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REVIEW

Current Status of M1 and M2 Macrophages Pathway as Drug Targets for Inflammatory Bowel Disease

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Abstract

Chronic inflammation of the gastrointestinal system is mediated by both the immune system activity and homeostasis, mainly through releasing of various cytokines and chemokines, as well as the transmigration of the inflammatory cells to the affected site. In between, macrophages are key mediators of the immune system, nearly located all over the gastrointestinal tract. Macrophages have vital influence on the inflammatory condition with both pro-inflammatory and anti-inflammatory functions. Their polarization status has been linked to numerous metabolic disorders such as inflammatory bowel disease (IBD). The equilibrium between the phenotypes and functions of inflammatory M1 and anti-inflammatory M2 cells is regulated by both extracellular and intracellular stimuli, determining how the disease progresses. Thereby, factors that interchange such balance in the direction of increasing M2 macrophages offer unique approaches for future management of IBD. This study reflects the novel IBD treatment targets via the immune system's pathway, reporting the latest treatments that regulate the M1/M2 macrophages distribution in a way to favor IBD.

Keywords Inflammatory bowel disease · M1 and M2 macrophages · Immune system · Inflammation · Gastrointestinal system

Introduction

IBD is a chronic relapsing/remitting immune inflammatory disorder that includes two main forms: Crohn's disease (CD) and ulcerative colitis (UC) (Zhu et al. 2018). IBD mainly occurs in the lower part of the gastrointestinal tract (GI), the largest immune comportment of the human body (Kühl et al. 2015). CD is often observed throughout the whole GI tract, from the mouth to the anus (Foey 2015); in contrast, UC begins in the rectum and extends proximal (Sotillo et al. 2017). IBD might cause morbidity, mainly due to the high incidence of weight loss, anemia, loss of appetite, abdominal

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pain, rectal bleeding, diarrhea, rectal urgency, malnutrition, and fever (Song et al. 2018).

The etiology of IBD is yet to be known; however, a set of factors have been implicated to the disease (Isidro and Appleyard 2016). Preliminary, a complex interaction between genetic predisposition and environmental influences is involved; although, genetic factors do not play impressive roles in progression of IBD (Farzaei et al. 2018; Isidro and Appleyard 2016; Seo et al. 2017; Wu et al. 2015). Abnormalities in the immune system, autoimmune and immune-mediated phenomena are the crucial reasons behind the IBD pathology (Farzaei et al. 2018; Wu et al. 2015). The main function of the immune system is to preserve the intestinal cells homeostasis, especially where they face external stimuli (Kühl et al. 2015). Rather than these factors, defects in the mucosal innate immune function are a preliminary factor involved in the IBD progression. Besides, inflammatory events and inflammatory mediators such as chemokines leukotriene, cytokines and prostaglandins may also contribute to the IBD, though, a diet full of fiber and fruits can reverse the effects and reduce the risk of the disease, for example, enriched dietary supplements of anthocyanins have therapeutic options for IBD patients (Farzaei et al. 2018).

Macrophages are the most common mononuclear phagocyte in the healthy intestinal lamina propria, with critical functions in the immune system. Following the microenvironmental alterations, macrophages are polarized into two phenotypes named, classically activated (M1) macrophages and alternatively activated (M2) macrophages (Kühl et al. 2015). Both phenotypes switch to each other during the inflammatory responses. It is believed that M1 and M2 cells are able to play dual actions, either by triggering the inflammatory events or by anti-inflammatory functions; they can promote the healing process and ameliorate the inflammation (D'Alessio et al. 2014). Accordingly, the immune system reacts either by pro-inflammatory or anti- inflammatory cytokines, depending on the macrophage's phenotype (Zhu et al. 2014). It was shown that M1 is a pro-inflammatory macrophage and M2 is an anti-inflammatory macrophage (Bosma et al. 2016). M1 cells produce high amount of some factors that can induce inflammation (Zhu et al. 2014); whereas, M2 macrophages exert anti-inflammatory responses through releasing the cytokines such as interleukin (IL)-4 and IL-10 (Song et al. 2018). Macrophages polarization has a great importance in progression and prognosis of inflammation (You et al. 2016). Under normal condition, immuno-pathogenesis is avoided by the inflammatory pathways; thus, the imbalance between M1 and M2 switching is the key point that initiates various disorders such as IBD (Zhu et al. 2014).

