induced male SD rats</td>
<td>Curcumin (15, 30, 60 mg kg⁻¹) for 10 days</td>
<td>5% DSS in drinking water for 7 consecutive days</td>
<td>Reverse increase transcription of TRPV1 and pTRPV1</td>
<td>Downregulate the colonic expression and phosphorylation of IRE1</td>
<td>[50]</td>
</tr>
<tr>
<td>6-gingerol</td>
<td>Zingiber officinalis Rosc.</td>
<td>DSS-induced male SD rats</td>
<td>6-gingerol, 8-gingerol, and 10-gingerol (30 mg kg⁻¹ once a day for 7 consecutive days)</td>
<td>5% (W/V) DSS in drinking water for 7 consecutive days</td>
<td>Lower Lcn2 level</td>
<td>Heal the inflamed mucosa, Regulating gene expression, Attenuated colitis symptoms</td>
<td>[61]</td>
</tr>
<tr>
<td>6-shogaol</td>
<td>Zingiber officinalis Rosc.</td>
<td>DSS-induced FVB/NJ mice</td>
<td>6-shogaol (15 mg kg⁻¹) for 7 days</td>
<td>2.5% (W/V) DSS in drinking water for 7 days</td>
<td>Lower the ulceration of the intestinal mucosa and the extent of neutrophil infiltration</td>
<td>Targeting inflammation, Targeting oxidative stress, Targeting immune cells</td>
<td>[53]</td>
</tr>
<tr>
<td>Paonol</td>
<td>Cynanchum paniculatum (Bge.) Kitag.</td>
<td>TNBS-induced male SD rats</td>
<td>Paonol (10 mL kg⁻¹) for 7 days</td>
<td>5% TNBS: 80 mg kg⁻¹</td>
<td>Reduce the levels of IL-17 and IL-6</td>
<td>Targeting inflammation</td>
<td>[71]</td>
</tr>
<tr>
<td>Epicatechin</td>
<td>Acacia catechu (L.f.) Willd.</td>
<td>DSS-induced male C57BL/6j mice</td>
<td>Epicatechin (100, 200, or 300 mg kg⁻¹) for seven days</td>
<td>2.3% DSS in drinking water for seven days.</td>
<td>Reduce TNF-α, IL-6, and NF-κB activation</td>
<td>Targeting inflammation, Targeting oxidative stress, Targeting immune cells</td>
<td>[73]</td>
</tr>
<tr>
<td>Compound</td>
<td>Source from Chinese medicine</td>
<td>Animal and model</td>
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</tbody>
</table>
| Proanthocyanidins | *Cynanchum paniculatum*(Bge.)Kitag. | TNBS-induced male Wistar rats | Proanthocyanidins (200 mg kg⁻¹) for 7 days | 5% TNBS: 80 mg kg⁻¹ 30 mg 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% (WT) 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  
Inhibit 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 | [76] |
|                  |                              | DSS-induced C57BL/6 male mice | Berberine hydrochloride (20 mg kg⁻¹, dissolved in distilled water) treated daily | 2% (WT) DSS in drinking water (two cycles for five days followed by 14 days of drinking water plus a third cycle only for five days) |                              |                                  | |
|                  |                              | DSS-induced C57BL/6 male mice | 5-ASA (200 mg kg⁻¹) alone and 5-ASA (200 mg kg⁻¹) plus berberine (20 mg kg⁻¹) orally once daily for 30 days | 2% (WT) DSS in drinking water (two cycles for five days followed by 14 days of drinking water plus a third cycle only for five days) |                              |                                  | |
| 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] |
| Oxymatrine        | *Sophora flavescens* Ait. | TNBS-induced male SD rats | Oxymatrine (63 mg kg⁻¹) for 15 days | TNBS (0.6 mL, 5%, dissolved in 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) | 3.0% DSS for 7 days | | [84] |
