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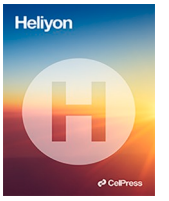

Review article

Traditional Chinese medicine treats ulcerative colitis by regulating gut microbiota, signaling pathway and cytokine: Future novel method option for pharmacotherapy

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ABSTRACT

Background: Ulcerative colitis (UC) is a chronic non-specific inflammatory disease with intestinal tract as the main site. The pathogenic of UC has not yet been clarified, and multiple mechanisms can lead to the pathogenesis of UC. Traditional Chinese medicine (TCM) offers an opportunity for UC treatment. TCM has become the preferred treatment for UC with characteristics of multiple targets, multiple pathways and high safety. This review attempted to summarize the characteristics of TCM (compound prescriptions, single Chinese herbs, and active ingredients) for UC treatment and discussed their pathogenesis based on analyzing the UC-related gut microbiota, signaling pathway and cytokine. In order to provide more systematic and diverse reference for TCM in the prevention and treatment of UC, and provide theoretical reference for clinical treatment of UC.

Materials and methods: The information was acquired from different databases, including Web of Science, PubMed, CNKI, Wanfang, and VIP databases. We then focused on the recent research progress in UC treatment by TCM. Finally, the deficiencies and future perspectives are proposed.

Results: Modern pharmacological studies have shown that the compound prescriptions (strengthening spleen, clearing heat and removing dampness, clearing heat and removing toxin), single Chinese herbs (replenishing Qi, clearing heat, tonifying blood, etc.), and active ingredients (alkaloids, polysaccharides, flavonoids, polyphenols, terpenes, etc.) have an efficiency in UC treatment by regulating gut microbiota, signaling pathway and cytokine.

Conclusions: TCM can achieve its purpose of UC prevention and treatment by acting in multiple ways, and TCM deserves further research and development in this field.

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1. Introduction

Ulcerative colitis (UC) is a lifelong inflammatory bowel disease with lesions mainly in the rectum, colonic mucosa and submucosa [1]. The main clinical manifestations of UC include mucos purulent stools, frequent defecation, tenesmus, weight loss, etc [2]. UC is usually accompanied eosinophilic esophagitis, gastroduodenitis, inflammation of upper gastrointestinal tract and other diseases, and in severe cases, complications such as colon cancer [3]. The global incidence rate of UC shows an increasing trend year by year, the incidence of UC in China is about 0.0116%, and the incidence in Europe and America is significantly higher than that in Asia [4]. At present, UC is mainly treated by surgical intervention, microbial agents and biological fecal microbiota transplantation [5]. Therapeutic drugs, mainly represented by biological drugs, are reported to be not only expensive but also have more side effects, including but not limited to liver disease, cancer, lupus-like syndrome, heart disease, central nervous system disorders, etc [6].

List of abbreviations

Akk bacteria	Akkermansia muciniphila
APS	Astragalus polysaccharide
BBR	Berberine
COP	Coptisine
DSS	Dextran sodium sulfate
FAP	Fructus arctii polysaccharide
GPS	Glycyrrhiza polysaccharide
GTP	Green tea polyphenol
IL	Interleukin
JAK	Janus kinase
LB	Licoflavone B
MAPK	Mitogen-activated protein kinase
MPO	Myeloperoxidase
MyD88	Myeloid differ-entiation primary response gene 88
NF-κB	Nuclear factor kappa-B
OMT	Oxymatrine
PI3K	Phosphatidyli-nositol 3-kinase
POP	Portulaca oleracea polysaccharide
RSV	Resveratrol
STAT	Signal transducer and activator of transcription
TCM	Traditional Chinese medicine
TLRs	Toll-like receptors
TNF	Tumor necrosis factor
UC	Ulcerative colitis

The structure and quantity of gut microbiota are extremely important for intestinal health, which is an important cytokine affecting or even determining the onset of UC. As clinical research subjects, they are often classified as beneficial, neutral and pathogenic bacteria according to their physiological functions. Signaling pathways and cytokines are both considerations in measuring the extent of UC development and important entry points for treatment [7]. The signaling pathways associated with UC mainly include mitogen-activated protein kinase (MAPK), nuclear factor kappa-B (NF-κB), Janus Kinase (JAK)/signal transducer and activator of transcription (STAT), Toll-like receptors (TLRs)/myeloid differ-entiation primary response gene 88 (MyD88), phosphatidyli-nositol 3-kinase (PI3K)/protein kinase B [8], and regulation of these pathways can play therapeutic effect on UC. In addition, signaling pathways such as the interleukin-13 (IL-13)/suppression of tumorigenicity 2 axis and Notch also have an effect on UC. The cytokines associated with UC include various interleukins, tumor necrosis factor (TNF), growth factors, etc., which can be broadly classified into pro-inflammatory and anti-inflammatory cytokines. The pro-inflammatory cytokines mainly include IL-1, IL-6, IL-8, IL-12, IL-15, IL-17, IL-23, TNF-α, etc., and the anti-inflammatory cytokines mainly include IL-2, IL-4, IL-10, IL-13, TGF-β, etc [9]. There is also a link between signaling pathways and cytokines, for example, JAK/STAT signaling pathways may affect cytokines such as IL-6, IL-12, IL-21, IL-23, TNF-α, and TLRs/My D88 signaling pathways may affect IL-2, IL-4, IL-5, IL-13, and other cytokines. The gut microbiota can influence the intestinal immune function, and its normal function also determines whether the gut microbiota can maintian balance. Cytokines and signaling pathways also act directly or indirectly on the gut microbiota as targets for the treatment of UC [10]. Different signal pathways and cytokines have diverse effects on gut microbiota. Most of them balance gut microbiota from the perspective of anti-inflammation and anti-oxidation. Reasonable regulation of related signaling pathways and cytokines can increase the number of beneficial bacteria and decrease the number of pathogenic bacteria, thereby restoring the physiological balance of gut microbiota.

2. Research progress in the treatment of UC with traditional Chinese medicine (TCM)

UC has not been fully explored, but also there is no very effective and safe treatment measures for UC. In contrast, although there is no disease name directly corresponding to UC, modern TCM scholars classify UC into the category of spleen and stomach diseases such as “diarrhea", “dysentery", and “fulminant dysentery" according to its clinical manifestations [11]. According to TCM, the location of UC is mainly in the intestine, and the large and small intestine division of the secretion and conduction, while have close relationship with the spleen, kidney and liver. Generally, patients have a deficient spleen, and if they feel actual evil such as damp-heat, epidemic and poisonous Qi or internal injury due to diet or emotion [12], which induces a loss of spleen transportation, evil fights with Qi and blood, and the intestinal lipid membrane and blood channels are injured. According to different etiologies, inducements and clinical manifestations, the TCM syndrome types of UC can be divided into six types: dampness stagnancy due to spleen deficiency syndrome, stagnation of liver Qi and spleen deficiency syndrome, yang deficiency of spleen and kidney syndrome, large intestine dampness-heat syndrome, heat-toxin exuberance syndrome, and cold-heat complex syndrome. The treatment principles and methods include strengthening spleen, clearing heat, removing dampness, removing toxin, and mildly regulating cold and heat, and should be combined with syndromes, paying attention to replenishing Qi, drying dampness, nourishing liver, and warming the kidney. UC is generally divided into active phase and remission phase. The active phase is dominated by branch excess, while the remission phase is dominated by root deficiency, so attention should be paid to distinguish between deficiency and reality during treatment. TCM treatment of UC has the advantages of precise efficacy, effective maintenance, decreased recurrence rate, and limited side effects [13], etc., and has achieved significant clinical effects whether used alone or in combination with modern medical technology (Fig. 1).

Regarding the treatment of diarrhea, during the Pre-Qin and Han dynasties, the “*Inner Canon of Yellow Emperor*" (Huangdi Neijing) provided a relatively complete explanation of the etiology and pathogenesis of diarrhea, and established the method of replenishing deficiency and purging excess. The "*Shennong's Herbal Classic herbal*" (Shennong Bencao Jing) listed many medicines for the treatment of diarrhea. The “*Treatise on Cold Damage Disorders*" (Shanghan Lun) grouped dysentery and diarrhea together as “xia li", emphasizing individualized treatment based on pattern identification from the Six Channels, which can be summarized into nine methods including resolving both the exterior and interior, promoting the circulation of qi to relieve stagnation, and regulating the liver and spleen. In the Jin, Tang, Song, Yuan dynasties, the “*Pulse Classic*" (Maijing), “*A-B Classic of Acupuncture and Moxibustion*" (Zhenjiu Jiayi Jing),