Current treatments of IBD include thiopurines, monoclonal antibodies, aminosalicylates, anti-tumor necrosis factor (TNF) therapy, infliximab, and adalimumab; though, diet, herbal medications, botanical/chemical supplements can also provide an acceptable possibility for IBD management, by means of alternative therapy (Dionne et al. 2017; Phatak et al. 2019; Vasudevan et al. 2019).

Recently, the possible therapeutic effects of herbal medicines in IBD have been reviewed. For example, anthocyanins play both protective and therapeutic roles in the management of IBD, predominantly through downregulating the inflammatory cytokines (Farzaei et al. 2018). Natural plant-derived compounds as dietary supplements can be used for prevention of IBD and remission induction (Farzaei et al. 2016). This view could be a new approach for prevention and/or treatment of both types of IBD.

In addition, the use of probiotics and prebiotics was proposed to modify the IG microbiome, offering a beneficial strategy for IBD treatment. Probiotics are living organisms that reach the intestine in active form, in which may possess defensive activity against pathogenic bacteria by inducing mucosal defense. Whereas, prebiotics are often nondigestible dietary substances (i.e., oligosaccharides, carbohydrates), capable of stimulating the growth and activity of beneficial gut bacteria. Since, they are nondigestible elements; thus, they cannot be adsorbed until they reach the colon and be fermented into digestible compartments (i.e., small-chain fatty acids, lactate). Up to date, there is no convincing evidence for beneficial effects of probiotics/prebiotics in CD, although prebiotics may improve the host quality of life. The efficacy of probiotics in UC has been implicated to the treatment of the disease at mild-to-moderate stages and in terms of the prevention of relapses. It is worth mentioning that the use of these nutraceuticals in IBD needs further characterization (Scaldaferri et al. 2013; Abraham and Quigley 2017; Gionchetti et al. 2017).

The outcomes of clinical studies indicated that currently approved IBD treatments can reduce the leukocytes in mucus of IBD patients (Swidsinski et al. 2007), improve mucosal healing (Swidsinski et al. 2007), prevent the recurrence of the disease following surgically induced remission, prevent relapses, and improve remission rates (Taylor and Irving 2011). For instance, 5-aminosalicylates (5-ASAs) are effective for induction and maintenance of remission in UC patients; corticosteroids induce remission in both UC and CD subjects; cyclosporin-A or tacrolimus is shown to induce remission in UC patients; while methotrexate is used to induce and maintain remission in CD individuals; and azathioprine is similarly effective in both IBD types (Neurath 2017).

Concerning innate immune system, Azathioprine [6-(1-methyl-4-nitroimidazol-5-yl)thiopurine] significantly repressed inducible nitric oxide synthase (iNOS) expression, thereby affecting macrophages (Moeslinger et al. 2006). In addition, 6-mercaptopurine downregulated macrophage activation and gut epithelium proliferation through inhibition

of GTPase Rac1 in vitro (Marinković et al. 2014). Various studies demonstrated that 5-ASA and its derivatives inhibited macrophages activities, leading to the suppression of inflammatory response (Liang and Ouyang 2008). A mixture of anti-TNF antibodies and infliximab, adalimumab or certolizumab-IgG were found to induce the differentiation of a regulatory subset of macrophages with wound healing potential via Fc receptor signaling, suggesting that they can effectively regulate the macrophages function in IBD (Vos et al. 2011a). In accordance, in infliximab-treated IBD patients, regulatory M2 macrophages suppressed T-cell proliferation and promoted wound healing (Vos et al. 2011b). In another study, administration of infliximab in CD patients enhanced the macrophage cytokine response to bacterial infection, leading to elevated macrophage TNF and IL-10 production by means of an infliximab-induced shift to M2 macrophages (Nazareth et al. 2014). This study tends to report the current data on the correlation between M1/M2 and IBD, in addition we provided a list of agents that are able to shift the M1/M2 ratio toward controlling IBD.