<p>|                  |                              | DSS-induced male BALB/c mice | Oxymatrine (25, 50 or 100 mg kg⁻¹) for 7 days |<br />
| | | [85] |</p>
<table>
<thead>
<tr>
<th>Compound</th>
<th>Source from Chinese medicine</th>
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<th>Dose and duration of inducer</th>
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<th>Mechanism</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theophylline</td>
<td>Viridis tea Camellia crassulacolumna</td>
<td>Acetic acid solution in adult male Wistar rats</td>
<td>Theophylline (10, 20 or 50 mg kg⁻¹) for 3 days</td>
<td>2 ml 3% acetic solution in the anus for 30 seconds</td>
<td>Reduce MPO activity, TNF-α, IL-1β and IL-6 concentrations</td>
<td>Targeting oxidative stress, targeting inflammation</td>
<td>[125]</td>
</tr>
<tr>
<td>Tanshinone Ila</td>
<td>Salvia miltiorrhiza Bge. Salvia sclarea L.</td>
<td>DSS-induced male BALB/c mice</td>
<td>Tanshinone Ila (200 mg kg⁻¹) for 7 days</td>
<td>3% DSS in drinking water</td>
<td>Alleviate inflammatory colitis possibly mediated, decrease production of MPO and ROS</td>
<td>Targeting immunocyte (neutrophils), targeting oxidative stress, targeting proteins, regulating gene expression</td>
<td>[92]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DSS-induced male BALB/c mice</td>
<td>Tanshinone Ila (5, 10, or 20 mg kg⁻¹ d⁻¹) for 10 days</td>
<td>4% (W/V) DSS in sterile, distilled water for 7 days</td>
<td>Induce CYP3A4 mRNA, protein expression was mediated by the transactivation of PXR</td>
<td>Targeting proteins, targeting inflammation, targeting oxidative stress</td>
<td>[93]</td>
</tr>
<tr>
<td>Shikonin</td>
<td>Lithospermum erythrorhizon Sieb. et Zucc. Arnebia euchroma (Royle) I.M. Johnst.</td>
<td>DSS-induced female BALB/c mice</td>
<td>Shikonin (6.25, 12.5, 25 mg kg⁻¹) on day 1 and on day 5</td>
<td>5% DSS in drinking water</td>
<td>Reduce the expression of cyclooxygenase-2, pSTAT-3, TNF-α and IL-1β, myeloperoxidase activity and the activation of NF-κB</td>
<td>Targeting proteins, targeting inflammation, targeting oxidative stress</td>
<td>[94]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AOM/DSS-induced female BALB/c mice</td>
<td>Shikonin (3.5 and 7.0 mg kg⁻¹)</td>
<td>1.5% (W/V) DSS for 7 days, followed by AOM (7.5 mg kg⁻¹, i.p.) for 3 weeks</td>
<td>Reduce the activation of NF-κB, IL-6 and NOS</td>
<td>Targeting proteins, targeting inflammation, targeting oxidative stress</td>
<td>[95]</td>
</tr>
<tr>
<td>Rhus (Rheum palmatum L. Rheum tanguticum Maxim. ex Balf. Rheum officinale Baill.)</td>
<td>Rhus (Rheum palmatum L. Rheum tanguticum Maxim. ex Balf. Rheum officinale Baill.)</td>
<td>DSS-induced male SD rats</td>
<td>Rhusbarb extract (10.0 ml kg⁻¹, with 0.5% CMC sodium solution)</td>
<td>5% (W/V) DSS in autoclaved drinking water for 7 days followed by 3% DSS for 14 days</td>
<td>Reduce the activities of β-glucosidase and microbial β-glucosidase, abrogate the enterohepatic recirculation</td>
<td>Targeting intestinal microflora</td>
<td>[97]</td>
</tr>
<tr>
<td>Rhein</td>
<td>Rheum palmatum L. Rheum tanguticum Maxim. ex Balf. Rheum officinale Baill.</td>