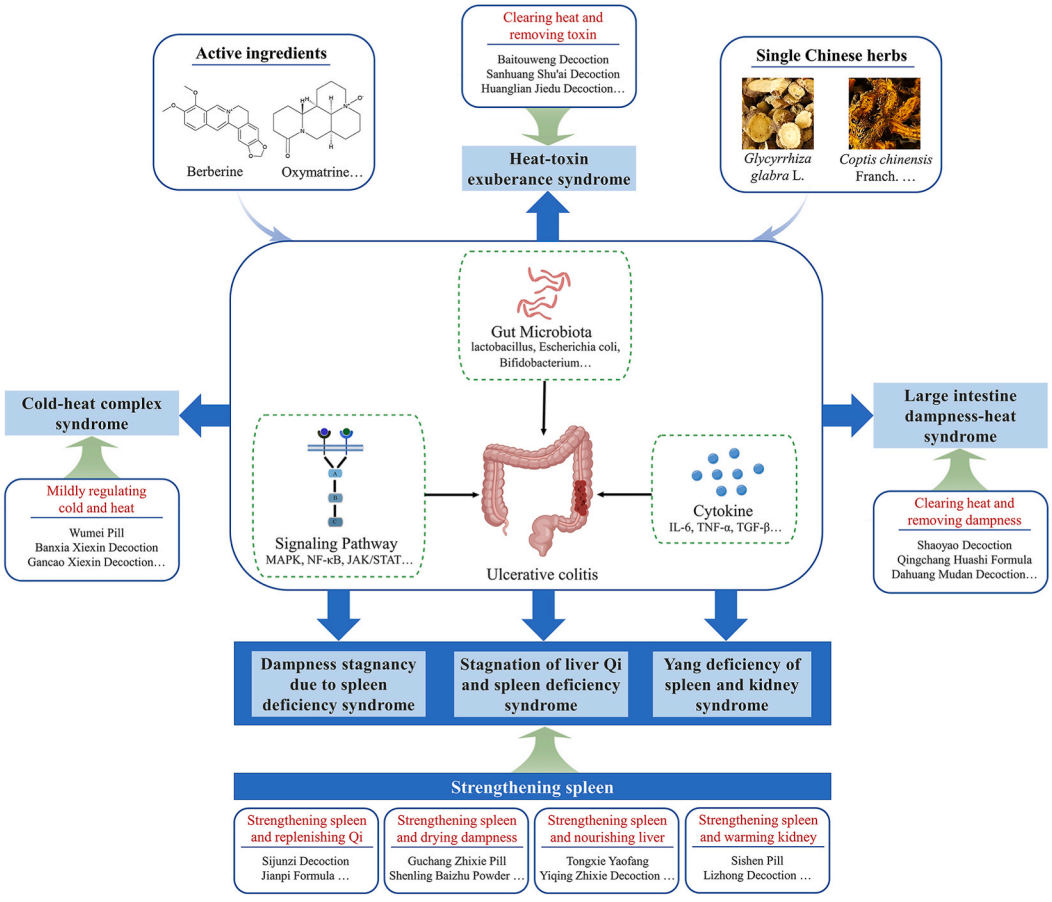

Fig. 1. Types of TCM for UC treatment together with the mechanism(s) involved.

"*Thousand Golden Prescriptions*" (Qianjin Fang), and *"Arcane Essentials from the Imperial Library"* (Wai Tai Mi Yao) further expanded the treatment methods for diarrhea from the perspective of pulse diagnosis, acupuncture, and herbal medicine. During the Ming dynasty, Yan Yong edited and integrated numerous ancient and modern prescriptions, including those for treating diarrhea. Meanwhile, each physician had their own understanding and treatment principles regarding the etiology, pathology, and treatment of diarrhea. In the end, Li Zhongzi summarized previous clinical experience into "Nine Methods for Treating Diarrhea", providing guidance for future generations in treating this condition.

Regarding the treatment of dysentery, during the Pre-Qin and Han dynasties, there was no unified name for dysentery. The "*Plain Question*" (Su Wen) first proposed the term "chang li" to describe the disease. The "*Treatise on Febrile and Miscellaneous Diseases"* (Shanghan Zabing Lun) was the first to include prescriptions for treating dysentery, such as Taohua Decoction, Baitouweng Decoction, and Wumei Pill. During the Wei, Jin, Southern and Northern Dynasties, Ge Hong used the character "li" for the first time in the "*Handbook of Prescriptions for Emergencies*" (Zhouhou Beiji Fang), and physicians during this period also deepened their understanding of the importance of Wumei Pill in treating dysentery. In the Sui and Tang dynasties, the "*General Treatise on Causes and Manifestations of All Diseases*" began to classify the etiology of dysentery into internal and external causes. Influenced by works like "*Thousand Golden Prescriptions*" (Qianjin Fang) and *"Arcane Essentials from the Imperial Library"* (Wai Tai Mi Yao), the importance of Wumei Pill in treating dysentery was further established, while *Coptis chinensis* Franch. and Zingiber officinale Roscoe. became commonly used herbs for treating dysentery. During the Song Dynasty, research on the etiology and pathogenesis of dysentery further developed, and prescriptions for treating dysentery focused on warming the middle burner and strengthening the spleen. During the Jin and Yuan dynasties, the Four Great Masters of the Jin and Yuan Dynasties represented a qualitative leap in the understanding of dysentery, entering a new stage. Ming dynasty physicians pursued innovation in the treatment of dysentery, while Qing dynasty physicians tended to organize and summarize the treatment methods for dysentery and construct relevant theoretical frameworks [14].

The pathological changes in intestinal gut microbiota and cytokines in UC vary depending on different patterns. For instance, in the large intestine dampness-heat syndrome of UC, the pathological changes in intestinal microbiota are characterized by a significant increase in streptococcus, proteobacteria, and verrucomicrobia, and a decrease in neisseria, prevotella, bacteroidetes, and firmicutes. In contrast, in the yang deficiency of spleen and kidney syndrome of UC, the pathological changes in intestinal gut microbiota are characterized by a decrease in bifidobacteria and lactobacillus, and an increase in escherichia coli and enterococcus [15]. Furthermore,

Table 1
Composition and dosage of compound TCM prescriptions based on strengthening spleen for the UC treatment.

Drugs	Composition	
Strengthening spleen		
strengthening spleen and replenishing Qi	Sijunzi Decoction	*Panax ginseng* C.A.Mey., *Poria cocos* (Schw.)Wolf, *Atractylodes macrocephala* Koidz., *Glycyrrhiza glabra* L.
	Jianpi Formula	*Codonopsis pilosula* (Franch.) Nannf., *Atractylodes macrocephala* Koidz., *Poria cocos* (Schw.)Wolf, *Glycyrrhiza glabra* L.
	Jiawei Chaishao Liujun Granule	*Bupleurum chinense* DC., *Paeonia lactiflora* Pall., *Citrus reticulata* Blanco, *Pinellia ternata* (Thunb.) Makino, *Pseudostellaria heterophylla* (Miq.) Pax, *Poria cocos* (Schw.)Wolf, *Atractylodes macrocephala* Koidz., *Glycyrrhiza glabra* L., *Hedyotis diffusa* Willd., *Panax notoginseng* (Burkill) F·H.Chen, *Pteris multifida* Poir
	Guchang Zhixie Pill	*Prunus mume* (Siebold) Siebold & Zucc., *Coptis chinensis* Franch., *Zingiber officinale* Roscoe, *Papaveris* Pericarpium, *Corydalis yanhusuo* (Y·H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su & C·Y.Wu, *Aucklandia lappa* DC.
	Changjianping Formula	*Coix lacryma-jobi* L., *Codonopsis pilosula* (Franch.) Nannf., *Atractylodes macrocephala* Koidz., *Poria cocos* (Schw.)Wolf, *Dolichos lablab* L., *Citrus reticulata* Blanco, *Lindera aggregata* (Sims) Kosterm., *Amomum villosum* Lour, *Dioscorea opposita* Thunb., *Platycodon grandiflorus* (Jacq.) A.DC., *Nelumbo nucifera* Gaertn., *Glycyrrhiza glabra* L.
strengthening spleen and drying dampness	Lichang Decoction	*Panax ginseng* C.A.Mey., *Atractylodes macrocephala* Koidz., *Poria cocos* (Schw.)Wolf, *Prunus mume* (Siebold) Siebold & Zucc., *Halloysitum* Rubrum, *Ailanthus altissima* (Mill.) Swingle, *Coix lacryma-jobi* L., *Radix Cynanchi* Paniculati, *Panax notoginseng* (Burkill) F·H.Chen, *Typha angustifolia* L., *Bletilla striata* (Thunb.) Rchb.f., *Sophora japonica* L., *Glycyrrhiza glabra* L.
	Anchang Yuyang Decoction	*Hedysarum Multijugum* Maxim., *Patrinia scabiosifolia* Link, *Coptis chinensis* Franch., *Atractylodes macrocephala* Koidz., *Coix lacryma-jobi* L., *Scutellaria baicalensis* Georgi, *Bletilla striata* (Thunb.) Rchb.f., *Aucklandia lappa* DC., *Areca catechu* L., *Paeonia lactiflora* Pall., *Angelica sinensis* (Oliv.) Diels, *Saposhnikovia divaricata* (Turcz. ex Ledeb.) Schischk., *Sanguisorba officinalis* L., *Glycyrrhiza glabra* L.
	Shenling Baizhu Powder	*Panax ginseng* C.A.Mey., *Poria cocos* (Schw.)Wolf, *Atractylodes macrocephala* Koidz., *Dioscorea opposita* Thunb., *Dolichos lablab* L., *Nelumbo nucifera* Gaertn., *Coix lacryma-jobi* L., *Amomum villosum* Lour, *Platycodon grandiflorus* (Jacq.) A.DC., *Glycyrrhiza glabra* L.
strengthening spleen and nourishing liver	Tongxie Yaofang	*Saposhnikovia divaricata* (Turcz. ex Ledeb.) Schischk., *Citrus reticulata* Blanco, *Paeonia lactiflora* Pall., *Atractylodes macrocephala* Koidz.
	Yiqing Zhixie Decoction	*Codonopsis pilosula* (Franch.) Nannf., *Poria cocos* (Schw.)Wolf, *Atractylodes macrocephala* Koidz., *Magnolia officinalis* Rehder & E.H.Wilson, *Coix lacryma-jobi* L., *Aurantii* Fructus, *Bupleurum chinense* DC., *Curcuma wenyujin* Y·H.Chen & C.Ling
strengthening spleen and warming kidney	Sishen Pill	*Myristica fragrans* Houtt., *Psoralea corylifolia* L., *Schisandra chinensis* (Turcz.) Baill., *Tetradium ruticarpum* (A.Juss.) T.G.Hartley
	Ershen Pill	*Psoralea corylifolia* L., *Myristica fragrans* Houtt.
	Lizhong Decoction	*Panax ginseng* C.A.Mey., *Zingiber officinale* Roscoe, *Atractylodes macrocephala* Koidz., *Glycyrrhiza glabra* L.