M1 and M2 as Two Macrophages Inflammatory Actors

Macrophages belong to phagocytic cells of the innate immune system, existing in the majority of human tissues. Macrophages exhibit a wide variety of functions including the maintenance of tissue homoeostasis, phagocytic clearance such as elimination of cellular debris and apoptotic cells, microbial killing, antigen processing, inflammation, anti-inflammation, immune suppression, as well as tissue repairing and remodeling during the process of wound healing (Dionne et al. 2017; Foey 2015; You et al. 2016). M1 macrophages are attributed to inflammation events by releasing mediators such as IL-12, IL-23, TNF-α and IL-1β; besides, they are able to increase reactive oxygen species (ROS) production. M1 cells participate in induction of T helper 1 cells (Th1) and Th17 responses, while expressing a low level of anti-inflammatory cytokine IL-10. It was evidenced that interferon-γ (INF-γ), lipopolysaccharide (LPS), TNF-α, and granulocyte–macrophage colony-stimulating (GM-CSF) can induce the M1 differentiation (Hidalgo-Garcia et al. 2018; Isidro and Appleyard 2016; Zhu et al. 2014, 2018).

M2 macrophages are polarized by IL-4, IL-13, and the macrophage colony-stimulating factor (M-CSF). M2 cells upregulate the IL-10 expression, mannose receptor, arginase-I, IL-1 receptor antagonist, and CD163 antigen (Zhu et al. 2014) (Table 1). Interchanging between the M1 and M2 phenotypes depends on both the environmental and immune responses.

M1 and M2 in IBD

IBD is a chronic inflammatory condition of the small/large intestine, where the largest population of macrophages accumulate in the GI mucosa and contribute in initiation and progression of IBD (Hidalgo-Garcia et al. 2018). In a recent study, it was suggested that intestinal transition of monocytes to proresolving macrophages plays a vital resolution role after inflammation induction, resulting in mucosal healing, tissue homeostasis, and remission of IBD (Na et al. 2019). Intestinal macrophages were also shown to produce a variety of cytokines to preserve tissue homeostasis (Grainger et al. 2017).

In brief, in the healthy intestinal mucosa, Ly6Chi (in mice) and CD14hi (in human) monocytes constantly enter the intestinal mucosa and differentiate into mature CX3CR1hi F4/80+ macrophages, where they function as phagocytic agents, and produce IL-10. Consequently, IL-10 induces regulatory T cells and monocytes, mainly through TGFβ production. In inflammation, the normal pattern of monocyte/macrophage differentiation alters. Both monocytes and CX3CR1hi macrophages, still producing IL-10,

Table 1 Correlation between M1 and M2 macrophages; polarization, expression and function

	M1 classical	M2 alternative
Polarizing stimulus	LPS, IFNγ, GM-CSF	IL-4, IL-13, IL-1β, IL-10,TGFβ
Cytokine expression	TNFα, IL-1β, IL-6, IL-12, IL-18, IL-23, IL-10^{low}	IL-12^{low}, IL-23^{low}, TGF β, IL-10^{high}, TNFα, IL-1β, IL-6
Phenotype	Pro-inflammatory	Anti-inflammatory
Antigen presentation	High	Low
Phagocytic activity	High	Low
Function	Pro-inflammatory	Anti-inflammatory
	Anti-microbial	Immuno regulation
	Tissue damage	Allergic response
	Th_1 response	Tissue repair
	Anti-tumoural	Th_2 response

GM-CSF granulocyte-macrophage colony-stimulating

are accumulated in mucosal inflamed sites and release large amounts of pro-inflammatory cytokines (i.e., IFNγ) and inflammatory chemokines. Besides, stimulated monocytes can also induce the TNFα and ROS productions by neutrophils (Bain and Mowat 2014).

