

REVIEW

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Intestinal barrier defense: the protective effect of plant-based traditional Chinese medicine

Shaofeng Wu^{1†}, Yu Ga^{1†}, Danyang Ma¹, Silu Hou¹, Qiaoyue Hui¹ and Zhihui Hao^{1,2,3,4*}

Abstract

Traditional Chinese medicine (TCM) plays a crucial role in maintaining the intestinal barrier, which is considered integral to overall health and is connected with the functions of the spleen and stomach and the balance of qi and blood. TCM principles, such as "separating the pure from the turbid," are related to gut flora equilibrium, with imbalances corresponding to the "struggle between good and evil." TCM supports the intestinal barrier through methods such as invigorating qi and strengthening the spleen. In this review, authoritative databases such as PubMed, Web of Science, and Google Scholar were systematically searched for studies on the protective effects of TCM and its constituents on the intestinal barrier from 2018 to 2025. The results show that TCM and its components have multiple advantages in maintaining intestinal barrier function. Classic formulations such as Qingchang Wenzhong and Huangqin decoction protect the intestines through various pathways, including regulating the gut microbiota and enhancing immune function. Single herbs such as *Coptis chinensis* (Huang Lian) and *Scutellaria baicalensis* (Huang Qin), whose properties include clearing heat and detoxifying qi, directly or indirectly promote intestinal health. Additionally, active compounds in TCM, such as flavonoids and saponins, contribute to intestinal homeostasis through mechanisms such as anti-inflammatory and antioxidant effects. The multicomponent, multitarget characteristics of TCM provide comprehensive and long-lasting efficacy in intestinal barrier protection. This article summarizes the current research status of TCM in treating intestinal barrier injury and highlights future research directions, offering a theoretical foundation and research insights for further exploration of the role of TCM in safeguarding intestinal barrier function.

Keywords TCM, Active ingredients, Intestinal barrier, Inflammation, Immune regulation

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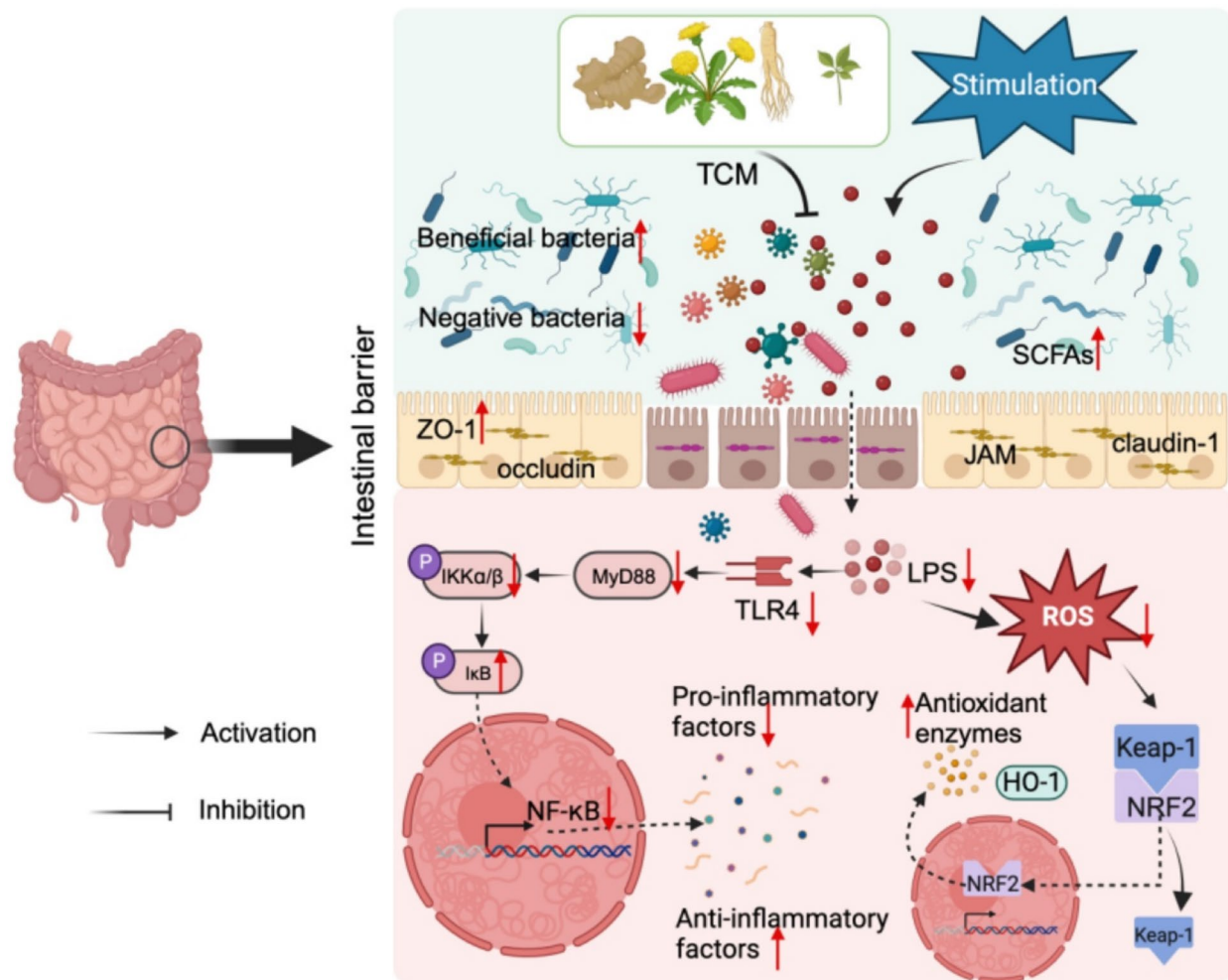
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Graphical Abstract



Introduction

The intestine is important for human digestion and absorption and is also the largest immune organ in the body [1]. The location of the gut exposes them to a variety of attacks, such as from pathogens and biological or chemical damage [2]. However, in most cases, organisms are able to maintain these barriers, and chronic inflammation is successfully avoided [3, 4]. The integrity of this barrier reflects not only the health of the organism but also a crucial defense against the impact of the external environment. The intestinal barrier is a physiological barrier that exists on the intestinal mucosa and is composed mainly of mucus, intestinal epithelial cells (IECs), and immune cells [5, 6]. Its primary purpose is to prevent the invasion of harmful substances and microorganisms and for the proper assimilation of nutrients and other outside

elements into the body [7]. This barrier system plays a key role in defense by maintaining mucosal integrity and regulating permeability [8]. A natural barrier against pathogen invasion is formed by interactions between enterocytes and the mucus layer of the gut barrier, which are closely associated with the immune system [9, 10]. This barrier state is affected by many factors, including diet [11], lifestyle [12, 13], and microbial community health [14]. In addition, defense of the intestinal barrier can also prevent the occurrence of a variety of diseases, such as inflammatory bowel disease (IBD) [15], liver diseases [16], Alzheimer's disease [17], type 2 diabetes [18], and cardiovascular diseases [19, 20], which are related to dysfunction of the intestinal barrier. The development of many chronic illnesses can be stopped or slowed by maintaining adequate barrier function. Therefore, the

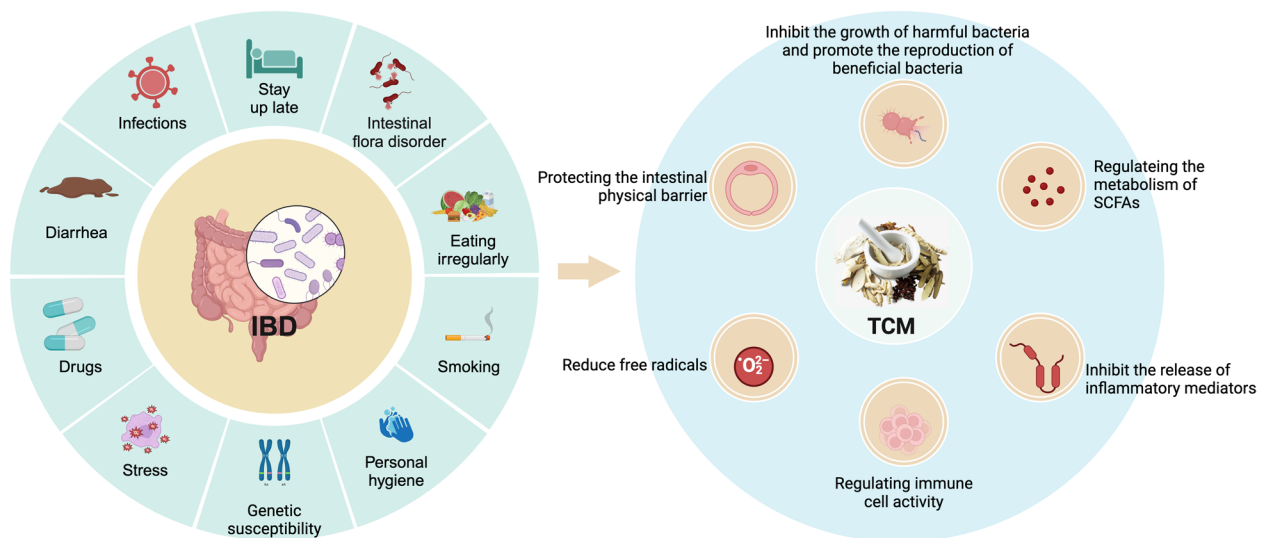


Fig. 1 Mechanisms through which TCM affects IBD. IBD is a chronic disease characterized by inflammation of the gastrointestinal tract. The exact predisposing factors are not fully understood. However, it is currently believed that the factors influencing IBD include genetic, environmental, and immune factors and intestinal flora disorders [27]. TCM has been used for centuries to treat a variety of diseases, including IBD. The mechanisms of traditional Chinese medicine in the treatment of IBD vary and include regulating intestinal flora, inhibiting the secretion of inflammatory factors, and scavenging free radicals [28]. TCM traditional Chinese medicine, IBD inflammatory bowel disease

study of the intestinal barrier is important for understanding and maintaining general health.