the levels of IL-1β in the heat-toxin exuberance syndrome of UC are higher than those in the stagnation of liver Qi and spleen deficiency syndrome of UC. The levels of IL-6 and IL-8 in the heat-toxin exuberance syndrome of UC are significantly higher than those in the stagnation of liver Qi and spleen deficiency syndrome of UC and the yang deficiency of spleen and kidney syndrome of UC. The level of IL-8 in the large intestine dampness-heat syndrome of UC is significantly higher than that in the stagnation of liver Qi and spleen deficiency syndrome of UC [16]. Therefore, targeted treatment can be applied more effectively based on the different pathological characteristics of each pattern of UC.

From the perspective of TCM, selecting corresponding compound prescriptions and single Chinese herbs according to different patterns of UC can maximize the advantages of TCM treatment. The effective ingredients of frequently used single Chinese herbs can be identified from a modern medical perspective to further verify the effectiveness of TCM in treating UC. For example, for the large intestine dampness-heat syndrome of UC, the main treatment method should be clearing heat and removing dampness, as well as astringing and stopping diarrhea, represented by compound prescriptions such as Shaoyao Decoction and Huangqin Decoction, which include *Coptis chinensis* Franch. whose main effective active ingredients is berberine (BBR). For the dampness stagnancy due to spleen deficiency syndrome of UC, the main treatment method should be strengthening spleen and drying dampness, represented by compound prescriptions such as Lichang Decoction, and Anchang Yuyang Decoction, which often include single Chinese herbs such as *Portulaca oleracea* L., *Hedysarum Multijugum* Maxim., and *Coptis chinensis* Franch., whose active ingredients ingredients mainly include amaranth polysaccharide, astragalus polysaccharide (APS), calycosin, and ginsenoside Rg1. For the yang deficiency of spleen and kidney syndrome of UC, the main treatment method should be strengthening spleen and warming kidney, represented by compound prescriptions such as Sishen Pill and Lizhong Decoction, with commonly used single Chinese herbs including *Tetradium ruticarpum* (A. Juss.) T.G.Hartley. and *Panax ginseng* C.A.Mey. whose effective active ingredients mainly include evodiamine and ginsenoside Rg1.

3. Compound TCM prescriptions for the UC treatment

Compound TCM prescriptions, as the main form of clinical treatment in TCM today, has a long history of flexible combinations, and is a cultural treasure of TCM that can combine the principles of compounding, clinical experience and rational innovation [17]. TCM broadly classifies UC into six types of evidence: dampness stagnancy due to spleen deficiency syndrome, stagnation of liver Qi and spleen deficiency syndrome, yang deficiency of spleen and kidney syndrome, large intestine dampness-heat syndrome, heat-toxin exuberance syndrome and cold-heat complex syndrome. The commonly used herbal compound prescriptions for different symptoms include Sijunzi Decoction, Shenling Baizhu Powder, Tongxie Yaofang, Sishen Pill, Ershen Pill, Shaoyao Decoction, Baitouweng Decoction and Wumei Pill [18].

3.1. Compound TCM prescriptions based on strengthening spleen

For UC with dampness stagnancy due to spleen deficiency syndrome, stagnation of liver Qi and spleen deficiency syndrome and Yang deficiency of spleen and kidney syndrome, the treatment should focus on strengthening the spleen. Their composition is summarized in Table 1.

3.1.1. Compound TCM prescriptions based on strengthening spleen and replenishing Qi

It was experimentally demonstrated that the number of beneficial bacteria such as bifidobacterium, lactobacillus, and pathogenic bacteria such as escherichia coli in the intestine decreased and the colonization resistance Akkermansia muciniphila (Akk bacteria) coli rose close to normal levels in the intestine of dextran sodium sulfate (DSS)-induced UC model after gavage with Sijunzi Decoction, indicating that the balance of gut microbiota tended to be normal. Sijunzi Decoction remarkedly suppressed the abundance of phylum Proteobacteria and genus Escherichia-Shigella in DSS-induced colitis, confirming that Sijunzi Decoction exerts anti-inflammatory activities in a gut microbiota-dependent manner and thus alleviates UC [19]. In addition, Sijunzi Decoction reduced the levels of pro-inflammatory cytokines, such as IL-1 β, TNF-α, and IL-6, and increased the levels of anti-inflammatory cytokines, such as IL-10, IL-37, and TGF-β, in the peripheral serum of UC model rats [20]. Pan Danfeng used Jianpi Formula combined with enteral nutrition treatment, gut microbiota diversity increased, relative abundance of lactobacillus and bifidobacteriaceae increased, and relative abundance of enterobacteriaceae and bacteroideae of enterobacteriaceae decreased [21]. Jiawei Chaishao Liujun Granule played a role in the treatment of UC by increasing the lactobacillus and bifidobacterium, decreasing the pathogenic bacteria enterococcus and escherichia coli, and the MEK-ERK-MLCK signalling pathway was inhibited, while the serum levels of TNF-α and IFN-γ decreased, the levels of IL-10 and IL-1β increased [22,23].

3.1.2. Compound TCM prescriptions based on strengthening spleen and drying dampness

Strengthening spleen and drying dampness is a treatment for UC due to spleen deficiency and dampness stagnancy. It is reported that oral Guchang Zhixie Pill combined with rehabilitation new liquid enema to treat UC can effectively improve gut microbiota, as shown by the number of anaerobic bacillus and bacteroideae increased significantly, while the number of eEscherichia coli and pseudomonas aeruginosa decreased significantly, while the inhibition to inflammatory factors IL-6, IL-17 and TNF-α was obvious [24]. For the treatment of UC due to spleen deficiency and dampness accumulation, Changjianping Formula is also a superior choice to the traditional western drug mesalazine [25].

Lichang Decoction has been shown to have beneficial effects on UC by strengthening spleen and removing dampness, as well as invigorating blood and regenerating muscle [26]. This decoction was found to significantly reduce the levels of p38 protein, a key protein in the p38-MAPK signaling pathway, in UC rat models, leading to an increase in bifidobacteriaceae and peptococcus, and a

decrease in saccharomycete [27]. Additionally, Lichang Decoction decreased levels of pro-inflammatory cytokines TNF-α and IFN-γ, while increasing levels of anti-inflammatory cytokines IL-10 and IL-1β. Compared to sulfasalazine, Lichang Decoction was found to be a more preferable treatment option for UC. When combined with another drug, bifidobacteriaceae and lactobacillus levels increased, while escherichia coli and fusobacterium nucleatum levels decreased. Levels of IL-17, IL-21, and TGF-3 also decreased, and IL-10 levels increased, suggesting that this combination is more suitable for UC patients with mild to moderate dampness stagnancy due to spleen deficiency syndrome [28]. Clinical studies have shown that the clinical efficacy of Lichang Decoction combined with Kuiyangling enemas in the treatment of UC is superior to that of mesalazine alone [29].

Anchang Yuyang Decoction, administered at various concentrations in DSS-induced colitis by gavage, has been found to increase intestinal mucosa repair factor expression and restore gut microbiota diversity [30]. The use of Anchang Yuyang Decoction in combination with mesalazine may have a better therapeutic effect by increasing the diversity and abundance of gut microbiota, increasing the abundance of beneficial bacteria such as blautia and faecalibacterium, decreasing the abundance of pathogenic bacteria such as escherichia-shigella, and affecting the signaling pathway mainly through NF-κB [31].