In IBD, macrophages migrate to the inflamed colonic mucosa, where they vigorously produce IL-1, IL-6, TNF-α, IL-12 as well as IL-23, and secrete reactive metabolites of oxygen, nitrogen, and proteases that can degrade the extracellular matrix. It was shown that in DSS-induced colitis mice, the population of M1 macrophages increases; while the M2 types reduce. Thus, reduction of M2 macrophages attenuates colitis through inducing the IL-10 secretion and upregulation of T-cell generation. Therefore, the neutralization of IL-10 partially reduces the effects of M2 macrophages and induces their transition to the lamina propria, and inflamed colonic mucosa, in a way to prevent inflammation spreading. The disequilibrium of M1 and M2 phenotypes was correlated with colitis progression in murine model of IBD (Zhu et al. 2014). In CD4+ CD45Rbhigh T cell transfer model and genetic mouse model, anti-TNF therapy enhanced the IL-10 production in CD206+ regulatory macrophages, leading to reduced intestinal inflammation in IBD subjects (Koelink et al. 2019).

In IBD, the population of classically activated M1 macrophages enhances; however, the markers of alternatively activated cells reduce, indicating the importance of M1 cells in IBD development. It seems that bacteria and bacterial products can have effect on M1 macrophages more than the other factors in IBD, resulting in stimulation of NO, TNF-α, IL-1β, IL-6, IL-12, and IL-23 secretions from M1 cells. Apart from the rest, IL-12 induces the Th1 differentiation, and INF-γ secreted by Th1, thus stimulating the M1 cells; this pathway is repeated constantly. On the other hand, IL-23 induces Th17 differentiation and the consequent IL-17 activation, promoting the recruitment of the large numbers of activated neutrophils toward the inflamed site (Kühl et al. 2015). In response to IBD, the population of Gram-positive bacteria increases, inducing C–C Motif Chemokine Ligand (CCL)2, CCL7, CCL8, and M1 macrophages. Together, these reactions provoke a pro-inflamed site, leading to a functional change in macrophages activities (Fig. 1a) (Skovdahl et al. 2018).

It was shown that in UC subjects, bacteria and their byproducts stimulate both M1 and M2 macrophages. In response to such condition, secretion of NO, TNF-α, IL-1β, IL-6, and IL-23 enhances from M1 cells; whereas, M2 macrophages excrete NO, TNF-α, IL-1β, IL-10, IL-6, IL-4, and IL-13. M1 macrophages secreted IL-1β which induces M2 cells; however, TNF-α secreted from M2 macrophages modulates M1 cells. M2-induced IL-10 secretion inhibits both M1 and M2. M1 macrophages induce IL-6 and IL-23, and also stimulate Th17 (Kühl et al. 2015).

In contrast, in UC patients, Th2 cells elevate the IL-4 secretion, thereby upregulating IL-10. The following processes are common between CD and UC, eventually, M1 cells are accumulated in pro-inflamed spot (Fig. 1b). In CD, pathogenic invasion only alters M1 macrophages; whereas in UC, they induce both M1 and M2 phenotypes.

M1 and M2 Interventions in IBD

We collected 22 studies up to 2019 from electronic databases of PubMed, Scopus and Google Scholar, related to the IBD management, approaching both M1 and M2 macrophages. The keywords of inflammatory bowel disease, Ulcerative Colitis, Crohn's Disease, macrophages, M1 and M2, IBD, UC, and CD were used as search terms.