<td>Transgenic zebrafish line (TG)</td>
<td>Rhein (different concentrations)</td>
<td>/</td>
<td>Reduce the inflammation-associated migration of immune cells</td>
<td>Targeting migration of immune cells</td>
<td>[98]</td>
</tr>
<tr>
<td>Emodin</td>
<td>Rheum palmatum L. Rheum tanguticum Maxim. ex Balf. Rheum officinale Baill.</td>
<td>DSS-induced male C57BL/6 mice</td>
<td>Emodin (5, 10 and 20 mg kg⁻¹) for 14 days</td>
<td>3% DSS</td>
<td>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</td>
<td>Targeting immune cell, targeting proteins</td>
<td>[99]</td>
</tr>
<tr>
<td>Cryosophol</td>
<td>Rheum palmatum L. Rheum tanguticum Maxim. ex Balf. Rheum officinale Baill.</td>
<td>DSS-induced male and female C57BL/6 mice</td>
<td>Cryosophol (5 mg kg⁻¹) for 7 days</td>
<td>5% (W/V) DSS for 7 days</td>
<td>Inhibit the production of IL-6, PGE2 and the expression of COX-2 levels</td>
<td>Targeting inflammation, targeting oxidative stress</td>
<td>[100]</td>
</tr>
<tr>
<td>Taurocholate</td>
<td>Zaccoys dhunnades (Cantor) Agkisrodon acutus (Guenther)</td>
<td>TNBS-induced male Balb/c mice</td>
<td>Taurocholate (20, 40, 60 mg kg⁻¹) for 7 consecutive days</td>
<td>TNBS (1 mg dissolves in 0.1 ml of 50% ethanol)</td>
<td>Reduce the level of MPO, decrease TNF-α, IFN-γ, IL-1β tissue levels</td>
<td>Targeting inflammation, targeting oxidative stress</td>
<td>[103]</td>
</tr>
<tr>
<td>Compound</td>
<td>Source from Chinese medicine</td>
<td>Animal and model</td>
<td>Dose (duration of treatment)</td>
<td>Dose and duration of inducer</td>
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<tr>
<td>Tauroursodeoxycholate</td>
<td>Selenarcots thibetanus (G. Cuvier) Ursus arctos L.</td>
<td>TNBS-induced male Balb/c mice</td>
<td>Tauroursodeoxycholate (20, 40, 60 mg·kg⁻¹) for 7 days</td>
<td>2.5% (W/V) TNBS: 100 µL</td>
<td>Decrease levels of TNF-α, IL-1β, IFN-γ, MPO</td>
<td>Targeting inflammation Targeting oxidative stress</td>
<td>[106]</td>
</tr>
<tr>
<td>Indirubin and isatin</td>
<td>Indigofera tinctoria L.</td>
<td>DSS-induced male C57BL/6 mice</td>
<td>Indirubin/isatin (10 mg·kg⁻¹) for 7 days</td>
<td>3% DSS in drinking water for 7 days</td>
<td>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 Suppress CD4⁺ T cell infiltration Inhibit the increase of PGE₂ levels Prevent the decrease of SOD activity Increase GSH-Rd, GSH-Px activity as well as the depletion of GSH levels</td>
<td>Targeting oxidative stress Targeting inflammation Targeting immunocyte</td>
<td>[109]  [110]  [126]</td>
</tr>
<tr>
<td>Brusatol</td>
<td>Brusea javanica(L.)Merr.</td>
<td>DSS-induced male BALB/c mice</td>
<td>Brusatol (0.25, 0.5, 1 mg·kg⁻¹) once a day for seven consecutive days</td>
<td>3% (W/T) DSS for seven consecutive days</td>
<td>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</td>
<td>Targeting inflammation Targeting oxidative stress Targeting signaling pathway</td>
<td>[116]</td>
</tr>
<tr>
<td>Allicin</td>
<td>Allium sativum L.</td>
<td>DSS-induced BALB/c mice</td>
<td>Allicin (10 mg·kg⁻¹) for 7 days</td>
<td>2.5% DSS in drinking water for seven days</td>
<td>Reduce the expression/activity of CD68 and MPOReduce 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</td>