As one of the classic prescriptions for strengthening spleen and drying dampness, Shenling Baizhu Powder has beneficial effects on the prevention and treatment of UC. Shenling Baizhu Powder could regulate the balance of gut microbiota by increasing prevotella and oscillospira and decreasing desulfovibrio and bilophila, thus promoting the recovery of UC disease [32]. In DSS-induced colitis, Shenling Baizhu Powder resulted in downregulation of TNF-α, IL-1β, and IL-6 levels, and significant upregulation of IL-4 and IL-10 levels [33]. Clinical studies showed that the combination of this formula with mesalamine is more effective than mesalamine alone in maintaining clinical and endoscopic remission in patients with UC [34].

3.1.3. Compound TCM prescriptions based on strengthening spleen and nourishing liver

Strengthening spleen and nourishing liver is an effective treatment for the stagnation of liver Qi and spleen deficiency syndrome type of UC. Tongxie Yaofang is a representative formula for this type of syndrome, which can tonify the spleen and soften the liver, dispel dampness, and stop diarrhea. Combining Mesalazine with Tongxie Yaofang has been shown to be more effective in improving beneficial bacteria such as lactobacillus and bifidobacteriaceae, while reducing the number of escherichia coli [35]. Yiqing Zhixie Decoction has also been found to be superior to mesalazine alone in inhibiting inflammatory factors, increasing the level of beneficial bacteria, reducing the number of pathogenic bacteria, and lowering the incidence of adverse effects [36]. After taking Yiqing Zhixie Decoction for 4 weeks in the morning and evening, the number of bifidobacteriaceae and lactobacillus in the gut microbiota of UC patients significantly increased, while the number of enterococcus faecalis and escherichia coli decreased. Additionally, the levels of inflammatory factors such as IL-6, IL-8, and TNF-α were inhibited, and the rate of adverse effects was substantially lower than that of mesalazine alone.

3.1.4. Compound TCM prescriptions based on strengthening spleen and warming kidney

Strengthening spleen and warming kidney is an effective treatment for the Yang deficiency of spleen and kidney syndrome type of UC. Sishen Pill is a formula that can warm the kidneys and warm the spleen, consolidate the intestines, and stop diarrhea. It is an important formula for treating five-shift diarrhea or prolonged diarrhea caused by the failure of the vital gate fire and fire not warming the earth. In a study by Jiang Qingqing [37], it was found that the mechanism of action of Sishen Pill volatile oil in the treatment of UC

Table 2
Composition and dosage of compound TCM prescriptions based on clearing heat and removing dampness, clearing heat and removing toxin, and clearing heat and removing toxin for the UC treatment.

Drugs	Composition
Clearing heat and removing dampness	
Shaoyao Decoction	*Paeonia lactiflora* Pall., *Scutellaria baicalensis* Georgi, *Coptis chinensis* Franch., *Rheum officinale* Baill., *Angelica sinensis* (Oliv.) Diels, *Areca catechu* L., *Aucklandia lappa* DC., *Cinnamomum cassia* (L.) D. Don, *Glycyrrhiza glabra* L.
Huangqin Decoction	*Scutellaria baicalensis* Georgi, *Paeonia lactiflora* Pall., *Glycyrrhiza glabra* L., *Ziziphus jujuba* Mill.
Qingchang Huashi Formula	*Scutellaria baicalensis* Georgi, *Coptis chinensis* Franch., *Aucklandia lappa* DC., *Angelica sinensis* (Oliv.) Diels, *Sanguisorba officinalis* L., *Paeonia lactiflora* Pall., *Angelica dahurica* (Hoffm.) Benth. & Hook.f. ex Franch. & Sav., *Glycyrrhiza glabra* L.
Dahuang Mudan Decoction	*Rheum officinale* Baill., *Paeonia* × *suffruticosa* Andrews, *Natrii* Sulfas, *Prunus persica* (L.) Batsch, Benincasae Semen
Clearing heat and removing toxin	
Baitouweng Decoction	*Pulsatilla chinensis* (Bunge) Regel, *Phellodendron chinense* C·K.Schneid. , *Coptis chinensis* Franch., *Fraxinus chinensis* Roxb.
Jiawei Baitouweng Decoction	*Fraxinus chinensis* Roxb., *Phellodendron chinense* C·K.Schneid., *Pulsatilla chinensis* (Bunge) Regel, *Coptis chinensis* Franch., *Agrimonia pilosa* Ledeb., *Panax notoginseng* (Burkill) F·H.Chen, *Arnebia euchroma* (Royle) I.M.Johnst., *Bletilla striata* (Thunb.) Rchb.f.
Sanhuang Shu'ai Decoction	*Scutellaria baicalensis* Georgi, *Coptis chinensis* Franch., *Phellodendron chinense* C·K.Schneid. , *Artemisia argyi* Levl. et Van
Huanglian Jiedu Decoction	*Scutellaria baicalensis* Georgi, *Coptis chinensis* Franch., *Phellodendron chinense* C·K.Schneid. , *Gardenia jasminoides* J.Ellis
Mildly regulating cold and heat	
Wumei Pill	*Prunus mume* (Siebold) Siebold & Zucc., *Asarum heterotropoides* F.Schmidt, Zingiber officinale Roscoe, *Coptis chinensis* Franch., *Angelica sinensis* (Oliv.) Diels, *Aconitum carmichaelii* Debeaux (Fuzi), *Zanthoxylum bungeanum* Maxim., *Cinnamomum cassia* (L.) J.Presl, *Panax ginseng* C.A.Mey., *Phellodendron chinense* C·K.Schneid., Mel
Banxia Xiexin Decoction	*Pinellia ternata* (Thunb.) Makino, *Zingiber officinale* Roscoe, *Coptis chinensis* Franch., *Scutellaria baicalensis* Georgi, *Panax ginseng* C.A. Mey., *Glycyrrhiza glabra* L., *Ziziphus jujuba* Mill.

is through the intervention of TLR/MyD88 signaling pathway, which regulates Tfh cell differentiation and affects gut microbiota. Sishen Pill volatile oil has also shown the best inhibitory effect on inflammatory factors compared with Ershen Pill volatile oil, *Schisandra chinensis* (Turcz.) Baill. volatile oil, and mesalazine. The effects of Sishen Pill on gut microbiota included inhibition of the abundance of conditionally pathogenic bacteria such as bacteroidales and staphylococcus and an increase in the abundance of potentially beneficial bacteria such as lachnospiraceae, which help reduce inflammation and protect the intestinal barrier. Combining Sishen Pill with Shenling Baizhu Powder for the treatment of UC in Yang deficiency of spleen and kidney syndrome has been found to be more effective than using either formula alone [38]. Compared to Ershen Pill composed of unconstituted *Myristica fragrans* Houtt. and *Psoralea corylifolia* L., Ershen Pill composed of a combination of salt-scorched *Psoralea corylifolia* L. and bran confit *Myristica fragrans* Houtt. was found to be more effective in reducing the abundance of large escherichia coli and enterococcus, while increasing the abundance of bifidobacteriaceae and lactobacillus, which can effectively regulate gut microbiota balance. Lizhong Decoction was found to be effective in improving gut microbiota disorder in UC patients. It resulted in a significant decrease in the abundance of conditionally pathogenic bacteria such as clostridium sensu stricto 1, enterobacter, and escherichia-shigella that are associated with intestinal inflammation. On the other hand, the abundance of beneficial bacteria such as blautia, muribaculaceae_norank, prevotellaceae UCG-001, and ruminiclostridium 9 associated with intestinal inflammation showed varying degrees of increase [39]. In the DSS-induced colitis, Lizhong Decoction could inhibit the production of pro-inflammatory cytokines, such as IFN-γ, TNF-α, IL-1β, IL-6, and promote the production of anti-inflammatory cytokines, such as IL-4, IL-10, and significantly down-regulate the mRNA levels of TLR4 and NF-κB [40]. Different extracts of Lizhong Decoction had different therapeutic effects on UC, among which ethyl acetate and n-butanol extracts had significant anticholangitis effects [41].

3.2. Compound TCM prescriptions based on clearing heat and removing dampness

In treating the large intestine dampness-heat syndrome type of UC, compound TCM prescriptions based on clearing heat and removing dampness have been effective. Their composition is summarized in Table 2. Shaoyao Decoction, traditionally used to treat damp-heat dysentery, has been shown to significantly decrease the serum levels of IL-6, IL-1 beta, and TNF alpha, while increasing the gut microbiota diversity and the abundance of firmicutes and proteobacteria, and reducing the abundance of bacteroides [42].

Huangqin Decoction could reduce the abundance of deferribacteraceae, deferribacteres, alcaligenaceae, and the pathogenic bacteria, and restore gut microbiota diversity in DSS-induced colitis [43]. Huangqin Decoction has also been shown to increase the relative abundance of Proteobacteria and Firmicutes at the phylum level, while decreasing the abundance of bacteroides, escherichia-shigella, parabacteroides, and ruminococcus torques, and increasing the abundance of blautia, lachnospiraceae NK4A136 group, rikenella, and C. leptum at the genus level [44]. In addition, Huangqin Decoction could against DSS-induced colitis by activating FFAR4-AMPK-PPARα pathway and inhibiting NOD2/NF-κB and TLR4/TLR5/MyD88 pathways [45].