In Vivo Studies

Plant Extracts and Phytochemicals

Ancylostoma caninum

Ancylostoma caninum is a hookworm. *A. caninum* excretory/secretory (ES) product is the mixture of protein and lipids released by this species. In a proteomic analysis, *A. caninum* ES product positively changed the levels of proteins involved in the intestinal homeostasis, tissue integrity and regeneration. These by-products upregulated the protein level of MUC13, a mucin implicated in the gastrointestinal homeostasis, in lamina propria of DSS-induced colitis mice model, rectifying the IBD pathogenesis. The amount of MUC2, the major intestinal mucin expressed by goblet cells of the small intestine and colon, was also increased in the intestinal epithelial cells. The mixture also downregulated Th1 and Th17 responses, and induced the IL-4, IL-10, and CD4 T cells.

The parasite products caused a significant reduction in the expression of enzymes involved in glutathione (GSH) metabolism in both lamina propria and the intestinal epithelial cells. Reduced GSH is known to contribute in transition from Th1 to Th2 response, affecting M1–M2 transformation (Sotillo et al. 2017) (Table 2).

Berberine

Berberine is the major alkaloid presented in root, bark, rhizomes and the stems of the genus *Berberis*, particularly *B. vulgaris*. Berberine improved the gut epithelial barrier and regulated the Treg/Th17 balance in IBD (Imenshahidi and Hosseinzadeh 2019). Berberine may contribute to UC prevention by regulating the Treg/Th17 balance, maintaining the gut microbial balance, and decreasing their diversity (Cui et al.

Table 2 In vivo studies targeting M1/M2 signaling pathway in IBD

References	Model of IBD	Type of animal	Treatment	Duration of treatment	No of animal and GP	Outcome	Adverse effects
Wei Zhu and Colleagues (2016a)	DSS-induced colitis	Male C57BL/6 (B6) mice	Baicalin (25, 50 and 100 mg/kg)	10 days Days 1–3: Baicalin Days 4–10: Baicalin + DSS	*N* = 6 mice in each group (1) vehicle (control) (2) DSS (colitis group) (3) DSS after treatment with baicalin (25 mg/kg) (4) DSS after treatment with baicalin (50 mg/kg) (5) DSS after treatment with baicalin (100 mg/kg)	* ↓ M1, ↑ M2, ↓ TNF-α, ↓ IL-23, ↑ IRF4, ↑ IL-10	Not mentioned
Madeleen Bosma and Colleagues (2016)	DSS-induced colitis	Male C57Bl/6N mice	FNDC4 (a member of the fibronectin type III domain family of proteins) (2.7 mg/kg)	hFc- FNDC4 or hFc control protein (on days 0, 2 and 4) DSS: 5 days	*N* = 3–10 mice in each group (1) DSS (2) Control (3) hFc (Fc-domain of human IgG1)- FNDC4 or hFc control protein + DSS	*↓ Cxcl9, Cxcl10 (Ip10), Tgfb1 and Csf1 *↓ TNF and CCL2 (MCP1) expression, *↓ M1, M2 regulation	Not mentioned
Yeshan Zhu and Colleagues (2016b)	DSS-induced colitis	Male CS7BL/6 mice	Lupeol	Days 1–7: DSS or water Days 3–12: Lupeol or vehicle	*N* = 12 mice in each group (1) negative control (2) Lupeol (3) DSS/vehicle (4) DSS/lupeol	*M1 → M2 *↓Expression of pro-inflammatory cytokines: TNF-α,IL-1β and IL-12 *↑Expression of pro-inflammatory cytokines: IL-10 *↓Expression of CD86 *↑Expression of CD206	Not mentioned
Se-Eun Jang and Colleagues (2014)	TNBS-induced colitis	Male ICR mice	*Lactobacillus plantarum* CLP-0611	L-Plantarum CLP-0611 after treatment with TNBS: was orally given once a day for 3 days	*N* = 6 mice in each group (1) Vehicle (2) Control group treated + TNBS (3,4) L-plantarum CLP-0611 + TNBS (5,6) L-plantarum CLP-0611 without TNBS (7) Mesalazine + TNBS	Lactic acid bacteria ameliorated IBD CLP-0611: *↓ IL-1β, TNF-α, ARG-11; ↑ IL-10, ARG-1, CD-206 *↑ M1 → M2	Not mentioned
Javier Sotillo and Colleagues (2017)	DSS-induced colitis	Female C57 BL/6 mice	*Ancylostoma conium* excretory/secretory (ES)	3 days	*N* = 4 mice in each group (1) DSS (2) DSS + ES (3) ES (4) neither DSS or ES	In intestinal layers: *Proteins in LP and IEC ↑ *↓ GSH => $Th_1 \rightarrow Th_2$ => ↑M1 → M2	Not mentioned