There are several connections and differences between traditional Chinese medicine (TCM) and modern medicine in the understanding of intestinal diseases and the intestinal barrier. TCM emphasizes holism and treatment based on syndrome differentiation, whereas modern medicine focuses on the exploration of microscopic mechanisms and pathophysiological processes. As the first line of defense between the gut and the external environment, the integrity of the intestinal mucosal barrier is crucial for preventing harmful substances from entering the body [21]. Modern medicine describes in detail the four components of the intestinal barrier—the mechanical barrier, biological barrier, chemical barrier, and immune barrier—while TCM indirectly maintains the integrity of the intestinal barrier by mediating the function of the viscera and the balance of qi and blood [21]. In addition, the intestinal flora is closely related to intestinal health, and its composition significantly affects the efficacy of TCM [22].

Global studies have shown that 74.1 million children under 5 years of age died due to IBD in 2015, with the highest mortality rates in sub-Saharan Africa and southern Asia, accounting for 89.48% of the total [23]. In 2016, 40.125 million children were diagnosed with IBD, 446 million were diagnosed with this condition, and 15.652 million were diagnosed with long-term malnutrition caused by IBD [24]. In 2017, there were an estimated 1.7

billion cases of childhood IBD and 525,000 deaths among children under 5 years of age each year globally [25]. In China, the incidence of childhood IBD is lower than that of respiratory diseases and remains one of the priority diseases despite progress in research and control. From 2014 to 2015, the incidence of IBD among children in all provinces of China ranged from 3.8 per 100,000 to 506.7 per 100,000. Children under 5 years old accounted for 53.7% of all IBD cases [26] (Fig. 1).

Animal models of "spleen deficiency diarrhea", "damp-heat diarrhea", and "Xiali" are characterized by intestinal flora disorder and barrier destruction [29–32]. The classification of diarrhea in TCM originated from the Ming Dynasty, and it was first divided into 5 types: cold-dampness, heat-dampness, rheumatism, middle-dampness, and dyspepsia by Wan Quan (a famous TCM scholar of the Ming Dynasty). It was further refined into eight types: middle-cold diarrhea, umbilical-cold diarrhea, food-damaging diarrhea, and spleen-deficiency diarrhea in the *Golden Mirror of Medicine*. Xiao et al. studied the effect of Shenling Baizhu powder on diarrhea through a rat model of functional diarrhea with spleen deficiency. High doses of Shenling Baizhu powder could reduce the diarrhea index, increase D-xylose levels and regulatory T-cell content, and increase interleukin-10 (IL-10) expression to improve functional diarrhea with spleen deficiency. It may be related to intestinal absorption and immune regulation [33]. The *atractylode Rhizoma* is bitter and sweet in taste, warm in nature, invigorates qi and

invigorates the spleen, drying dampness and promoting water. It is used in combination with *Poria cocos* and ginseng for invigorating qi and invigorating the spleen, poor food and loose stool, and abdominal distension. Fan et al. reported that Pingwei powder is effective at treating spleen deficiency diarrhea, improving colon pathology and intestinal barrier function, and regulating the intestinal flora [29]. Dong et al. reported that Sijunzi decoction improved spleen deficiency syndrome by regulating the microbiota-gut-metabolite axis to relieve diarrhea and other symptoms, which confirmed the rationality of its compatibility and provided a scientific basis for the clinical application of TCM [34].

Despite advances in the pharmacological management of intestinal barrier-associated disorders, major therapeutic bottlenecks remain [35]. Conventional chemical drugs and biologics (e.g., anti-inflammatory agents, immunosuppressants, and targeted biologics) can effectively control inflammation and symptoms in many patients; however, they may be limited by adverse effects, incomplete or unsustained mucosal healing, recurrence after treatment withdrawal, and a restricted ability to comprehensively restore barrier-microbiota-immune homeostasis [36]. Moreover, microbiota-based therapies such as fecal microbiota transplantation have shown promise for certain conditions, but their broader implementation faces practical and translational challenges, including donor variability and screening burden, safety concerns, potential transmission risks, difficulties in standardization (preparation, dosing, and delivery routes), regulatory constraints, and uncertain long-term durability of engraftment and clinical benefit [37]. Collectively, these limitations highlight an unmet need for complementary strategies capable of multilevel, sustained regulation across the barrier-microbiota-immune axis.

There are both connections and fundamental differences between TCM and Western medicine in conceptualizing intestinal disorders and intestinal barrier dysfunction. Western medicine tends to define barrier injury through measurable structural and functional alterations, covering mechanical, chemical, immune, and biological (microbiota-related) barriers, and seeks to identify causal molecular and cellular pathways that drive disease initiation and progression [38]. In contrast, TCM emphasizes holism and syndrome differentiation, interpreting intestinal dysfunction as part of a systemic imbalance involving the spleen-stomach and the regulation of qi, blood, and body fluids. Importantly, these perspectives are not mutually exclusive. The intestinal barrier is a multilayer, multiscale system in which epithelial integrity, mucus and antimicrobial defenses, immune surveillance, and the microbiota

coevolve dynamically; therefore, a therapeutic strategy that can simultaneously modulate inflammation, oxidative stress, epithelial restitution, mucus/tight junction (TJ) restoration, and microbiota homeostasis may provide advantages over single-target approaches [35].

In this review, the "integration of TCM and Western medicine" is used in a substantive and operational sense rather than a rhetorical one. Specifically, integration refers to an evidence-based, complementary framework that combines Western medicine's standardized diagnosis and barrier-related endpoints (e.g., inflammation and oxidative stress indices, epithelial permeability, TJ/mucus markers, and microbiota-derived features) with TCM syndrome differentiation and multicomponent interventions [39]. Such integration can be implemented through (i) biomarker-supported stratification that links TCM syndromes to objective barrier phenotypes [40]; (ii) add-on or adjunctive use of TCM formulas/active constituents alongside conventional therapies to enhance mucosal healing, improve barrier resilience, and reduce relapse risk; (iii) mechanistic interpretation using modern pharmacology and systems approaches (multiomics, network analysis, and microbiome-metabolite profiling) to map TCM actions along the barrier-microbiota-immune axis [41]; and (iv) rigorous attention to quality control, dose standardization, pharmacokinetics, and herb-drug interaction assessment to ensure safety and reproducibility [42]. This integrative perspective provides a clearer rationale for systematically summarizing TCM-based strategies for intestinal barrier protection and repair.

Modern medical philosophy guides the use of TCM and its components because they are easily accessible, inexpensive, and excellent options for treating intestinal barrier damage [43]. These medications may be from plants, animals, or minerals [44]. However, they usually do not include materials from genetically modified plants and animals or materials that have been fermented by microorganisms or chemically modified. Currently, natural drugs are being studied worldwide, and the pathological mechanisms of enteritis and intestinal injury are being discussed in depth [45]. Unlike chemical drugs, natural drugs and monomers have a variety of pharmacological components that can achieve multitarget treatment of intestinal barrier injury [46, 47]. Research has demonstrated that natural medications and monomers clearly impact the deterioration of the intestinal mechanical barrier [48], immune barrier [49], and ecological barrier [50] and inhibit intestinal bacterial translocation [51]. Here, we present an overview of the current research status and advancements in TCM and its role in safeguarding intestinal barrier function posttrauma.

Structure and function of the intestinal barrier

Composition of the intestinal barrier

Intestinal epithelial barrier

The intestinal barrier is an important line of defense against pathogen invasion and is essential for maintaining local and systemic homeostasis [52]. The intestinal epithelium is a rapidly renewing monolayer organized into villi and crypts, which enables nutrient absorption while restricting pathogen entry. Intestinal epithelial stem cells residing in crypts support epithelial proliferation and regeneration, and IECs are continuously renewed within several days [53]. When epithelial renewal or integrity is compromised, luminal microbes and antigens can penetrate deeper layers and trigger inflammatory responses. IECs constitute the backbone of the epithelial barrier, while specialized epithelial lineages (e.g., Paneth and goblet cells) contribute to barrier defense mainly through antimicrobial factors and mucus production [54–56]. In addition to serving as a physical barrier, IECs sense microbial molecules via pattern-recognition receptors and coordinate local innate immune responses through cross-talk with mucosal immune cells [57]. Together, mucus, IECs, and epithelial secretory programs form an integrated mucosal barrier that maintains intestinal microenvironmental stability.

Tight junctions (TJs)

TJs are the major intercellular sealing structures between IECs and are critical determinants of paracellular permeability, thereby maintaining intestinal barrier integrity [58]. The core TJ components include claudins, occludin, and zonula occludens proteins (ZO-1/2/3), which coordinate junction assembly and link TJs to the cytoskeleton [59, 60]. Disruption or downregulation of TJ proteins is frequently associated with increased intestinal permeability and barrier dysfunction under inflammatory conditions [61]. Therefore, the expression of proteins related to TJs (e.g., ZO-1, occludin, and claudin-1) is widely used as a representative indicator to evaluate barrier injury and repair.