Qingchang Huashi Formula, derived from the sutra formula Shaoyao Decoction, has been found to regulate the gut microbiota structure of UC patients with large intestine dampness-heat syndrome [46]. At the gate level, the level of firmicutes was up-regulated while the level of bacteroides was reduced. At the genus level, Akk bacteria, eubacterium fissicatena group, turicibacter, adlercreutzia, romboutsia, parasutterella, parabacteroides, erysipelatoclostridium, faecalitalea, olsenella decreased in abundance, while alistipes, odoribacter, ruminiclostridium, ruminococcaceae_uncultured, and other genera increased in abundance, and some genera were able to return to normal gut microbiota levels [47]. In addition, Qingchang Huashi Formula could ameliorate DSS-induced colitis by inhibiting the expression of pro-inflammatory cytokines such as IL-1α, IL-6, IL-8, IL-1β, and TNF-α, increasing the production of anti-inflammatory cytokines such as IL-4, IL-10, and IL-13, as well as blocking the NLRP3/IL-1β signalling pathway [48].

Emodin and paeonol are the main active ingredients in Dahuang Mudan Decoction, which is used to treat large intestine dampness-heat syndrome in UC. Emodin plays a therapeutic role in restoring gut microbiota balance, leading to a significant increase in the abundance of firmicutes and actinobacteria, and a significant decrease in the abundance of proteobacteria, enterobacteriaceae, and bacteroidetes [49]. The abundance of bacteroides bacteria also decreases, while lactobacillus, lactococcus, escherichia, and proteus hauser increase in abundance. However, paeonol may play an overall role in aggravating the disease instead. Additionally, Dahuang Mudan Decoction could alleviate DSS-induced colitis by inhibiting the TLR4/MyD88/NF-κB pathway and the levels of IL-6, TNF-α, IFNγ, IL-10, IL-17A, IL-21 and IL-22 [50].

Other compound formulas used to treat large intestine dampness-heat syndrome UC include Qingkui Yuyang Decoction [51], Shaohuang Anchang Decoction [52], Qingchang Jiedu Decoction [53,54], Changqingshu Formula [55], and Sanren Decoction [56], all based on the basic theories of TCM such as clearing heat and dampness, regulating Qi and blood, etc. These formulas have also shown good efficacy in treating UC. For example, the mechanism of action of Qingkui Yuyang Decoction involves elevating the abundance of bifidobacterium, lactobacillus, and clostridium butyricum while decreasing the abundance of enterococcus and enteric bacilli. Sanren Decoction has been shown to have more prominent clinical efficacy for acute episodes of large intestine dampness-heat syndrome in UC [56].

3.3. Compound TCM prescriptions based on clearing heat and removing toxin

The treatment for the heat-toxin exuberance syndrome type of UC involves clearing heat and removing toxins. Their composition is summarized in Table 2. Baitouweng Decoction is a potent remedy for febrile dysentery, and it works by cooling the blood and clearing heat, making it an effective treatment for UC. Chen conducted a study on the mechanism of action of Baitouweng Decoction for UC using high-throughput sequencing, which showed a decrease in the ratio of firmicutes to bacteroidetes and a decrease in proteobacteria at the phylum level. At the genus level, there was a decrease in the relative abundance of shiga bacillus, while the relative abundance of

lactobacillus and Akk bacteria increased. Furthermore, the IL-6/STAT3 signaling pathway was inhibited, and the production of IL-6, IL-1β, and TNF-α was suppressed [57]. These findings were further validated by the team of Hu Jingyi [58]. Jiawei Baitouweng Decoction was found to promote the repair of intestinal mucosal barrier by inhibiting the p38 MAPK/MLCK signaling pathway, and its efficacy was directly proportional to the concentration of the drug solution [59]. This decoction is more specific for UC in heat-toxin exuberance syndrome, and the combination of mesalazine with Jiawei Baitouweng Decoction resulted in a clinical efficacy of 96.7% [60].

Sanhuang Shu'ai Decoction is another remedy that can remove heat and stop dysentery, and it has been found to increase the abundance of Lactic acid bacterium and ruminococcus in gut microbiota while decreasing the abundance of enterococcus faecalis. Sanhuang Shu'ai Decoction could ameliorate the symptoms of DSS-induced colitis by inhibiting the NF-κB signalling pathway, and decreasing the levels of pro-inflammatory cytokines such as IL-6, IL-1β and TNF-α [61]. Furthermore, most of the suppressor flora of Sanhuang Shu'ai Decoction belonged to conditionally pathogenic bacteria [62].

Huanglian Jiedu Decoction is a basic formula that is useful for clearing heat and detoxifying UC in the heat-toxin exuberance syndrome. The effect of Huanglian Jiedu Decoction on gut microbiota in UC patients was studied, and it was found that at the phylum level, the abundance of actinobacillus and escherichia-shigella decreased, while the abundance of firmicutes increased compared to preintervention [63]. At the genus level, the abundance of Actinomyces and E. coli decreased, while the abundance of veillonella, clostridium, blautia, proteus hauser, and flavobacterium increased. It is important to note that high doses of Huanglian Jiedu Decoction can have an antibiotic-like destructive effect, while low doses can reduce enterococcus. Therefore, high doses of Huanglian Jiedu Decoction are not recommended when treating UC. This decoction also could reduce the levels of pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6, and inhibit the JAK2/STAT3 signalling pathway to regulate cell proliferation and apoptosis, thereby ameliorating the symptoms of DSS-induced colitis [64].

3.4. Compound TCM prescriptions based on mildly regulating cold and heat

For UC patients with cold-heat complex syndrome, a crucial therapeutic approach is to mildly regulate cold and heat within the body. Their composition is summarized in Table 2. Wumei Pill, a classic formula for the treatment of prolonged diarrhea and dysentery caused by a combination of cold and heat and weakness of righteous energy, has been shown to significantly increase the relative abundance of veillonella, flavobacterium, lactobacillus, peptococcus, eubacteriun, and bifidobacterium in the gut microbiota of patients who took it in combination with mesalazine for one month, mostly attributed to firmicutes and Bacteroidetes. This is in contrast to patients who only took mesalazine [65]. These findings suggest that the combination of Wumei Pill and mesalazine is more effective in treating UC than mesalazine alone.

Banxia Xiexin Decoction, as a representative formula for mildly regulating cold and heat, can effectively reduce the richness of Patescibacteria at the phylum level and reduce the richness of clostridium_sensu_stricto_1, candidatus_saccharimonas, and eubacterium_fissicle-na_group at the genus level. It can also increase the abundance of bacteroides and bifidobacterium, and reduce the levels of pro-inflammatory cytokines IL-6 and TNF-α [66]. For UC patients with more deficient stomach Qi in distention and stuffiness, Gancao Xiexin Decoction may be more suitable than Banxia Xiexin Decoction, with the addition of *Glycyrrhiza glabra* L. Gancao Xiexin Decoction has been shown to significantly increase the content of beneficial bacteria bifidobacterium and lactic acid bacteria, and decrease the content of escherichia coli at the microscopic level. Its mechanism of inhibiting pro-inflammatory cytokines is consistent with Banxia Xiexin Decoction [67].

4. Single Chinese herbs for the UC treatment

As the basic unit of TCM compound prescriptions, the significance of active ingredients to single Chinese herbs can be counterbalanced to the significance of single Chinese herb to a compound prescription. Single Chinese herb can also exert its effect through multiple pathways, multiple targets and multiple components, making the efficacy no longer monotonous. The representative single herb for the treatment of UC can be mainly classified as replenishing Qi, clearing heat and tonifying blood.

The single Chinese herbs with high frequency of clinical use in the treatment of UC concludes *Glycyrrhiza glabra* L., *Coptis chinensis* Franch., *Poria cocos* (Schw.) Wolf., etc [68]. From the perspective of modern pharmacology, single Chinese herb for UC is rich in active ingredients and has better effects in balancing gut microbiota.

4.1. Glycyrrhiza glabra L

Glycyrrhiza glabra L. belongs to the category of TCM known as replenishing Qi herbs, which has the effects of tonifying the spleen, benefiting the Qi, clearing heat and detoxifying, dispelling phlegm and relieving cough, relieving urgency and pain, and harmonizing various medicines. It is an important Chinese herb in various compound prescriptions, such as Sijunzi Decoction, Jianpi Formula, etc. Through modern pharmacological research, *Glycyrrhiza glabra* L. has been found to inhibit NLRP3 inflammatory vesicle-mediated immune inflammatory responses to achieve efficacy in alleviating UC [7].