Table 2 (continued)

References	Model of IBD	Type of animal	Treatment	Duration of treatment	No of animal and GP	Outcome	Adverse effects
Chengzhen Li and Colleagues (2015)	TNBS-induced colitis	Male BALB/C mice	Berberine	9 days	$N=10$ mice in each group (1) Control group (2) TNBS treated group (3) Berberine treated group (100 mg/kg)(4) Berberine treated group (50 mg/kg)	*↑ IL-22↑, IgA; IL-6+, ↓ IL-1β+, TNF-α+ *↓ M1 proportion *↑ratio of IRF4 *↓Th1 and Th2 *↓ IFN-δ *↓ Expression of T-bet, PSTA and PSTAT3 *Undo the phosphorylation of NF-KB *↓ Proportion of CD4+CD25+FOX3+T cell *Restored lost body weight *↓Colon shortening *↓MPO level *↓Mϕ filtration into the colon *↓NF-Kβ	Not mentioned
Ji-young Song and Colleagues (2017)	DSS-induced colitis	C57 BL mice	MSC-EX (150 µgr/mouse-day)	10 days: Days 0–25: DSS Days 25–35: MSC-EX	$N\geq 5$ mice in each group (1) Control group (2) DSS+PBS (3) DSS+MSC-EX	*↓ IL-1β, IL-16, CXCL10, MCP, CXCL9, TIMP, IL-17; ↑IL-10 and TGF-β *↑M1 → M2 by ↓ MCP1-CXCL9 and iNOS	Not mentioned

Table 2 (continued)

References	Model of IBD	Type of animal	Treatment	Duration of treatment	No of animal and GP	Outcome	Adverse effects
Woo-Jin Song and Colleagues (2018)	DSS-induced colitis	Male C57bl/6j mice	Canin adipose Tissue-derived (cAT)-MSC-produced TSG-6	10 days	$N=4$–6 mice in each group (1) Control group (2) PBS (3) CAT-MSC (4) SiCTL-CAT-MSC (5) SiTSG6-CAT-MSC	*↓Body weight loss and shortening of colon length *↓Inflammatory responses and apoptosis *↓TNF-α, IL-6, IL-10 *↑M2 macrophage switching *Regulate colonic expression of pro and anti-inflammatory cytokines *Improve extent of bowel wall thickening, crypt damage and filtration of inflammatory cell *Induce phenotype switching from M1 to M2 *↓Inflammatory responses and apoptosis in colon *↑Proportion of CD11b + cells expressing CD206 *↓mRNA expression of inducible iNOS and IL-6 *↑LPS-stimulated CPBMC-Derived macrophages in CAT-MSC group compared with control group *↑M2 markers: CD206, ARG1	Not mentioned
Hong Jun Park and colleagues (2018)	DSS-induced colitis	Female C57BL/6 mice	Adipose tissue-derived MSCs (ASCs)	2 days: day 6 and 16	$N=6$ mice in each group (1) DSS (2) DSS + ASCs (3) ASCs (4) DSS + ASCs + Celecoxib	*↑ mRNA of CD206, CD68, CCL18, legumain and IL-10, markers of M2 macrophages *↑ M1 → M2 by ASCs IL-1b and IL-18 *↑ NLRP3, Cox-2,↑ PGE2↑	Not mentioned