<td>Targeting oxidative stress Targeting inflammation Targeting signaling pathway</td>
<td>[117]</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Vitis vinifera L.</td>
<td>DSS-induced Specific pathogen-free BALB/c mice</td>
<td>Resveratrol (50, 100 mg·kg⁻¹) per day for 14 days</td>
<td>5% DSS for 7 days</td>
<td>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</td>
<td>Targeting inflammation Inhibition of the HIF-1α-Th17 pathway (Targeting signaling pathway)</td>
<td>[122]</td>
</tr>
</tbody>
</table>
### Table 2 Compounds from Chinese medicines effective on ulcerative colitis (in vitro/ ex vivo studies)

<table>
<thead>
<tr>
<th>Name</th>
<th>Source</th>
<th>Cell/specimen</th>
<th>Dose/concentration</th>
<th>Reported activity</th>
<th>Mechanism</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baicalin</td>
<td>Scutellaria baicalensis Georgi</td>
<td>CD4+CD29+T cells IL23R gene</td>
<td>5, 10, 20, 40 μmol·L⁻¹</td>
<td>Upregulate expression of IFN-γ, IL-4, TGF-β1 and IL-10</td>
<td>Activating transcription factor expression</td>
<td>[8]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5, 10, 20, 40 μmol·L⁻¹</td>
<td>Downregulate expression of IFN-γ, IL-5, IL-6, RORC, Foxp3 and T-bet</td>
<td>Targeting inflammation</td>
<td>[127]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decrease ratios of T-bet/GATA-3, p-STAT4/STAT4 and p-STAT5b/STAT5b</td>
<td>Targeting signal transduction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increase p-STAT6/STAT6 ratio</td>
<td>Targeting receptor</td>
<td></td>
</tr>
<tr>
<td>Cardamonin</td>
<td>Alpinia katsumadai Hayata</td>
<td>THP-1 human monocytes RAW264.7 murine macrophages</td>
<td>Cardamonin lipopolysaccharide (1 μg·mL⁻¹)</td>
<td>Inhibit NO release and iNOS expression Inhibited NF-κB DNA-binding in LPS-stimulated cells and nuclear extracts Inhibited IFN-γ-stimulated iNOS induction and GAS/GAF-DNA binding</td>
<td>Targeting transcription factor binding to DNA Targeting oxidative stress</td>
<td>[12]</td>
</tr>
<tr>
<td>Dimethyl cardamonin</td>
<td>Alpinia katsumadai Hayata</td>
<td>RAW264.7 cell</td>
<td>Dimethyl cardamonin lipopolysaccharide (1 μg·mL⁻¹)</td>
<td>Inhibit production of NO and PGE2 Inhibited TNF-α, IL-6, IL-1β, iNOS and COX-2 Decrease 1-Lipoxygenation and degradation Decrease TNF-α, IL-6 and IL-1β</td>
<td>Blocking NF-κB activation (Targeting signal transduction pathway) Targeting inflammation</td>
<td>[11]</td>
</tr>
<tr>
<td>Chlorogenic acid</td>
<td>Lonicerapajaroa‘e Thunb., Lonicerapajaroa‘e Thunb. Crataegus pinnatifida Bge. Eucommia albobovis Oliv.</td>
<td>Caco-2 cells (IPEC-J2) Intestinal epithelial cell line (IPEC-J2)</td>
<td>1 mmol·L⁻¹ and H₂O₂ for 24h 25, 50 and 100 mmol·L⁻¹</td>
<td>Inhibit H₂O₂-induced IL-8 production (via suppression of PKD- NF-κB signaling) Reducing 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</td>
<td>Targeting oxidative stress Targeting signal transduction pathway Targeting inflammation</td>
<td>[128]</td>
</tr>
<tr>
<td>Gallic acid</td>
<td>Rheum palmatum L., Eucalyptus robusta Smith Corinna officinalis Sieb et Zucc.</td>
<td>RAW264.7 macrophages Human colon CCD-18Co myofibroblastic HT-29 cell lines Human colon HT-29 cells</td>