Immune system

The intestinal immune barrier maintains mucosal homeostasis by balancing immune tolerance to commensals with protective responses against pathogens. IECs contribute to immune surveillance by producing cytokines/chemokines and sensing microbial signals via pattern recognition receptors, including Toll-like receptors (TLRs) and NOD-like receptors (NLRs), which can regulate epithelial homeostasis and repair [62–64]. Antigen-presenting cells such as dendritic cells (DCs) sample luminal cues and instruct T-cell responses,

thereby shaping tolerance or inflammation in the lamina propria [32, 65, 66]. When barrier integrity is impaired, microbial products may activate Toll-like receptor 4 (TLR4)-myeloid differentiation primary response gene 88 (MyD88)-nuclear factor-kappa B (NF- κ B) signaling and amplify proinflammatory cascades, further aggravating barrier dysfunction [67]. Overall, coordinated innate and adaptive immune responses are essential for maintaining intestinal homeostasis and determining the outcome of barrier injury.

Role of the intestinal microbiota in maintaining intestinal homeostasis

The intestinal microbiota is increasingly recognized as an integral component of the mucosal barrier and contributes to intestinal homeostasis through coordinated crosstalk with the mucus layer, epithelium, and mucosal immune system [68]. A key feature of homeostasis is maintaining appropriate spatial separation between microbes and the epithelium, which limits unnecessary immune activation [69]. Microbiota-derived metabolites, particularly short-chain fatty acids (SCFAs), such as butyrate, support epithelial energy metabolism and can strengthen barrier integrity by promoting TJ assembly and epithelial repair [70]. In addition, microbial tryptophan metabolites can activate aryl hydrocarbon receptor (AhR)-related protective pathways (e.g., IL-22-associated responses) that support mucosal healing [70, 71]. When microbial composition or function is disrupted, barrier integrity may weaken, and inflammatory circuits can be amplified, linking dysbiosis to chronic intestinal inflammation and systemic consequences.

Regulation of intestinal barrier function by microbial metabolites

Microbial metabolites are important functional mediators that link the gut microbiota to epithelial and immune homeostasis [72, 73]. Among them, SCFAs (acetate, propionate, and butyrate) not only serve as energy substrates but also regulate epithelial barrier integrity and mucosal immunity; butyrate, in particular, has been associated with improved mucosal repair and enhanced TJ function, and SCFA-sensing G protein-coupled receptors (GPCRs) (e.g., GPR43) are involved in restraining inflammatory responses [74–76]. Bile acids undergo microbial conversion to secondary bile acids, which can affect intestinal inflammation and barrier function in a context-dependent manner [77, 78]. In addition, microbial tryptophan metabolism generates indole derivatives that activate AhR signaling and may promote barrier protection in colitis models [79, 80]. Overall, maintaining microbial metabolic homeostasis is critical for supporting barrier integrity and balanced mucosal immunity. The

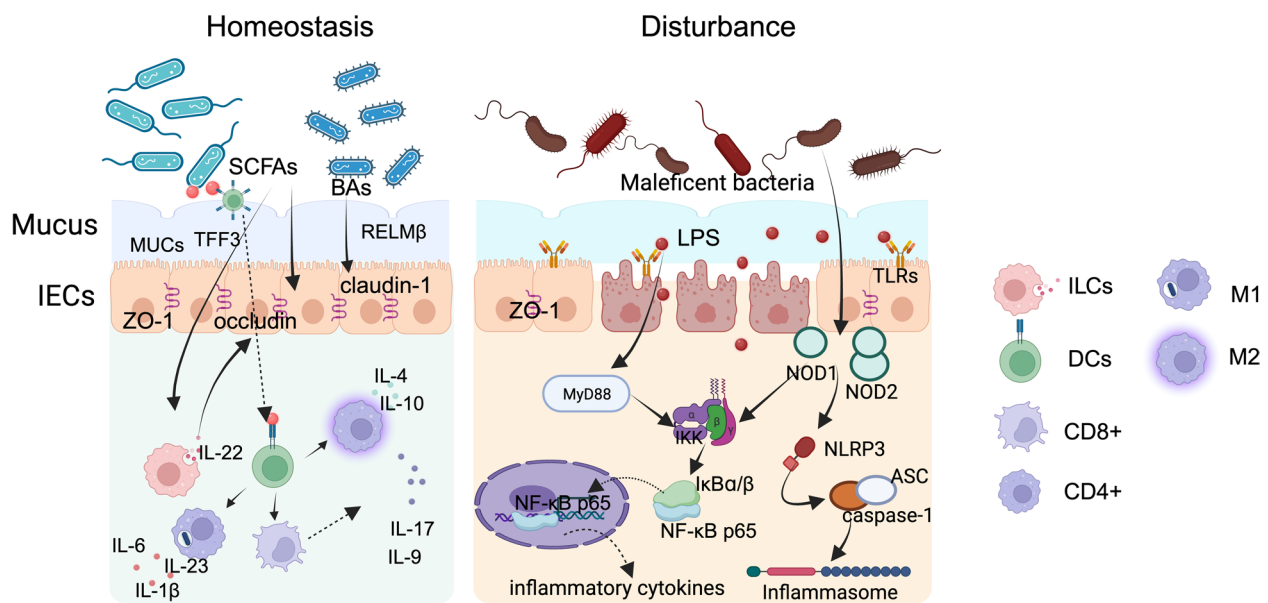


Fig. 2 In a normal state, intestinal barrier function involves SCFAs from beneficial bacteria that energize IECs and increase the synthesis of TJ proteins, such as occludin, claudin, and ZO-1. These proteins seal IECs, preventing paracellular transport. The lamina propria houses various immune cells from both the innate (e.g., innate lymphoid cells (ILCs), M1, M2, and DCs) and adaptive (e.g., CD8+ and CD4+) immune systems. In cases of barrier disruption, TJ proteins are compromised, and TLRs, along with NOD1, recruit LPS from harmful bacteria, triggering inflammatory responses via the MyD88/NFκB signaling pathway. Moreover, it exacerbates intestinal inflammation by activating inflammasomes through the NLRP3/caspase-1 pathway. SCFAs short-chain fatty acids, BAs bile acids, IECs intestinal epithelial cells, TFF3 trefoil factor 3, RELMβ resistin-like molecule beta, IL-4 interleukin-4, TJ tight junction, DCs dendritic cells, TLRs toll-like receptors, NLRP3 NOD-like receptor pyrin domain-containing 3, LPS lipopolysaccharide, caspase-1 cysteinyl aspartate specific proteinase 1, ASC apoptosis-associated speck-like protein containing a caspase recruitment domain

modulatory effects of the gut microbiota and its metabolites on gut barrier function under both physiological and pathological conditions are shown in Fig. 2.

Mechanism through which TCMs protect the intestinal barrier

The protective effects of TCM on the intestinal barrier are mediated through multiple mechanisms, including anti-apoptotic, antioxidant, and anti-pyrototic actions (Tables S1–S4). These effects likely arise from the synergistic interplay among diverse bioactive constituents in TCM. Notably, the specific TCM interventions and the dominant mechanisms may vary across disease contexts and among individuals.

Regulation of the immune system

In exploring the protective effect of TCM on the intestinal barrier, researchers have investigated not only the molecular mechanisms of its immunoregulatory effects but also the comprehensive impact of TCM at an overall level. Scientists are investigating the interactions among various immunoregulatory active ingredients in TCMs to elucidate their roles in synergistic immunoregulation

processes. Numerous scholars have addressed intestinal barrier damage by leveraging the immunoregulatory mechanisms of TCM.

Macrophages play a crucial role in maintaining the homeostasis of the intestinal microenvironment by switching between different functional phenotypes in response to various signals. These phenotypes include classically activated macrophages (M1), which secrete proinflammatory cytokines, and alternatively activated macrophages (M2), which secrete anti-inflammatory cytokines (Fig. 3). Numerous studies have confirmed that certain TCM compounds, such as Wei Ting (*Polygonatum odoratum* var. *pluriflorum*), Compound Sophorae Decoction, and Qingchang Wenzhong decoction, can regulate the polarization direction of macrophages [81–83]. These compounds inhibit proinflammatory polarization to the M1 type and promote anti-inflammatory polarization to the M2 type. Furthermore, these drugs can increase the secretion of anti-inflammatory cytokines such as IL-10 while reducing the production of proinflammatory cytokines such as IL-6, IL-1β, and tumor necrosis factor-α (TNF-α). The ERK/p-NF-κB signaling pathway may be involved in the regulation of macrophages by Baitouweng decoction [84, 85]. Additionally, ginsenoside Rg1 has been shown to improve symptoms of experimental