Zhang extracted licoflavone B (LB) from the residue of the licorice flavones and continuously intervened in C57BL/6 mice with DSS-induced colitis for 2 weeks and found that high doses of LB can help improve intestinal barrier damage, inflammatory response, and adjust gut microbiota homeostasis [69]. The mechanism can be not only to down-regulate pro-inflammatory cytokines TNF-α, IL-6 and IL-1β, but also to up-regulate the inflammatory factor IL-10, and to reduce the expression levels of P-ERK, P-p38 and P-JNK, and to block the MAPK signaling pathway. Low dose LB is more focused on achieving therapeutic goals by increasing the abundance of gut

microbiota. Glycyrrhizic acid can reduce the stimulation of lipopolysaccharide on macrophages, and glycyrrhizinic acid can inhibit the pro-inflammatory cytokines IL-6 and IL-1β, while glycyrrhiza polysaccharide (GPS) can affect the immune system and gut microbiota of the organism [70]. In the serum of mice in different dose groups of GPS, the serum levels of TNF-α, IL-1 and IL-6 were significantly reduced while the levels of IL-10 were significantly increased thus inhibiting the inflammatory response of UC and reducing the imbalance of gut microbiota. Licochalcone A can inhibit NF-κB, reduce the production and release of pro-inflammatory cytokines in leukocytes and macrophages, exert anti-inflammatory effects, and promote Nrf2 activation to alleviate the disease from an antioxidant perspective. The inflammation reduction also facilitates the balance of the gut microbiota. In addition, the main gut microflora involved in the therapeutic effects of licochalcone A on DSS-induced colitis include ruminococcaceae, defluviitaleaceae, streptococcaceae, moraxellaceae, akkermansiaceae, bacillaceae, and bifidobacteriales, etc. Licochalcone A could alleviate UC by increasing the relative abundance of beneficial gut barrier-beneficial bacteria such as akkermansiaceae and decreasing the levels of gut barrier-harmful bacteria such as prevotellaceae and bacillaceae [71].

4.2. *Coptis chinensis Franch*

Coptis chinensis Franch. belongs to the category of TCM known as clearing heat and removing dampness herbs. It's main effects are to clear heat and dry dampness, and to relieve fire and detoxify. It is an important Chinese herb in various compound prescriptions, such as Shaoyao Decoction, Huangqin Huacai Decoction, Qingchang Huashi Formula, etc. The main chemical constituents of *Coptis chinensis* Franch. are alkaloids, represented by BBR as well as xanthophylline, which are also the main active ingredient of *Coptis chinensis* Franch. in the treatment of UC [68]. Coptisine (COP) can inhibit the activation of NF-κB by blocking the translocation of NF-κB p65 from the cytoplasm to the nucleus and blocking the phosphorylation of IκBα. At the same time, COP can down-regulate the expression levels of TNF-α, IFN-γ, IL-1β, IL-6, IL-17 and other pro-inflammatory cytokines, and up-regulate the expression levels of IL-10, TGF-β and other anti-inflammatory cytokines [72].

4.3. *Portulaca oleracea L*

Portulaca oleracea L. belongs to the category of TCM known as heat-clearing and detoxifying herbs, which has the effect of clearing heat and detoxifying, cooling blood and stopping bleeding and stopping dysentery. It is an important Chinese herb in various compound prescriptions, such as Kushen Decoction. Modern pharmacological research has proven that *Portulaca oleracea* L. can resist bacteria, resit oxidation, enhance immune function and regulate body metabolism.

The team of Manal A. Alfwuaires [73] extracted the ethanolic extract of Portulaca Herba leaves (POE) from *Portulaca oleracea* L., and established an AA mouse model using rectal injection of acetic acid (AA) and continuous oral administration of POE for 7 days, finding that POE can alleviate the damage of intestinal mucosal barrier by down-regulating the levels of pro-inflammatory cytokines such as IL-1, IL-6, IL-17 and TNF-α. After performing POE high performance liquid chromatography analysis, the range of active ingredients of *Portulaca oleracea* L. for the treatment of UC was determined. Quercetin, rutin and other components in the active ingredients can inhibit the immune inflammatory response caused by NLRP3 inflammatory vesicles by suppressing the expression of IL-1β and blocking the expression of MAPKs and NF-κB signaling pathways. In particular, quercetin can also improve gut microbiota, thereby down-regulating TLR/NF-κB related proteins inactivates Th/T17 cells and maintains intestinal health.

4.4. *Paeonia lactiflora Pall*

Paeonia lactiflora Pall. belongs to the category of TCM known as blood-tonifying herbs. which can nourish blood and regulate menstruation, astringent Yin and stop sweating, soften the liver and relieve pain, and calm liver Yang. It is an important Chinese herb in various compound prescriptions, such as Tongxie Yaofang. Modern research has proved that *Paeonia lactiflora* Pall. has hepatoprotective, analgesic, anti-inflammatory and antispasmodic effects.

Total glucosides of paeony, an active component of *Paeonia lactiflora* Pall., can inhibit TLR4/NF-κB signaling pathway and suppress the levels of pro-inflammatory cytokines, such as IL-1 β and TNF-α, and oxidative stress factors such as malondialdehyde and myeloperoxidase, which in turn improved the symptoms of UC [74]. In addition, total glucosides of paeony restored the dysbiosis of the gut microflora by decreasing the accumulation of indole-3-lactic acid in the colon of mice with colitis [75]. Yan et al. intervened in the treatment of DSS-induced colitis with the aqueous extract of Water extract of *Paeonia lactiflora* Pall. and found that not only the total amount of gut microbiota increased, but also the diversity of gut microbiota and the abundance of beneficial bacteria were restored, specifically manifested as the abundance of norank_f_muribaculaceae, lactobacillus and Akk bacteria decreased, while the abundance of bacteroides, escherichia-shigella, romboutsia and fusobacterium increased [76].

4.5. *Baphicacanthus cusia (Nees) Bremek*

Baphicacanthus cusia (Nees) Bremek. belongs to the category of TCM known as heat-clearing and detoxifying herbs. Its functions include clearing heat and detoxifying, cooling blood and eliminating spots, reducing fire and calming shock, etc. It is an important Chinese herb in various compound prescriptions, such as Qingdai San, Qingchang Wenzhong Formula, and Xilei San. Modern research has found that the main chemical component of *Baphicacanthus cusia* (Nees) Bremek. for UC is indigo, which can increase the relative abundance of the beneficial genera ruminococcus_1, ruminococcaceae_UCG-005, norank_f_erysipelotrichaceae, butyricicoccus and bifidobacterium and decrease the relative abundance of the harmful genus escherichila-shigella [77]. *Baphicacanthus cusia* (Nees)

Bremek. could alleviate UC by inhibiting the activation of the TLR4/MyD88/NF-κB signalling pathway and reducing serum and tissue levels of TNF-α, IL-1 β and IL-6 in DSS-induced colitis [78]. However, the safety of *Baphicacanthus cusia* (Nees) Bremek. for the treatment of UC is still debatable. To date, a number of studies have reported adverse events associated with *Baphicacanthus cusia* (Nees) Bremek., including mild headache and digestive discomfort, and even liver and renal dysfunctions, intussusception and pulmonary arterial hypertension. In conjunction with the well-documented efficacy of *Baphicacanthus cusia* (Nees) Bremek. in pre-clinical and clinical settings, a benefit-risk evaluation should be conducted prior to its use to determine the appropriateness of using *Baphicacanthus cusia* (Nees) Bremek. in patients, rather than dismissing it out of hand [79].

4.6. *Dendrobium nobile Lindl*

Dendrobium nobile Lindl. is the stem of Dendrobium officinale Kimura et Migo, an orchid plant, which can benefit the stomach and generate fluid, nourishe yin and clear heat [80]. *Dendrobium nobile* Lindl. has the anti-inflammatory, antibacterial and immunomodulatory effects in the field of modern medical research, suggesting that it could be considered as a therapeutic agent for UC [81]. Dendrobium officinale leaf phenolics could act in multiple ways to ameliorate DSS-induced colitis, mainly by decreasing the relative abundance of parasutterella_excrementihominis, ligilactobacillus_murinus, increasing the relative abundance of relative abundance of faecalibaculum_rodentium, and promoting the production of short-chain fatty acids; down-regulating the levels of TLR4, phosphorylated IKKα/β, and NF-κB p65, and inhibiting the expression of the TLR4/NF-κB inflammatory signalling pathway; and restoring zonula occludens 1, Occludin and Claudin-1 and other tight junction proteins expression to repair the intestinal barrier function; inhibiting the secretion of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 [82].

4.7. *Others*

In addition to the above-mentioned *Glycyrrhiza glabra* L., *Coptis chinensis* Franch., *Portulaca oleracea* L., *Paeonia lactiflora* Pall., *Baphicacanthus cusia* (Nees) Bremek. and *Dendrobium nobile* Lindl., there are also herbal medicines such as *Chenopodium quinoa* Willd., *Salvia miltiorrhiza* Bunge and *Atractylodes lancea* (Thunb.) DC. which have regulatory effects on the development of UC, see Table 3.

5. TCM ingredients for the UC treatment

Active ingredients of TCM are the main research subjects of TCM at the modern pharmacological level. With the increasing maturity of extraction and separation technology of TCM, combined with the main TCM research for clinical treatment of UC, it was found that alkaloids, polysaccharides, flavonoids, polyphenols and terpenoids are representative active ingredients for the treatment of UC [91].