<td>0–200 μg·mL⁻¹ for 24 h Mango extract</td>
<td>Decrease the expression of p65-NF-κB Suppress the protein expression levels of p-NF-κB, NF-κB, 3-kinase (PI3K, p58β), HIF-1α, p70 ribosomal protein S6 kinase (p70S6K1), and RPS6 protein Inhibit the IGF-1R- AKT/mTOR axis</td>
<td>Targeting signal transduction pathway Targeting protein</td>
<td>[23]</td>
</tr>
<tr>
<td>Ursolic Acid</td>
<td>Corinna officinalis Sieb et Zucc.</td>
<td>Peritoneal Macrophages</td>
<td>5, 10, 20 μmol·L⁻¹</td>
<td>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</td>
<td>Targeting inflammation Inhibition of LPS binding to TLR4 (Targeting signaling pathways) Targeting oxidative stress Targeting proteins</td>
<td>[29]</td>
</tr>
<tr>
<td>Triptolide</td>
<td>Tripterygium wilfordii Hook. f.</td>
<td>SW480 and Caco 2 cells</td>
<td>0, 10, 30, 100 or 300 mmol·L⁻¹ for 24 h, 48 h or 72 h</td>
<td>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</td>
<td>Targeting inflammation Targeting signal transduction pathway Targeting proteins</td>
<td>[123]</td>
</tr>
<tr>
<td>Andrographolide</td>
<td>Andrographis paniculata (Burm.f.) Nees.</td>
<td>Peripheral blood mononuclear cells (PBMCs)</td>
<td>10, 20 and 30 μg·mL⁻¹</td>
<td>Up-regulate expression of Th17 cells Increase expression of IL-23, IL-17A, ROR-γt and p-STAT3</td>
<td>Targeting inflammation Targeting oxidative stress Targeting gene transcription and protein</td>
<td>[37]</td>
</tr>
<tr>
<td>Name</td>
<td>Source</td>
<td>Cell/specimen</td>
<td>Dose/concentration</td>
<td>Reported activity</td>
<td>Mechanism</td>
<td>Ref</td>
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<tr>
<td>Curcumin</td>
<td><em>Curcuma Longa</em> L.</td>
<td>HEK293 cells</td>
<td>1, 3, 10 mmol·L⁻¹</td>
<td>Inhibit membrane TRPV1</td>
<td>Targeting anti-nociceptive action</td>
<td>[50]</td>
</tr>
<tr>
<td>6-shogaol</td>
<td><em>Zingiber officinale</em> Rosc.</td>
<td>264.7 macrophage and colon-26 cells</td>
<td>50, 100, 200, 500, 1000 μg·mL⁻¹</td>
<td>Decrease TNF-α, IL-6, IL-1β</td>
<td>Remain the cell viability</td>
<td>[61]</td>
</tr>
<tr>
<td>Epicatechin</td>
<td><em>Acacia catechu</em> (L.I.) Willd.</td>
<td>Murine macrophage cell line RAW264.7</td>
<td>0.1, 1, 10 mmol·L⁻¹</td>
<td>Inhibit effect on NF-κB activation, Increase SOD, GSH-Px and CAT activity</td>
<td>Targeting inflammation</td>
<td>[73]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Murine intestinal epithelial cell line IEC6</td>
<td></td>
<td>Decreased the concentration of MDA</td>
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<tr>
<td>Berberine</td>
<td><em>Coptidis rhizoma</em> (species: <em>Coptis chinensis</em> Franch, genus: Var. asperma Don, family: Ranunculaceae)</td>
<td>Lymphocyte</td>
<td>0.3, 1, 3, 10, 30, 100 mg·mL⁻¹</td>
<td>Inhibit the lymphocyte proliferation, Reduce and occlude the tight junction (TJ) protein ZO-1</td>
<td>Targeting immune cell</td>
<td>[80]</td>
</tr>
<tr>
<td>Tanshinone Ia</td>
<td><em>Salvia miltiorrhiza</em> Bge.</td>
<td>CACO-2 cell culture (an epithelial cell line derived from human colon adenocarcinoma)</td>
<td>Berberine chloride solution (2.7 mmol·L⁻¹) for 24 h</td>
<td></td>
<td>Targeting protein</td>