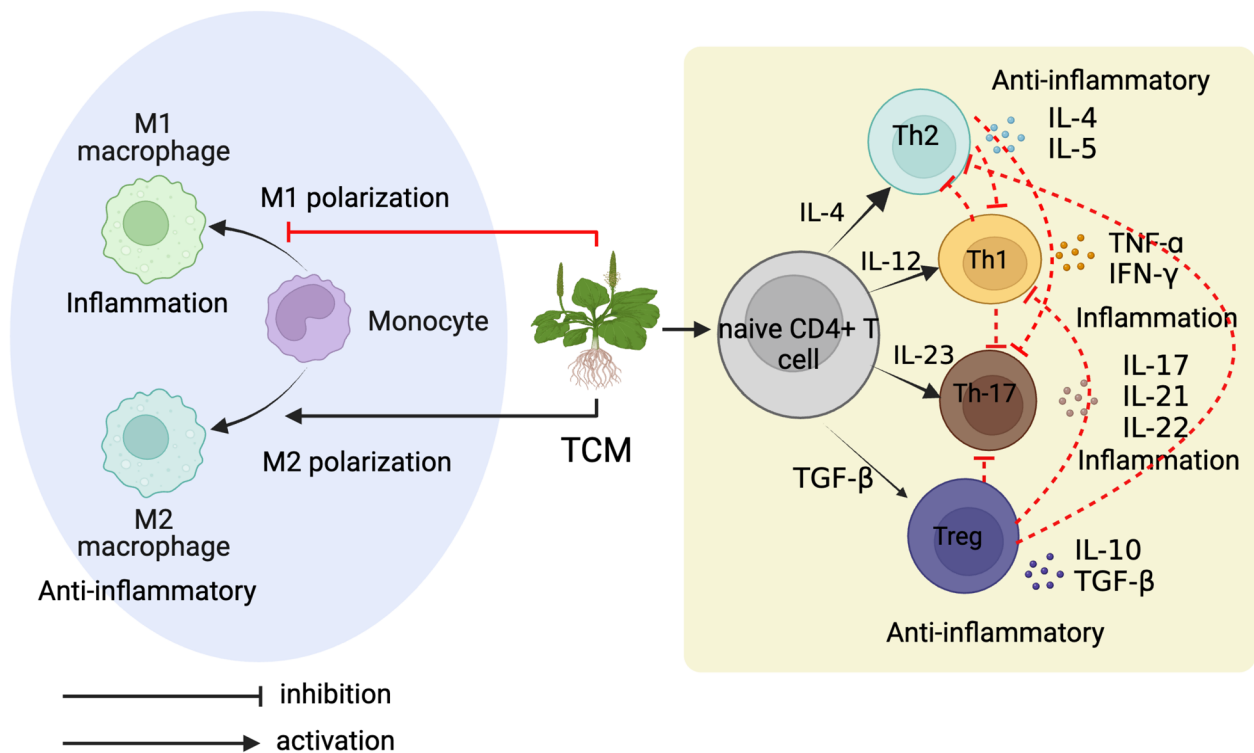


Fig. 3 Immunomodulatory mechanisms of TCM. Traditionally, TCM regulates the immune function of the body as a whole by "strengthening" and "eliminating pathogens". TCM suggests that positive qi (equivalent to the body's immunity) and evil qi (harmful factors that disrupt the body's internal balance) interact to enhance the body's immune ability by regulating positive qi. Recent studies have shown that TCM can enhance the cellular and humoral immune functions of the body and promote the physiological functions of lymphocytes, monocytes, macrophages and hematopoietic stem cells. It can also have immunosuppressive functions, reduce the release of inflammatory factors, and inhibit antibody production and T-cell proliferation. *TNF-α* tumor necrosis factor-alpha, *IFN-γ* interferon-gamma, *TGF-β* transforming growth factor-beta, *Th1* T helper 1 cell, *Th2* T helper 2 cell, *Th17* T helper 17 cell, *Treg* regulatory T cell, *CD4* cluster of differentiation 4

colitis by regulating the balance between M1 and M2 macrophage polarization [86].

Th cells, including T helper 1 (Th1), T helper 2 (Th2), T helper 9 (Th9), and T helper 17 (Th17) cells, are key regulators of the immune system. They play a crucial role in the pathogenesis of IBD. Treg cells are essential for maintaining intestinal homeostasis and inhibiting excessive immune responses by finely regulating adaptive immune responses. Two subtypes of T cells, Th1 and Th17, can promote the progression of IBD, and they enhance the inflammatory response through the secretion of specific cytokines, such as interferon-gamma (IFN-γ) and IL-17. In contrast, Th2 and Treg cells play a role in suppressing inflammation through the secretion of cytokines such as IL-4, IL-5, and IL-10, which can counteract the pro-inflammatory effects of Th1 and Th17 cells. In the field of TCM, research on the immune off-axis effects of Th1/Th2 and Th17/Treg cells is particularly active. Pi-Pa-Run-Fei-Tang, Jingfang Granule, Baitouweng Decoction, Shenling Baizhu San, and other TCM prescriptions have been shown to regulate the Th17/Treg cell ratio,

significantly regulating the adaptive immune system [84, 87–89]. In addition, the effective components of TCM can also be adjusted by altering the Th17/Treg ratio. Patchouli alcohol, extracted from *Pogostemon cablin* Benth., was able to reduce serum levels of TNF-α, IFN-γ, IL-1β, IL-6, and IL-17 and regulate the balance of Th17/Treg differentiation [90]. Studies have shown that berberine regulates intestinal immune balance by increasing secretory immunoglobulin A (SIgA) expression and reducing immune cell infiltration [91]. Oligosaccharides isolated from *Rehmannia glutinosa* have been reported to inhibit macrophage infiltration and restore Th17/Treg cell dysfunction [92]. Therefore, TCM shows promise in protecting the intestinal barrier by modulating immune responses, particularly through regulating macrophage polarization and Th cell ratios.

Protecting TJs

Intestinal TJ proteins constitute a group of proteins situated between the epithelial cells of the intestinal mucosa. These proteins create TJs within the intestinal epithelial

layer, acting as "glue" to preserve the integrity and function of the intestinal barrier. Numerous studies highlight that specific components of TCM also contribute to the protection of intestinal TJ proteins. For instance, Li et al. demonstrated that luteolin significantly increased the expression levels of occludin, claudin-1, and ZO-1 in dextran sulfate sodium (DSS)-induced ulcerative colitis (UC) mice, thereby maintaining the function of the intestinal epithelial barrier [93]. Studies have shown that after treatment with modified Gegen Qinlian decoction and its metabolites baicalein, berberine and glycyrrhizic acid, the activity of diamine oxidase and D-lactic acid in serum significantly decreased, and the levels of ZO-1, occludin, and claudin 1 in colon tissues increased, suggesting that the therapeutic effect of modified Gegen Qinlian decoction may be related to a reduction in intestinal permeability [94]. Puerarin extracted from *Puerariae Lobatae* alleviated 5-Fluorouracil-induced intestinal mucositis in mice through claudin-1, occludin, and ZO-1 expression [95]. Current research on the protection of intestinal TJ proteins by TCM faces certain shortcomings. First, the complexity of TCM, involving various herbal components, lacks standardized research methods, making it challenging to compare results across different studies. Additionally, most studies on the intestinal barrier protection of TCMs rely heavily on in vitro and animal experiments, with insufficient clinical research data to validate the feasibility and safety of these effects in humans. In summary, despite promising findings, more high-quality, multicenter studies are needed to comprehensively understand the role and potential risks of TCM in intestinal barrier protection.

Antioxidant effects

Under normal physiological conditions, the human body can continuously produce reactive species such as reactive oxygen species (ROS) and superoxide anions. Although potentially damaging, most of these substances are effectively cleared by antioxidant substances such as superoxide dismutase (SOD), glutathione reductase, and vitamin E in the body. The remaining ROS play key roles in maintaining normal vascular tone and in cell membrane receptor-mediated signaling processes. However, when the human body is subjected to harmful stimuli such as disease, infection, and stress, the production of ROS in the body may increase dramatically, and its oxidative effect exceeds the scavenging capacity of the antioxidant system, leading to oxidative stress. Oxidative stress is a complex biochemical process involving the interaction of multiple oxidative and antioxidant pathways. In the case of intestinal injury, ROS production is also correspondingly increased, which may exacerbate damage to the intestinal barrier. Fortunately, TCM, through

its unique antioxidant mechanism, is able to protect the intestinal barrier. TCMs contain a variety of bioactive components, which can regulate the balance of oxidation and antioxidation through a variety of pathways, thereby reducing the negative effects of oxidative stress on the intestine and maintaining intestinal health. Yu Shi An Chang Fang, a typical Chinese medicine prescription, may effectively manage oxidative stress by increasing the activities of antioxidant enzymes such as SOD, catalase (CAT), and glutathione peroxidase (GPX), while reducing tissue malondialdehyde (MDA) levels [96]. Shaoyao-Gancao Decoction (SGD) is made up of *Paeonia lactiflora* Pall. and *Glycyrrhiza uralensis* Fisch. fried with honey. SGD was first described in the medical literature by Shanghan Lun (Treatise on Febrile Diseases), written by Zhang Zhongjing in the Han Dynasty. SGD has been reported to alleviate DSS-induced colitis in mice by increasing the levels of SOD, glutathione (GSH), and CAT; reducing the content of MDA; and suppressing the TLR4/NF- κ B signaling pathway [97, 98]. *Ilex rotunda* Thunb. promotes the expression of SOD, GSH, and CAT by activating the NRF2/heme oxygenase-1 (HO-1) pathway, thereby enhancing cellular antioxidant defense [99]. Bryostatins can activate the NRF2/HO-1 pathway, increase the expression of antioxidant enzymes, and mitigate DSS-induced intestinal barrier damage [100]. These multilayered mechanisms provide a broad and promising basis for research on the antioxidant effects of TCMs on the protection of intestinal barrier function.

Regulating the structure and diversity of the gut microbiota

TCM has demonstrated significant potential in regulating the structure and diversity of the intestinal flora. Multiple studies have indicated that certain TCM ingredients can influence the richness and species composition of the gut microbiome. For instance, evodiamine derived from *Tetradium ruticarpum* has been identified as a regulator of the intestinal microbiota. It promotes the growth of beneficial bacteria, such as *Lactobacillus*, *Ruminococcus*, and *Prevotella*, while inhibiting the reproduction of harmful bacteria such as *Fusobacterium* and *Lachnospira*. This action contributes to maintaining a balanced intestinal microecology [101]. Furthermore, *Poria cocos* has been demonstrated to enhance the structure of the gut microbiota. It increases the abundance of probiotics and contributes to improving overall microbial diversity [102]. Sun et al. demonstrated that Yishen Qingli Heluo Granule restored the abundance of intestinal microbiota and increased the relative abundance of SCFA-producing bacteria, such as Lactobacillaceae, *Lactobacillus*, and *Lactobacillus gasseri*. This contributed to increased SCFA concentrations, including total SCFAs, acetic acid,

and butyric acid [103]. Huang-Lian-Jie-Du Decoction can restore intestinal flora homeostasis in UC mice by inhibiting the growth of pathogenic bacteria while preventing a reduction in beneficial bacteria. Additionally, it significantly corrects intestinal flora dysfunction in UC mice [104]. Recent research has revealed that phillygenin, a distinctive fingerprint lignan component extracted from *Forsythia suspensa* (Thunb.) Vahl, can stimulate the production of SCFAs in the gut of mice with carbon tetrachloride-induced liver fibrosis. Specifically, phillygenin enhances the generation of acetate, propionate, and butyrate, which are crucial SCFAs. This action helps to rectify the metabolic disturbances in bile acids (BAs) that occur in these mice, thereby potentially contributing to the mitigation of liver fibrosis and the restoration of gut health [105]. These findings offer valuable support for the application of TCMs in maintaining intestinal health, promoting nutrient absorption, and revealing the potential mechanism of interaction between TCMs and intestinal microorganisms.