5.1. *Alkaloids*

Alkaloids are nitrogenous compounds, mainly including alkaline compounds existing in plants and alkali-free organic compounds with obvious biological activities [8,91]. The alkaloids for the treatment of UC mainly include BBR, oxymatrine (OMT), tetrandrine, ect., which are mainly distributed in TCMs of Ranunculaceae and Tetrandraceae, such as *Coptis chinensis* Franch., *Phellodendron chinense* C·K.Schneid., *Sophora flavescens* Aiton, *Stephania tetrandra* S.Moore, etc. The mechanisms of alkaloids in treating UC are mainly through down-regulation of signaling pathways such as PI3K/AKT, NF-κB, and affecting the expression of cytokines such as IL-1β, IL-6 and TNF-α.

Table 3
Regulation of other single herbs on UC gut microbiota, signaling pathway, and cytokine.

TCM	Mechanism of action	Reference
Chenopodium quinoa Willd.	Firmicutes↑; bacteroides, pathogenic helicobacter↓; TNF-α, IL-1β↓	[83]
Salvia miltiorrhiza Bunge	Inhibition of STAT3 phosphorylation and nuclear translocation; IL-17A, TNF-α↓	[84]
Atractylodes lancea (Thunb.) DC.	Inhibition of MAPK/NF-κB pathway	[85]
Curcuma longa L.	Inhibition of PI3K/AKT pathway and NF-κB pathway; IL-1β、IL-6、IL-12, TNF-α↓	[8]
Citrus reticulata Blanco	Akk bacteria, Mucispirillum and other beneficial bacteria↑; Inhibition of Nrf2/NLRP3 pathway	[86]
Rheum officinale Baill.	nterobacteriaceae and Turicibacter↓, Unspecified-S24-7 and Rikenellaceae↑; Inhibition of mTOR/PI3K/AKT signaling pathway; TNF-α, IL– 6, IL-1β↓	[87]
Aloe vera (L.) Burmf.	Activation of PKC/ERK and inhibition of PI3K/AKT pathway; IL-6, IL-1β, TNF-α↓; IL-10↑	[88]
Schisandra chinensis (Turcz.) Baill.	Actinomycetes and Streptococcus↓; Proteobacteria, Bacteroidetes, Odoribacter, Turicibacter, Oscillospira and Ruminococcus↑; Inhibition of TLR4/NF-κB/NLRP3 inflammatory vesicle pathway; IL-1β, TNF-α, IL-18↓	[89]
Scutellaria baicalensis Georgi	Lactobacillus, Ruminococcaceae, Lachnospiraceae, Bifido-bacterium, Roseburia and Rikenellaceae↑; Enterococcus, Streptococcus, Turicibacter and Parasutterella↓; Inhibition of NF-κB pathway and NLRP3 inflammatory vesicles; IL-1β, IL-18, TNF-α↓	[90]

↑: Up-regulation; ↓: Down-regulation

5.1.1. BBR

BBR is the active ingredient in the treatment of UC form *Coptis chinensis* Franch., *Phellodendron chinense* C·K.Schneid. and *Berberis silva-taroucana* C·K.Schneid. BBR could inhibit the TNF-α and NF-κB signaling pathways and the expression of mRNA, regulate helper T cells, thus restoring the barrier protection function of the intestine and optimizing the structure of the gut microbiota for the purpose of treating UC [9]. BBR could inhibit the Phospholipase A2-Cyclooxygenase 2-Prostaglandin E2-Prostaglandin E receptor 2 pathway and STAT3 by modulating the gut microbiota and reduce the level and function of Prostaglandin E2, thereby reversing the levels of pro-inflammatory cytokines, such as IL-6, IL-17, IL-22, and thus alleviating colonic inflammation in DSS-induced colitis [92]. In addition, BBR significantly increased the diversity of the gut microbiota in DSS-induced colitis, including increasing the abundance of f_muribaculaceae, bacteroides, dubosiella, allobaculum and Akk bacteria, and decreasing the relative abundance of intestinal pathogens such as desulfurvibrio which in turn enhanced the intestinal barrier function [93,94]. Clinical studies have shown that berberine combined with mesalazine significantly shortened the relief time of abdominal pain, diarrhea and mucopurulent stools in patients compared with mesalazine alone, significantly improved the clinical symptoms of patients, improved the clinical efficacy, and had a better safety, which is of good clinical relevance [95].

5.1.2. OMT

OMT is an alkaloid mainly extracted from *Sophorae* Flavescentis Radix [96]. OMT effectively increased muribaculaceae, bifidobacterium abundance, lachnospiraceae, and ruminococcaceae, inhibited staphylococcaceae and bacteroides growth and regulated the intestinal flora structure in DSS-induced colitis [97]. OMT can inhibit PI3K/AKT and TLR9/MyD88/NF-κB signaling pathways and down-regulate pro-inflammatory cytokines such as IFN-γ, and MCP-1 to alleviate the disorder of gut microbiota caused by the decline of intestinal immune function caused by pro-inflammatory cytokines, thus alleviating the inflammatory damage of intestinal tissues [98,99]. OMT can protect the colonic mucosal barrier in DSS-induced colitis, inhibit inflammatory and oxidative responses and its mechanism is related to the RhoA/ROCK signaling pathway inhibiting the differentiation of Th17 cells and promoting the differentiation of Treg cells. More and more studies have shown that OMT is a valuable phytochemical, but how to extract it on a large scale and overcome its low oral utilisation deserves in-depth research to determine its safety in humans and to achieve therapeutic results [100].

5.1.3. Others

In addition, tetrandrine and evodiamine, which are extracted from the root of *Stephania tetrandra* S.Moore and the fruit of *Tetradium ruticarpum* (A.Juss.) T.G.Hartley respectively, can improve the symptoms of UC, such as diarrhea and bloody stool. The main mechanisms are the inhibition of NF-κB signaling pathway and inflammatory factors such as IL-1β and TNF-α [101].

5.2. Polysaccharides

Polysaccharides are a kind of polymeric sugar polymeric carbohydrate formed by the condensation and dehydration of more than 10 monosaccharides. Polysaccharides can interact with the gut microbiota to increase beneficial bacteria such as Lactobacillus spp. and Bifidobacterium spp. in the intestine and reduce the isotope abundance ratio of pathogenic bacteria such as Enterococcus spp [102]. Since the human body lacks polysaccharide hydrolases, the interaction time of polysaccharides and gut microbiota is also relatively prolonged. Common polysaccharides used in the treatment of UC include fructus arctii polysaccharide (FAP), portulaca oleracea polysaccharide (POP), APS, etc.

5.2.1. FAP

FAP has the functions of antibacterial, anti-inflammatory, regulating the immune system, etc., mainly through regulating gut microbiota and inflammatory factors to treat UC. The purified product of FAP, ALP-1, has a significant effect on optimizing the structure of Staphylococcus, Bacteroidetes, Proteobacteria, and can also significantly downregulate the levels of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α [102].

5.2.2. POP

POP have antioxidant, antitumor, anti-aging, antibacterial and anti-inflammatory, and growth-promoting effects, and can increase the number of beneficial bacteria such as Lactobacillus and Bifidobacterium in the gut microbiota and elevate the level of the anti-inflammatory factor IL-10 as well as down-regulate the level of the pro-inflammatory cytokines IL-6 and TNF-α for the purpose of treating UC [103,104]. In addition, it has been shown that POP could increase the total proportion of bacteroidetes and firmicutes, maintain the levels of retinol and short-chain fatty acids in the intestinal tract; regulate the TNF-α/NF-κB and IL-6/STAT3 signalling pathways, and inhibit the levels of NF-κB and myeloperoxidase (MPO) to alleviate the inflammation in DSS-induced colitis [105].

5.2.3. APS

APS is a natural bioactive compound extracted from *Hedysarum Multijugum* Maxim., which has the effect of strengthening spleen and replenishing Qi, and modern pharmacological studies have shown that APS has the functions of antiviral, antimicrobial, antitumor, antioxidant, and antiageing [106]. APS could increase the number of beneficial bacteria such as bifidobacteria and lactobacilli in the intestinal tract, and inhibit the PI3K/AKT, TIGIT/CD155, NF-κB and Nrf2/HO-1 signalling pathways and the NLRP3 inflammatory vesicles activation. APS significantly reduces the expression of pro-inflammatory cytokines such as IL-2, IL-6, IL-12p70, IL-23, and TNF-α, and promotes the production of anti-inflammatory factors such as TGF-β1, which then ameliorates DSS-induced colitis

[107,108].

5.3. Flavonoids

Flavonoids belong to plant secondary metabolites, which are mostly combined with sugars to form glycosides or carbon glycosides, or exist in free form. Its mechanism of treating UC is mostly related to the blocking of NF-κB signaling pathway [8]. Calycosin is one of the main effective ingredients of *Hedysarum* Multijugum Maxim. for UC, with a wide range of effects such as antioxidation, antiviral, antitumor, antibacterial and antiviral. Calycosin can also improve the immune function of the body and alleviate the symptoms of UC patients, and the main therapeutic mechanism is blocking the NF-κB signaling pathway. Naringenin, which can be extracted from the fruit of Citrus grandis, has antioxidant, antitumor, antibacterial and other effects. Its treatment function for UC is similar to that of Calycosin [8]. Baicalein, one of the active ingredients of Scutellariae Radix for UC, can block the TLR4/MyD88 signaling pathway, upregulate TGF-β content, enhance the protective barrier of the intestine, and alleviate the symptoms of UC. Baicalin, a combination of baicalein and glucuronide, has a more complex mechanism than baicalein for the treatment of UC, which is associated with PI3K/AKT and NF-κB signaling pathways, which in turn affects the secretion and release of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-8 [9]. Honeysuckle flavonoids inhibit the NF-κB signalling pathway and exert antioxidant and anti-inflammatory effects to alleviate TBNS-induced colitis [109].