Table 2 (continued)

References	Model of IBD	Type of animal	Treatment	Duration of treatment	No of animal and GP	Outcome	Adverse effects
Jessicca D. Abron and colleagues (2018)	DSS-induced colitis	Female wild-type C57BL/6 mice	Genistein (10 mg/kg)	14 days	*N* = 6 mice in each group (1) Naïve (2) DSS + vehicle (3) DSS + genistein	*↓M1 (CD11b + CD11c) (both mucosal and systemic M1) *↑M2 (F4180 + CD206) *Mediates colitis by skewing M1 towards M2 polarization *Suppress inflammatory response in DTH *Inhibits nitric oxide and prostaglandin E2 pathways in lipopolysaccharide induced macrophage *↓TNBS induced colitis in rat through (COX-2) and MPO*↓TNF-α, IL-6, IL-1β, MCP1 in serum of DSS *↓Systemic inflammatory cytokine from mucosal organs *↓Body weight and colon length *↓M1 in spleen and MLNs and CLP *↓CD4 cell in spleen and CLPL *↑CD4 in MLN *↑M2 in spleen and MLN and CLPL *Induced M2 macrophage highly express ARG-1 *↓T cells (both CD4 and CD8) in spleen and CLP *↑T cells in MLN	Not mentioned
Supriya R. Hyam and colleagues (2013)	TNBS-induced colitis	Male CS7BL/6 mice	Arctigenin (30 and 60 mg/kg) or sulfasalazine (50 mg/kg)	3 days	*N* = 7 mice in each group (1) Control (2) TNBS (3) Arctigenin (4) Sulfasalazine	*Inhibit P13K, AKT and NF-kβ *Inhibit pro-inflammatory cytokines expression *↓IL-1β, TNF-α, IL-6; ↑IL-10	Not mentioned

Table 2 (continued)

References	Model of IBD	Type of animal	Treatment	Duration of treatment	No of animal and GP	Outcome	Adverse effects
Yan You and colleagues (2016)	DSS-induced colitis	Wild-type littermate mice	SNX10	7 days	$N=6$ mice in each group (1) Control (2) SNX10 group	*↓Weight loss, epithelial destruction, crypt loss in colon and histological score of acute colitis *↓Inflammation and tissue damage in colon *↓IL-6, IL-12, IL-23, IL-1β and TNF-α *↑Polarization M2 and ↑ population of M2-type *↑IL-10	No adverse effect
Zhao Cheng and colleagues (2017)	Colitis by oxazolone (oxz)	BALB/C mice	BM1M-M2MS (Bone marrow cell-derived innate macrophages-derived M2 macrophages) (1×10^6 cells)	8 days	$N=20$ mice in each group (1) Ethanol (2) OXZ + ethanol (3) OXZ + BMIM–M2M 20 mice	*↓ Inflammation *↓Severity of inflammatory infiltration and mucosal damage *↑ Body weight *↑ IL-4 and IL-1β typical Th2 cytokine	Not mentioned
Cheng-Ying Chiu and colleagues (2012)	DSS-induced colitis	C57BL/6 mice	17-HDPA *n*-6 and 1 or 17-HDPA *n*-6 and 17-HDHA or NACL	8 days	$N=5$–12 mice in each group (1) control (2) 17-HDPAn-6 (3) 10/17-HDPAn-6 (4) 17-HDHA (5) NaCl	*↓Body weight loss *↓Colon epithelial damage and macrophage infiltration *↑Phagocytosis activity *↓Severe colitis signs in colonoscopy *↓Disease activity index	Not mentioned

Table 2 (continued)