Anti-apoptotic effect

In fact, TCMs exhibit a noteworthy antiapoptotic effect in the process of protecting the intestinal barrier. Studies have reported that *Tetrastigma hemsleyanum* Diels et Gilg can downregulate the expression of Bax/Bcl2 and cleaved cysteinyl aspartate specific proteinase 3 (caspase-3), thereby inhibiting apoptosis in a mouse model of intestinal mucosal barrier dysfunction induced by intraperitoneal injection of LPS [106]. Zhuo et al. reported that emodin upregulated Bcl2 levels and downregulated Bax and cleaved caspase-3 expression levels in mice with acute pancreatitis [107]. Similarly, TCM prescriptions have demonstrated antiapoptotic effects. Qingjie Fuzheng, for example, reduced apoptosis in jejunal tissue by increasing Bcl-5 expression and decreasing Bax expression [108]. Nevertheless, the antiapoptotic mechanism of TCM in the protection of the intestinal barrier requires further investigation.

Antipyroptotic effect

TCM may protect against intestinal barrier damage through antipyroptotic effects. Pyroptosis is a novel form of programmed cell death characterized by caspase-1 dependence and the release of numerous proinflammatory factors. [109]. As shown in Fig. 4, the mechanism of pyroptosis can be categorized into classical and nonclassical pathways. In the classical pyroptosis pathway, inflammasomes such as NOD-like receptor pyrin domain-containing 3 (NLRP3), NLRC4, absent in melanoma 2 (AIM2), and Pyrin are activated. They cleave pro-caspase-1 to generate active caspase-1, which subsequently cleaves gasdermin D (GSDMD) protein, resulting

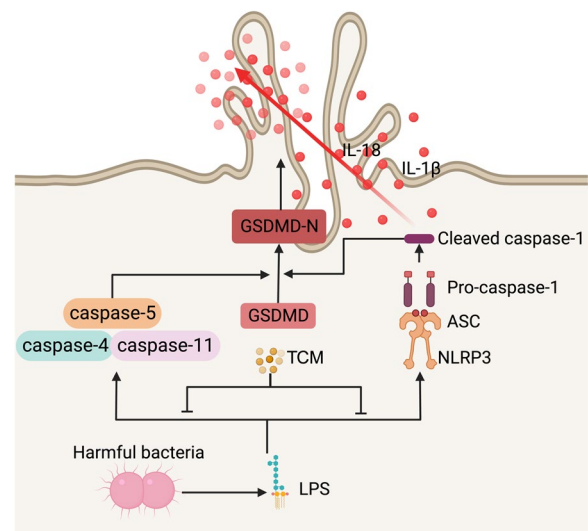


Fig. 4 Schematic representation of the classical and nonclassical pathways that trigger pyroptosis. GSDMD gasdermin D

in the formation of active N-termini and C-termini. The N-terminus promotes cell membrane perforation and cell death. Additionally, caspase-1 can process pro-IL-1 β to form active IL-1 β , which is then released into the extracellular matrix, amplifying the inflammatory response [110]. In the nonclassical pyroptosis pathway, LPS can directly bind to caspase-4/5/11. On the one hand, activated caspase-4/5/11 can cleave GSDMD protein, and the N-terminus of GSDMD protein can mediate membrane lysis and pyroptosis. Additionally, it can activate the NLRP3 inflammasome, leading to the activation of caspase-1 and ultimately the production and release of IL-1 β [111]. In a study by Ye et al., Yu Shi An Chang Fang downregulated the expression levels of the pyroptosis-related proteins NLRP3, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and cleaved caspase-1. It hindered the cleavage of GSDMD protein, slowing the formation of the N-terminus and reducing cell membrane perforation and pyroptosis [96]. Currently, studies on the nonclassical pathway of pyroptosis involving TCM are limited, and further exploration is necessary to understand its mechanisms comprehensively.

Anti-ferroptosis effect

Ferroptosis is a regulated form of cell death that is dependent on iron and ROS. It represents a distinct type of cell death, different from apoptosis, necrosis, and autophagy [112]. As shown in Fig. 5, ferroptosis is triggered by an imbalance between the generation and degradation of lipid ROS within cells. Inducers of ferroptosis, either directly or indirectly, impact GPX through various

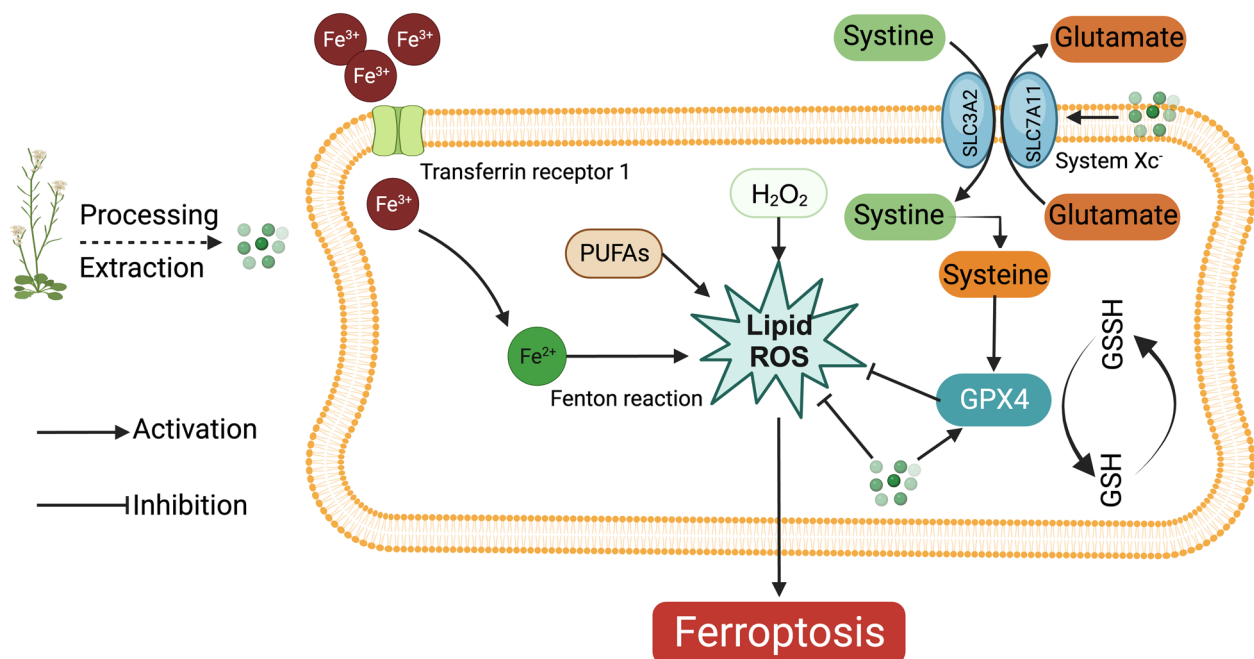


Fig. 5 The mechanism through which TCM acts against intestinal ferroptosis involves key factors such as excess iron and PUFAs. Elevated iron levels, acquired through transferrin receptor 1 uptake or degradation of iron storage proteins, make cells susceptible to ferroptosis via the Fenton reaction. The availability of cysteine and GSH, which are regulated by the cystine-glutamate antiporter system Xc⁻ or the transsulfuration pathway, play crucial role. GSH, a key cofactor through which GPX4 clears lipid peroxides, is essential for preventing ferroptosis. Ferroptosis is initiated by the inhibition of system Xc⁻ or GPX4 activity, ultimately leading to cell death. TCM mitigates ferroptosis mainly by promoting the expression of system Xc⁻-related proteins, such as SLC7A11 and SLC3A2; increasing the synthesis rate of GPX4; and reducing the levels of ROS and iron ions. GPX4 glutathione peroxidase 4, PUFAs polyunsaturated fatty acids, ROS reactive oxygen species

pathways, leading to a diminished antioxidant capacity in cells, the accumulation of ROS, and ultimately, oxidative cell death. GPX4 plays a pivotal role in cell survival and serves as the core regulatory protein in ferroptosis. GPX4 can degrade small molecular peroxides and certain lipid peroxides, thus inhibiting lipid peroxidation. Studies have indicated that downregulation of GPX4 expression renders cells more susceptible to ferroptosis. Conversely, overexpression of GPX4 leads to increased tolerance to ferroptosis [113]. Indeed, ferroptosis suppressor protein 1 (FSP1), SLC7A11, and NRF2 are recognized as negative regulators of ferroptosis and play crucial roles in anti-ferroptotic defense mechanisms [114]. The anti-ferroptotic effects of TCM are manifested primarily through the upregulation of GPX4, SLC7A11, and NRF2 expression coupled with the downregulation of ROS and iron ion levels [115, 116]. Further studies are warranted to elucidate the mechanisms by which TCM affects intestinal anti-ferroptosis activity.