<td>[78]</td>
</tr>
<tr>
<td></td>
<td><em>Salvia sclarea</em> L.</td>
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<tr>
<td>Tanshinone Ia</td>
<td></td>
<td>Neutrophils</td>
<td>10 mg·mL⁻¹, dissolved in DM15</td>
<td></td>
<td>Targeting oxidative stress</td>
<td>[92]</td>
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<tr>
<td></td>
<td></td>
<td>HepG2 cells and LS174T cells</td>
<td>2.5, 5, 10, 20, or 40 μmol·L⁻¹ for HepG2 cells, 2.5, 5, 10, 20 μmol·L⁻¹ for LS174T cells</td>
<td>Inhibit the mRNA expression of inflammatory mediators iNOS, and MCP</td>
<td>Targeting inflammation</td>
<td>[130]</td>
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<td>Targeting of PAR</td>
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<tr>
<td>Shikonin</td>
<td><em>Lithospermum erythrorhizon</em> Sieb. et Zucc. <em>Arnebia euchroma</em> (Royle) I.M. Johnst.</td>
<td>Human epithelial colorectal adenocarcinoma Caco-2 cells</td>
<td>50–1.56 μmol·L⁻¹</td>
<td>Induce the proapoptotic Bcl-2</td>
<td>Targeting gene expression</td>
<td>[95]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The intestinal epithelial cell line (IEC)-18</td>
<td>1.0–0.1 μmol·L⁻¹</td>
<td>Inhibit the antiapoptotic caspase 3</td>
<td>Targeting inflammation</td>
<td>[96]</td>
</tr>
<tr>
<td>Rhein</td>
<td><em>Rheum palmatum</em> L., <em>Rheum tanguticum</em> Maxim. ex Balf. <em>Rheum officinale</em> Baill.</td>
<td>RAW264.7 mouse macrophage cells</td>
<td>1, 5, and 20 μmol·L⁻¹</td>
<td>Decrease IL-6, IL-1β, and TNF-α</td>
<td>Targeting inflammation</td>
<td>[98]</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Reduce the phosphorylation levels of NF-κB p65 and the suppression of NLRP3 expression</td>
<td>Targeting oxidative stress</td>
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<td>Reduce NO production and suppress the protein expressions of iNOS and COX-2</td>
<td>Targeting protein</td>
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<td>Up-regulate the expression of antibody 1xβ</td>
<td>Targeting inflammation</td>
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<td>Decrease the release of IL-8</td>
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<tr>
<td>Cryophanol</td>
<td><em>Rheum palmatum</em> L., <em>Rheum tanguticum</em> Maxim. ex Balf. <em>Rheum officinale</em> Baill.</td>
<td>TG-elicited macrophages</td>
<td>2, 20 μmol·L⁻¹</td>
<td>Inhibit the production of IL-6, PGE2 and the expression of COX2 levels</td>
<td>Targeting inflammation</td>
<td>[100]</td>
</tr>
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<td></td>
<td>Decrease NF-κB (p65) and caspase-1 activation</td>
<td>Targeting oxidative stress</td>
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<td></td>
<td></td>
<td></td>
<td>Targeting protein</td>
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</table>
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-xB, NO), reducing the activity of MPO, MDA, IFN-γ, and iNOS. In addition 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 druggability. 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**


[95] 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.


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.