5.4. Polyphenols

Polyphenolic compounds are composed of several phenolic groups. Its main mechanisms for the treatment of UC are to inhibit MAPK, NF-κB signaling pathways and downregulation of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 [8]. Increasing polyphenol intake can increase the number and variety of beneficial bacteria such as lactic acid bacteria and bifidobacteria, and inhibit the growth of pathogenic bacteria such as Escherichia coli and clostridium difficile [110].

5.4.1. Curcumin

Curcumin is the main effective ingredient of *Curcuma longa* L. in the treatment of UC [111]. It mainly exerts its therapeutic effect on UC by regulating signaling pathways, such as TLR/MyD88, MAPK, and PI3K/AKT, and inhibiting pro-inflammatory cytokines, such as IL-1β, TNF-α, IL-33, CCL-2, IL-6, and TGF-β1 [112]. Curcumin has been found to increase the killing power of pathogenic gram-positive and gram-negative bacteria while promoting the production of short-chain fatty acids to protect the intestinal mucosa and reduce the proliferation of bacteria responsible for intestinal inflammation. Its combination with sulfusalazine can significantly reduce the recurrence rate. Kang found that curcumin treatment given to DSS-induced colitis at concentrations above 95% resulted in the suppression of M1-type macrophages and activation of M2-type macrophages [113]. In a meta-analysis study involving 385 subjects, it was shown that curcumin-assisted therapy may be effective in relieving clinical symptoms in patients with UC without causing serious adverse effects [114].

5.4.2. Resveratrol (RSV)

RSV is extracted from the rhizome of *Reynoutria japonica* Houtt., and has anti-inflammatory, antioxidant, and cardiovascular protective activities [115]. The main mechanisms of RSV for the treatment of UC are the inhibition of PI3K/AKT, MAPK, Notch1, and NF-κB signaling pathways and downregulation of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 levels [116]. RSV can enrich six groups of bacteria such as Clostridium, Akk bacteria, and rothia [117]. Akk bacteria regulate the structure of the gut microbiota of UC mice by participating in metabolic pathways such as triacylglycerol and cardiolipin biosynthesis. Clinical trials have demonstrated the significant inhibitory effect of RSV on inflammatory markers such as NF-κB, hs-CRP, and TNF-α, and high antioxidant potency [110].

5.4.3. Others

Green tea polyphenol (GTP) extracted from tea and ellagic acid from various fruits can also be used to treat UC. GTP can not only improve the regeneration of intestinal epithelial cells and the formation efficiency of intestinal mucus, but also reduce the number of pathogenic bacteria such as Clostridium perfringens and increase the number of beneficial bacteria such as Bifidobacterium and Lactobacillus [110]. GTP plays a role in treating UC by blocking the JAK/STAT signaling pathway, down-regulating TNF-α and IL-6 pro-inflammatory cytokines, and up-regulating IL-10 anti-inflammatory cytokines. Ellagic acid can alleviate TNBS-induced colitis by inhibiting RhoA/ROCK/MLC, MAPK, and NF-κB signalling pathways and pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α [118].

5.5. Terpenoids

Terpenoids are the general term for all polymers of isoprene and their derivatives. Generally, terpenoids can be classified as monoterpenoids, sesquiterpenoids, diterpenoids, sesterterpenoids, triterpenoids, tetraterpenes, and multiterpenes based on the number of isoprene units included in the molecule. Total triterpenoids of papaya can regulate PPARγ/SIRT1/NF-κBp65 signaling pathway, down-regulate pro-inflammatory cytokines TNF-α, IL-1β, IL-6, IFN-γsp in blood, and up-regulate anti-inflammatory cytokines IL-4, IL-10 levels [119]. Triptolide can enhance intestinal immune function and increase the level of the anti-inflammatory factor IL-17 to achieve the purpose of treating UC [7]. Parthenolide is used to treat UC mainly by inhibiting NF-κB signalling pathway [8].

5.6. Others

Ginsenoside Rg1 is a tetracyclic triterpenoid derivative that exists in *Panax ginseng* C.A.Mey. Ginsenoside Rg1 can mitigate the significant increase of the relative abundance of proteobacteria caused by DSS and the significant decrease of the relative abundance of verrucomicrobia, while increasing the relative abundance of beneficial bacteria such as norank_f_muribaculaceae, Akk bacteria and lactobacillus [120]. The increase of conditional pathogenic bacteria such as odoribacter and bacteroides also decreased under the intervention of ginsenoside Rg1. Another study found that the effects of ginsenoside Rg1 on the gut microbiota of DSS-induced colitis are the decreases of the relative abundance of Staphylococcus, Bacteroides, eubacterium_fissicatena_group and the increases of the relative abundance of lachnospiraceae_NK4A136_group and norank_f_lachnospiraceae. After intervention with ginsenoside Rg1 in DSS-induced colitis, the expression levels of IL-6, IL-33, CCL-2 and TNF-α were significantly downregulated and the expression levels of IL-4 and IL-10 were significantly upregulated in DSS-induced colitis [121]. In addition, the modulation of the Nogo-B/RhoA signaling pathway is also the key to the anti-colitis effect of ginsenoside Rg1. Zhong [122] through intragastric administration of astragaloside IV in DSS-induced colitis, found that it can play a role in treating UC by blocking the Notch signal pathway and restoring the balance of Th17/Treg cells. The main mechanisms of ursolic acid for the treatment of UC are to downregulate the three classical inflammatory pathways of MAPKs, IL-6/STAT3 and PI3K, upregulate the levels of verruca microbia, and reduce serum IL-6 levels. And its mechanism for preventing UC is to activate the AMPK/FOXO signaling pathway [123].

6. Conclusion and future perspective

UC is a digestive system disease with an unknown cause, and modern medical treatments for UC often lead to toxic side effects for patients. Therefore, it is crucial to develop a safer and more effective protocol for UC prevention and treatment. In this paper, we review existing studies on UC therapeutic pathways and discuss the research progress of herbal medicines in UC prevention and treatment, including compound prescriptions, single Chinese herbals, and active ingredients. We elucidate their efficacy and mechanism of action, focusing on causative factors and herbal medicines as the main therapeutic means.

TCM believes that pathogens such as dampness-heat, phlegm turbidity, Qi stagnation, food accumulation, and blood stasis can cause visceral lesions in the spleen, liver, kidney, etc., leading to symptoms such as diarrhea and dysentery. These correspond to modern medicine's understanding of UC. According to specific clinical manifestations, TCM uses dialectical classification to differentiate and treat UC based on different types of syndromes, treating both the root causes and symptoms, and following the principle of adapting treatment to individual cases according to the three causes. TCM applies targeted therapeutic methods to treat UC.

We find that herbal medicine's main pathways to alleviate UC symptoms include (1) balancing gut microbiota structure, (2) regulating related signaling pathways, and (3) regulating cytokines. Chinese medicine compound prescriptions, single Chinese herbals, and active ingredients have multi-target and multi-pathway characteristics in treating UC, simultaneously accounting for multiple pathways. For example, the mechanism of action of Jiawei Chaishao Liujun Granule, Quinoa, and Polysaccharide from FAP involves (1) (3), while the mechanism of action of Lichang Decoction, *Glycyrrhiza glabra* L., and BBR involves (1) (2) (3). In conclusion, TCM can achieve its purpose of UC prevention and treatment by acting in multiple ways, and TCM deserves further research and development in this field.

Although TCM has a long history of treating UC and its feasibility and advantages have been confirmed by modern medical research, there are still some deficiencies that need to be addressed. Firstly, few studies have investigated the effects of TCM concoction, dosage form, and herb quality on the efficacy of UC treatment, and the factors influencing the efficacy of TCM compound prescriptions, single Chinese herbs, and active ingredients are relatively single. Secondly, the efficacy evaluation indexes of TCM for UC include gut microbiota, signaling pathways, cytokines, etc., and it is unclear whether these can be used as authoritative clinical efficacy evaluation indexes. Finally, the changes in gut microbiota, signaling pathways, and cytokines in the active and remission stages of UC need to be further studied and explored. Therefore, we hope that subsequent scholars can explore the mechanism of action of TCM compound prescriptions, single Chinese herbs, and active ingredients for the treatment of UC in a multidimensional manner, with the aim of providing more uniform and standardized criteria for clinical efficacy evaluation.

Ethics approval and consent to participate

Not applicable.

Data availability statement

No data was used for the research described in the article.

Additional information

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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