In summary, intestinal barrier injury is driven by interconnected disturbances across epithelial integrity, mucus and antimicrobial defenses, mucosal immune signaling, and microbiota-derived metabolic cues. These key nodes provide a mechanistic framework for interpreting

therapeutic interventions. In the next section, we summarize the protective effects of TCM formulas, single herbs, and active constituents by mapping functional outcomes and representative biomarkers to the mechanistic nodes outlined above.

Protective effects of TCMs on the intestinal barrier

To avoid redundancy and strengthen logical flow, this section focuses on evidence of barrier protection, while mechanistic interpretations are linked to the preceding sections. For each protective outcome, we highlight typical biomarkers and briefly indicate the most relevant signaling nodes.

TCM prescription

TCM is indeed a valuable resource in the quest for drugs to protect the intestinal barrier. Chinese classical prescriptions, derived from the wisdom of scholars across past dynasties through extensive clinical practices, represent the quintessence of TCM. WangShiBoChiWan (WSBCW) was a pediatric prescription formulated by Wang Luqing, a renowned physician in Nantong during the Qing Dynasty's Daoguang reign (approximately 1840), on the basis of a secret formula passed down by

the Ninth Emperor of the Qing Dynasty. Originally in decoction form, through extensive clinical practice and ongoing exploration, it was processed into micropills. These micropills are as small as rapeseeds, uniformly sized, and devoid of any noticeable bitter taste. This innovative medication boasts a unique design and surpasses traditional pills, powders, and decoctions, earning it the title of "China's premier pill." It comprises *Rhizoma coptidis*, *Buibus Fritillariae cirrhosae*, *Radix et Rhizoma Rhei*, *Rhizoma Arisaematis*, and *Fructus crotonis*. With respect to Chinese folk wisdom, WSBCW has been widely utilized for centuries to address gastrointestinal disorders among both children and adults. Recent studies have demonstrated that WSBCW significantly upregulates the expression of ZO-1, ZO-3, and Claudin-3 while inhibiting the expression of inflammatory factors. These effects contribute to the therapeutic impact of WSBCW in mice with castor oil-induced irritable bowel syndrome with diarrhea (IBS-D) [117]. With the ongoing advancements in science and technology, scientists have successfully extracted berberine, a crucial alkaloid, from *Coptidis Rhizoma*. This alkaloid has notable anti-inflammatory, antioxidative, and antitumor properties. Research has demonstrated that berberine can effectively alleviate DSS-induced UC, indicating promising therapeutic potential [49]. Additionally, the active compound emodin extracted from *Rhubarb* has been utilized in modern medical research for treating related conditions such as intestinal barrier dysfunction. Research conducted by Xun et al. indicated that adding emodin to feed alleviates lipopolysaccharide-induced intestinal mucosal barrier damage in piglets by modulating the gut microbiota [118].

Additionally, Fan et al. utilized the formula BaWei Bai-DuSan, which contains ingredients such as *Platycodon grandiflorus* (Jacq.) A.DC., *Phellodendri Cortex*, *Hippophae rhamnoides* L., *Prunus dulcis* (Mill.) D.A. Webb, *Lonicera japonica* Thunb., *Lilium brownii* var. *viridulum* Baker, *Polygonatum sibiricum* Delar. ex Redouté, and *Panax ginseng* C.A. Mey. to treat cecal ligation and puncture (CLP) model mice. Their study demonstrated that this formula upregulated TJ protein levels, inhibited inflammation, and increased the number of beneficial flora in a mouse model induced by CLP (cecal ligation and puncture) [119]. Research has shown that active ingredients extracted from this prescription, such as berberine, chlorogenic acid, and amygdalin, also have excellent intestinal barrier protective effects [120–122].

Ganluyin is derived from the "Taiping Huimin He Dose Bureau Prescription" and is a classic formula for treating oral ulcers caused by stomach heat and damp heat in the spleen and stomach. The main ingredients of this formula include *Eriobotrya japonica* (Thunb.) Lindl., *Rehmannia*

glutinosa (Gaertn.) DC., *Asparagus cochinchinensis* (Lour.) Merr., *Citrus aurantium* L., *Artemisia scoparia* Waldst. & Kit., *Ophiopogon japonicus* (L.f.) Ker Gawl., *Dendrobium nobile* Lindl., *Glycyrrhiza uralensis* Fisch., and *Scutellaria baicalensis* Georgi. In a separate study, Xiong et al. employed the classic TCM prescription Ganluyin to ameliorate DSS-induced UC. These findings revealed that Ganluyin increased the expression of occludin, claudin-1, and ZO-1 while inhibiting the LPS/TLR4/NF- κ B pathway. These findings suggest that it has the potential to improve UC by enhancing the activity of TJ proteins and suppressing inflammatory pathways [123]. In summary, the unique pharmacological characteristics of active substances in TCM compound formulas play important roles in protecting the intestinal barrier. These active substances maintain intestinal barrier integrity through various pathways, such as regulating intestinal immunity, antioxidation, and anti-inflammation, and modulating the intestinal microbiota.

Over the past five years, our system has reviewed various traditional classical prescriptions in Table S1 for treating intestinal barrier dysfunction, including formulations such as Qingchang Wenzhong Decoction, Tong-fu-fei Decoction, Dahuang Mudan Decoction, and Yishen Qingli Heluo Granule. These prescriptions show promise and merit further development and utilization.

Single TCM

Recent studies have revealed that, in addition to the above-mentioned formulations, individual TCMs can also safeguard the intestinal barrier. These protective effects may involve diverse mechanisms, including the upregulation of intestinal TJ proteins, antioxidant and anti-inflammatory actions, and the regulation of intestinal flora.

Coptis chinensis (Huang Lian) has diverse pharmacological effects, such as antioxidant, anti-inflammatory, antibacterial, and antiviral effects. Research by Meng et al. indicated that *Coptis chinensis* can mitigate CLP-induced sepsis by enhancing the presence of beneficial Firmicutes and Bacteroidetes bacteria while also sustaining Tregs and IL-10 levels [124]. Xie et al. reported that *Coptis chinensis* effectively mitigated the trinitrobenzene sulfonic acid-induced disturbance of intestinal flora homeostasis in rats. This intervention resulted in a notable reduction in species richness and a decrease in the abundance of beneficial bacteria, including lactic acid bacteria, to address UC [125]. Piper sarmentosum can alleviate the LPS-induced inflammatory response in porcine intestinal epithelial cells (IPEC-J2). This is characterized primarily by the downregulation of IL-1 β , IL-6, and TNF- α and the inhibition of the NF- κ B signaling pathway [126]. Sargassum, a significant economic resource in the ocean, has been found to alleviate enteritis and dysbiosis

in a murine model of food allergy. This effect is attributed to its ability to regulate the balance of intestinal flora, inhibit the release of inflammatory factors, and upregulate the expression of TJ proteins. Table S2 highlights certain individual TCMs that exhibit positive effects in safeguarding the intestinal barrier.

TCM ingredients

Polysaccharides

Polysaccharides, which are complex carbohydrate polymers formed by the linkage of at least ten monosaccharide units through glycosidic bonds, play crucial roles in the growth and development of living organisms. These biomolecules have garnered significant attention for their potential applications in the clinical treatment of diseases and the enhancement of overall health. Some polysaccharides have already been utilized in medical therapies, demonstrating their value in promoting wellness and combating various health conditions [127]. Xiao et al. reported that polysaccharides extracted from *Tremella tremella* significantly improved UC symptoms, reduced inflammatory cell infiltration, and enhanced intestinal barrier function in a DSS-induced UC model in a mouse model and an LPS-stimulated Caco-2 cell model, suggesting potential therapeutic value for UC [128]. Apart from *Polygonum japonicum* polysaccharide, other polysaccharides extracted from TCM have been shown to have significant protective effects on the intestinal barrier. For example, *Poria cocos* polysaccharides are derived from *Poria cocos*, a commonly used TCM. Its polysaccharide components have been shown to enhance intestinal barrier function by promoting the proliferation and migration of intestinal epithelial cells and regulating the balance of the intestinal flora [129–131]. In addition, *Ganoderma lucidum* polysaccharides contain a variety of bioactive polysaccharides that enhance immune, antitumor and antioxidation effects. In terms of intestinal health, *Ganoderma lucidum* polysaccharide can improve intestinal barrier function and reduce the inflammatory response [132]. In addition, *Lycium barbarum* polysaccharides, derived from the traditional tonic medicine *Lycium barbarum*, have been shown to promote immune function, antiaging, and antifatigue effects. Studies have shown that *Lycium barbarum* polysaccharides can protect the intestine from damage and enhance the integrity of the intestinal barrier [133, 134]. *Fructus mori* polysaccharide notably decreased the concentrations of TNF- α , IL-1 β , and IL-6 but significantly increased the levels of ZO-1, occludin, and claudin-1 [135]. In mice, acrylamide-induced intestinal barrier function damage was observed. *Ganoderma atrum* polysaccharide

reversed the decreases in GSH, CAT, and SOD activity; the increase in MDA; and the decrease in the expression of TJ proteins caused by acrylamide [136]. Furthermore, polysaccharides show promise for treating intestinal barrier damage caused by heavy metals. According to Hao et al., *Flammulina velutipes* polysaccharide increases inflammatory cytokine levels and increases the abundance of *Bacteroides*, along with decreasing the abundance of *Desulfovibrionales* and *Clostridium*, in cadmium-induced gut injury in mice [137]. These TCM polysaccharides act through different mechanisms, including directly enhancing the barrier function of intestinal epithelial cells, regulating intestinal flora, inhibiting inflammatory responses, and promoting intestinal repair. They have shown great potential in maintaining intestinal health and preventing related diseases.

Total flavones (TFAs)

TFAs are a group of complex compounds extracted from TCMs that are known for their diverse biological activities. These biological activities are attributed to the unique chemical structure and functional properties of TFAs. In particular, TFAs extracted from *Abelmoschus manihot* (L.) Medik. have been reported to contain multiple flavonoid glycosides, including quercetin-3-O-robinobioside, gossypetin-3-O-glucoside, quercetin-3'-O-glucoside, isoquercetin, hyperoside, myricetin, gossypetin, and quercetin. Together, these components can alleviate the DSS-induced imbalance of the gut microbiota and promote the expression of TJ proteins, thereby helping to maintain the integrity of the intestinal barrier [138].

In addition, TFAs from *Lonicera rupicola* Hook.f. & Thomson have shown the potential to alleviate colonic inflammation and oxidative stress by regulating the PI3K/AKT signaling pathway. This mechanism of action helps to restore epithelial barrier function and improve the intestinal microenvironment. Therefore, the total flavonoid content of *Lonicera rupicola* Hook.f. & Thomson have comprehensive protective effects on DSS-induced UC in mice [139]. These findings highlight the potential value of TCM-TFAs in maintaining intestinal health and treating related diseases.

Oligosaccharides

Functional oligosaccharides are saccharides with a low degree of polymerization. They not only exist widely in nature but also have attracted much attention because of their unique physiological functions. These oligosaccharides not only have multiple biological activities, such as anti-tumor, anti-virus, anti-caries, anti-constipation, and

immune-enhancing effects but also have a significant protective effect on intestinal health [140]. At present, more than 25 types of functional oligosaccharides are known, including isomaltose oligosaccharides, fructooligosaccharides, xylo-oligosaccharides, galactooligosaccharides, soybean oligosaccharides, and mannose oligosaccharides [141].

In recent years, with the in-depth study of TCMs, researchers have developed industrial strategies for the production of novel oligosaccharides from TCMs, providing new possibilities for obtaining functional oligosaccharides. In particular, *Rehmannia* oligosaccharides (RGO) significantly reduced LPS-induced intestinal inflammation and intestinal barrier damage in mice. RGO can comprehensively protect intestinal function by increasing the expression of intestinal barrier-related proteins, reducing the level of inflammatory factors, increasing the activity of digestive enzymes, increasing the content of SCFAs, and regulating the composition of intestinal microorganisms [92]. *Bletilla* oligosaccharides (BOs) have also been shown to protect the intestinal barrier. It effectively alleviates intestinal barrier dysfunction by inhibiting the release of inflammatory factors, increasing the secretion of mucin, and enhancing the expression of TJ proteins. In addition, BOs have a protective effect on UC through the regulation of intestinal flora and metabolites, providing a new strategy for the treatment of UC [142]. Fructooligosaccharides were isolated from *Polygonatum cyrtoneura* Hua, and their potential to enhance intestinal barrier function should not be overlooked. Studies have shown that fructooligosaccharides can alleviate DSS-induced histopathological damage, improve intestinal barrier function, downregulate the expression of proinflammatory cytokines, upregulate the expression of antioxidant genes, inhibit the destruction of the mucosal barrier, and promote the growth of probiotics, thereby significantly improving intestinal barrier damage [143].

In summary, functional oligosaccharides show great potential for maintaining intestinal health and preventing and treating related diseases. With increasing research, these natural compounds are expected to be more widely used in the fields of medicine, food and health products in the future.

Essential oil

Essential oils, the quintessence of nature, are the byproducts of plant secondary metabolism. They not only endow plants with unique fragrances but also harbor a wealth of biological activities. According to the European Pharmacopeia, essential oils are typically extracted from plant materials through processes such as water distillation, steam distillation, or specific mechanical methods,

which transform the aromatic components of a plant into a liquid form [144]. The chemical composition of essential oils is extremely complex and includes more than 20 different chemical components [145]. Among them, terpenes, aromatics, and aliphatic compounds are the main constituents, accounting for 20% to 70% of the total concentration of essential oils [146]. These components exist in varying concentrations, together forming the unique chemical and sensory characteristics of the essential oil. The biological activities of essential oils are very broad, with antibacterial, antiviral, and antifungal properties, making them highly valuable in the medical field [146]. In this review, we report that the *Atractylodes* oil (AO) of *Atractylodes lancea* (Thunb.) DC. has been shown to have significant therapeutic effects on a rat model of IBS-D. AO significantly improved IBS-D symptoms by increasing body weight, diarrhea scores, and the levels of IL-10 and aquaporins (AQP 3 and AQP 8). In addition, AO reduced the expression of inflammatory factors such as TNF- α and IL-6, upregulated the SCF/c-kit signaling pathway, enhanced the expression of TJs, and inhibited the MLCK/MLC 2 pathway, thereby protecting the intestinal mucosa [147]. Garlic essential oil (GEO) also protected the intestinal barrier. In a chronic unpredictable mild stress model, GEO suppressed the NLRP3 inflammasome, increased the expression of TJ proteins, increased the concentration of SCFAs, and promoted the growth of beneficial SCFA-producing bacteria, thus exerting an antidepressant effect on rats [148]. These findings reveal the potential of essential oils in improving intestinal diseases and mental health, providing a new perspective for the medical application of essential oils. Substances not described above are recorded in Table S3.

Monomers

Flavonoids

Flavonoids, a group of plant-derived secondary metabolites, exhibit diverse physiological activities and pharmacological effects. This class is divided into six major groups: flavonones, flavonols, flavones, anthocyanidins, flavan-3-ols, and isoflavones, with more than 4000 identified compounds. Genistein, a specific flavonoid, has been commonly used to improve intestinal TJ barrier dysfunction. Zhang et al. demonstrated that genistein alleviates DSS-induced colonic injury by inhibiting the TLR4/NF- κ B signaling pathway and enhancing the expression of TJ proteins [149]. Quercetin, a flavonol obtained from vegetables and fruits, dose-dependently increased the expression of ZO-1 and Claudin1. Additionally, it activates the AhR pathway by facilitating the nuclear translocation of AhR, thereby improving intestinal barrier integrity in mice with UC [150].

Alkaloids

Researchers have identified hundreds of thousands of alkaloids. Currently, more than one hundred alkaloid drugs are in clinical use [151]. Alkaloids, known for their potent pharmacological activities, play a significant role in treating various human diseases, particularly intestinal disorders. In their study, Yao et al. demonstrated that matrine upregulated the abundance of *Barnesiella intestinihominis* and downregulated the abundance of *Helicobacter ganmani*, leading to the inhibition of the PPAR- α signaling pathway and improvement in intestinal barrier integrity, thus providing protection against DSS-induced colitis in mice [152]. In an in vitro model, alkaloids have been shown to regulate epithelial barrier function. For instance, Hanfangchin A promotes the expression of occludin in Caco-2 cells by modulating the AhR/miR-429 pathway [153].

Polyphenols

Polyphenols are indeed secondary metabolites that are commonly distributed in plants. Polyphenols, which are classified into various subclasses, such as flavonoids and curcuminoids, are secondary metabolites that are commonly distributed in plants. Recent studies highlight their diverse pharmacological activities, including antioxidative, anti-inflammatory [154], and antibacterial effects [155]. Previous research has indicated that certain polyphenols, such as resveratrol, chlorogenic acid, and hesperetin, enhance intestinal barrier function. Resveratrol can alleviate ROS-induced intestinal barrier damage by activating NRF2 signaling and promoting the expression of antioxidant enzymes in IPEC-J2 cells [156]. Supplementation with chlorogenic acid has been shown to alleviate chronic stress-induced intestinal damage in mice through the inhibition of the P38/mitogen-activated protein kinase (MAPK)/NF- κ B pathway [157]. Furthermore, hesperidin enhances AMP-activated protein kinase (AMPK) phosphorylation, leading to an increase in the expression of TJ-related proteins such as occludin, MarvelD3, JAM-1, and claudin-1 in Caco-2 cells [158].

Terpenoids

Terpenoids constitute the largest class of natural products, predominantly extracted from plants but also found across all forms of living organisms, serving as sources of energy, biological building blocks, and signaling molecules. Terpenoids are categorized into three main groups on the basis of their structure: monoterpenoids, sesquiterpenoids, and diterpenoids. Among them, triterpenoids have been extensively studied for their potential to regulate various biological functions, particularly their anti-proliferative, anti-angiogenic, anti-metastatic,

and apoptosis-inducing activities [159]. In this review, we identified seven terpenoid compounds, namely, clematichinenoside AR, astragaloside IV, taraxasterol, gypenosides, ursolic acid, obacunone, and saikosaponin-d (Table S4), which significantly protect the intestinal barrier. These triterpenoids function primarily by modulating the structure of the gut microbiota; influencing the metabolism of SCFAs; increasing the expression of the mucin protein mucin 2 (MUC2) and TJ proteins; and exerting anti-inflammatory, antioxidant, and antiapoptotic effects to protect the intestinal barrier. These findings provide a scientific basis for the potential application of triterpenoids in maintaining intestinal health and treating related diseases.

Ginsenosides

Species within the genus *Panax*, including ginseng, American ginseng, and Sanqi, have been used as medicinal plants for more than 5000 years [160]. Ginsenoside Rb1, one of the most abundant and important compounds isolated from the genus *Panax*, has been proven to have numerous beneficial effects on the human body, including effects on the central nervous system, cardiovascular system, immune system, and antitumor activity [161]. In addition to reviewing ginsenoside Rb1, this article also covers other ginsenoside compounds, such as ginsenoside Rg1, ginsenoside Rc, ginsenoside Rk3, and ginsenoside Rh4. These compounds protect the intestinal barrier through their anti-inflammatory effects and by promoting the expression of TJs.

Anthraquinone

Anthraquinones, including emodin, aloe-emodin, rhein, chrysophanol and emodin methyl ether, are a group of active substances widely present in Chinese herbal medicines such as rhubarb, *Polygonum cuspidatum*, and *Polygonum multiflorum*. These components have some acidic properties because of their phenolic hydroxyl functional groups. Free anthraquinones are relatively less polar, whereas glycosidic compounds formed by binding to glycosidic bonds have increased polarity. Owing to their chemical structure, anthraquinones have a variety of pharmacological effects, including anti-inflammatory, antibacterial, antitumor, antiviral and antidiarrheal effects. In terms of maintaining the intestinal barrier, anthraquinones have been shown to have significant anti-inflammatory effects through interference with key links in the inflammatory process. Specifically, rhein has been shown to protect IEC-6 cells from TNF- α -induced barrier damage by restoring the expression of the TJ protein ZO-1, reducing myosin light chain (MLC) phosphorylation and inhibiting NF- κ B activation. In addition, rhein

reduced the LPS-induced expression of the inflammatory factors IL-1 β and IL-6 and inhibited the expression of inflammation-related molecules such as TLR4, NLRP3, and caspase 1 [162]. Similarly, emodin has been shown to inhibit intestinal inflammation, enhance intestinal barrier function, and prevent the secondary translocation of *Escherichia coli* in septic mice. Proteomic studies revealed that JNK2 is a direct target of emodin and that its downstream effectors NF- κ B and AP-1 are involved in the regulation of the inflammatory response. Emodin also increases the diversity of gut microbes and decreases the abundance of potential pathogenic bacteria, thereby reducing the risk of bacterial translocation during sepsis and providing a significant protective effect on the intestinal barrier [163].

Phenylpropanoids

Phenolic compounds are secondary metabolites that are found extensively in plants and are widely distributed in fruits, vegetables, grains, beverages, spices, and herbal medicines. These compounds have various biological activities, including antimicrobial, antioxidant, anti-inflammatory, antidiabetic, and anticancer properties, as well as protective effects on the kidneys, nervous system, heart, and liver [164]. Specifically, ferulic acid, a phenolic compound, has been shown to improve the gut microbiota dysbiosis induced by a high-fat diet, increase the accumulation of SCFA-producing bacteria in the gut and their receptor expression, reduce the levels of endotoxin-producing bacteria and serum endotoxins, and strengthen intestinal barrier function by inhibiting the colonic TLR4/NF- κ B inflammatory pathway [165]. Furthermore, research has indicated that anethole can improve the growth performance of weaned piglets infected with *E. coli* by protecting gut barrier function, reducing inflammatory responses, and increasing the abundance of beneficial bacteria. Piglets treated with anethole presented increased feed conversion rates, less intestinal morphological damage, and reduced expression of inflammatory factors, revealing the potential anti-inflammatory and gut-protective effects of anethole [166].

Other compounds

In the field of exploring protective compounds of the intestinal barrier, several other substances in addition to those mentioned above have been shown to have significant protective effects. For example, aloin A (AA), an anthrone compound, significantly protected against DSS-induced colitis by alleviating inflammatory symptoms, reducing the inflammatory response, preventing colon shortening and apoptosis, and promoting cell proliferation. AA enhances intestinal barrier function

by enhancing the secretion of TJ proteins and MUC2, and its mechanism of action may involve the inhibition of the Notch signaling pathway, suggesting that AA may be a potential candidate drug for the treatment of UC [167]. On the other hand, the furan compound atracylodin (ATL) also had significant therapeutic effects on a DSS-induced UC mouse model. ATL reduces colonic macrophage activation and the inflammatory response by inhibiting MAPK signaling. In addition, ATL is able to protect the intestinal barrier by regulating the balance of intestinal flora, increasing beneficial flora and reducing harmful flora. In an LPS-induced macrophage model, ATL suppressed the expression of inflammatory factors and reduced lactate production and glyceraldehyde-3-phosphate dehydrogenase activity, which in turn inhibited the translation of TNF- α [168]. Eleutheroside E (EE), a glucoside, also positively affects intestinal barrier function. Studies have shown that 0.1 mg/mL EE can increase transepithelial electrical resistance, reduce cell permeability, and increase the mRNA and protein expression of TJ proteins such as claudin-3 and ZO-1. EE pretreatment significantly attenuated the inflammatory response induced by soybean agglutinin (SBA), which was mediated by the upregulation of the anti-inflammatory cytokines IL-10 and TGF- β and the downregulation of the proinflammatory cytokines IL-6, TNF- α , and IFN- γ [169]. Therefore, EE was not only able to improve the mechanical barrier function of IPEC-J2 cells but also effective against SBA-induced barrier dysfunction, demonstrating its potential as an intestinal protective agent. No description of other compounds in Table S4.

Conclusion and prospects

This review summarizes recent evidence that TCM, including classical formulas, single herbs, and bioactive constituents, can protect and repair intestinal barrier function through multilevel regulation across the barrier–microbiota–immune axis. Across diverse experimental settings, TCM interventions repeatedly converge on several core mechanisms: attenuation of inflammation and oxidative stress, reinforcement of epithelial TJs and mucus/antimicrobial defenses, modulation of immune homeostasis, and restoration of dysbiotic microbiota and their metabolites. These multicomponent and multitarget features provide a plausible rationale for the sustained barrier benefits reported in preclinical models and emerging clinical studies.

To move the field from "promising evidence" to reproducible and clinically actionable strategies, future work should focus on several operational priorities derived from the evidence gaps highlighted in this review. First, barrier-related endpoints and experimental reporting should be standardized by adopting a harmonized set of

structural and functional readouts, including permeability, TJ and mucus integrity, epithelial restitution, antimicrobial defense, and immune profiling, while key model parameters such as species or strain, diet, antibiotic exposure, disease induction, and sampling timepoints should be consistently documented. Second, studies should establish clear "formula or herb, chemical basis, exposure, and effect" causal chains by integrating chemical profiling and batch-to-batch quality control with pharmacokinetics, tissue exposure, and pharmacodynamic responses at barrier sites, thereby identifying marker compounds and bioavailable fractions that best explain *in vivo* barrier outcomes. Third, microbiota-dependent and microbiota-independent mechanisms should be disentangled using targeted mechanistic designs, for example, antibiotic depletion, fecal microbiota transplantation, gnotobiotic or defined-consortium models, and metabolite supplementation, supported by paired multiomics that link microbial functions and metabolites to host pathways. Fourth, TCM syndrome differentiation should be translated into biomarker-supported stratification by connecting syndromes to measurable barrier phenotypes and inflammatory or metabolic signatures and then prospectively testing syndrome-guided interventions in barrier-defined subgroups while identifying predictive biomarkers of response. Fifth, clinically realistic trials should prioritize mucosal healing and relapse prevention, use barrier-aligned operational endpoints, and evaluate TCM as an adjunct to standard care with rigorous randomization and blinding, predefined primary endpoints, and clinically meaningful follow-up. Finally, safety, herb-drug interactions, and regulatory readiness should be strengthened through systematic assessment of chronic toxicity, hepatorenal risk signals, immunological risks, and interactions mediated by metabolic enzymes and transporters, together with standardized Chemistry, Manufacturing and Controls frameworks that ensure authenticated raw materials, contaminant control, stability, and dose consistency. Overall, while current evidence supports TCM as a multitarget approach for intestinal barrier protection and repair, the next phase should emphasize standardization, mechanistic causality, biomarker-guided stratification, and clinically aligned trial designs to accelerate the development of credible, scalable, and globally applicable interventions for intestinal barrier injury.

Abbreviations

TCM	Traditional Chinese medicine
DSS	Dextran sulfate sodium
CLP	Cecal ligation and puncture
IECs	Intestinal epithelial cells
TFF3	Trefoil factor 3
RELM β	Resistin-like molecule beta
ILCs	Innate lymphoid cells

DCs	Dendritic cells
TLRs	Toll-like receptors
NLRs	NOD-like receptors
Th17	T helper 17
LPS	Lipopolysaccharide
TLR4	Toll-like receptor 4
SCFAs	Short-chain fatty acids
GPCRs	G protein-coupled receptors
UC	Ulcerative colitis
IBS-D	Irritable bowel syndrome with diarrhea
IPEC-J2	Porcine intestinal epithelial cells
AhR	Aryl hydrocarbon receptor
TJ	Tight junction
PUFAs	Polyunsaturated fatty acids
TNF- α	Tumor necrosis factor- α
caspase	Cysteine aspartate specific proteinase
HO-1	Heme oxygenase-1
AO	Atractylodes oil
MyD88	Myeloid differentiation primary response gene 88
AA	Aloin A
EE	Eleutheroside E
WSBCW	WangShiBoChiWan
BO	Bletilla oligosaccharides
RGO	Rehmannia oligosaccharides
SBA	Soybean agglutinin
MAPK	Mitogen-activated protein kinase

Supplementary Information

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Supplementary Material 1. Table S1 Classic traditional prescriptions for intestinal protection. Table S2 Single TCM for intestinal protection. Table S3 Mixtures extracted from TCM for intestinal protection. Table S4 Monomers from TCM for intestinal protection.

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Authors' contributions

S.W.: Conceptualization, Writing original draft, Visualization, Software, Tables. Y.G.: Writing original draft, Figures, Visualization, Software. D.M.: Writing original draft. S.H.: Writing original draft. Q.H.: Writing original draft. Z.H.: Conceptualization, Funding acquisition, Resources, Supervision. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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