References	Model of IBD	Type of animal	Treatment	Duration of treatment	No of animal and GP	Outcome	Adverse effects
S.-E. Jang and colleagues (2013)	TNBS-induced colitis	Male ICR mice	*Lactobacillus brevis*G-101 (LAB)	8 days	$N=6$ mice in each group (1) Normal control (2) LPS (3) Treated with 1×10^3 CFU of Lact-brevis G-101 and LPS (4) Treated with 1×10^4 CFU of Lact-brevis G-101 and LPS (5) Treated with 1×10^5 CFU of Lact-brevis G-101 and LPS	*↓LPS-induced NF-κB and AP1 activation *↓TNBS-induced MPO activity *↓P-IRAK-1, P-P65, P-P38, P-ERK, P-JNK and P-AKT *↓TNBS-induced iNOS and COX-2 expression *↑Anti-inflammatory cytokine IL-10 expression *↓Expression of pro-inflammatory cytokines; IL-1β, IL-6 and TNF-α *↓Expression of M1 macrophage markers: ARG-I, TNF-α and IL-1β *↑Expression of M2 macrophage markers: ARG-II, IL-10 and CD206 *↑Pro-inflammatory transcription factors: NF-κB and AP1 *↓Phosphorylation of MAPKs *↑M1 → M2 *↓colitis by ↓TLR-4 linked NF-κB and AKT signaling pathway and polarizing M1–M2	Not mentioned

Table 2 (continued)

References	Model of IBD	Type of animal	Treatment	Duration of treatment	No of animal and GP	Outcome	Adverse effects
Hyo-Min Jang and colleagues (2017)	TNBS-induced colitis	Male ICR mice	4-Methoxylonchocarpin (ML) (5 and 10 mg/kg)	7 days	*N* = 5–12 mice in each group (1) Normal control (2) TNBS 3) TNBS + ML (5 mg/kg) (4) TNBS + ML (10 mg/kg) (5) TNBS + sulfasalazine (50 mg/kg)	*↓TNBS-induced colitis in mice *↓Colon shortening, macroscopic score, cell disruption, infiltration of activated macrophages in colon *↓TNBS-induced activation of NF-κB, phosphorylation of TAK1 and IKB *↓Expression of COX-2 and iNOS *↓Expression of TNF, IL-1β and IL-17 *Restoring TNBS-suppressed IL-10 expression *↓Expression of M1 macrophages *↓Polarization of M2 macrophages to M1 *↓Th1 and Th17 cell differentiation by ↑ IL-6 expression	Not mentioned
Su-Min Lim and colleagues (2015)	TNBS-induced colitis	Male C57BL/6 mice	Timosaponin AIII and sarsasapogenin	4 days	*N* = 6 mice in each group (1) Normal control (2) TNBS (3) TNBS + Timosaponin AIII (5 mg/kg) (4) TNBS + Timosaponin AIII (10 mg/kg) (5) TNBS + sarsasapogenin (5 mg/kg) (6) TNBS + sarsasapogenin (10 mg/kg) (7) TNBS + sarsasapogenin (50 mg/kg)	*↓LPS-stimulated COX-2 and iNOS expression *↓Colon shortening *↓Macroscopic score *↓TNBS-induced MPO *↓Edema and epithelial cell disruption *↓Expression of colon tight junction proteins ZO-1 *↓Expression of TNF-α, IL-1β, IL-6, IL-17 and IFN-γ *↑TNBS-mediated downregulation of IL-10 expression *↓Expression of ARG-II, COX-2 and iNOS *↓TNBS-induced differentiation into Th17 cell *↓Pro-inflammatory cytokines	

Table 2 (continued)

References	Model of IBD	Type of animal	Treatment	Duration of treatment	No of animal and GP	Outcome	Adverse effects
Xing Zhang and colleagues (2017)	DSS-induced colitis	Female C57BL/6 mice	Compound edaravone (C.EDA) (10 mg/5 mL) and (+)-Borneol (10 mg/5 mL)	10 days	*N* = 5 mice in each group (1) Normal (2) DSS (3) DSS + EDA (3 mg/kg) (4) DSS + EDA (6 mg/kg) (5) DSS + EDA (12 mg/kg) (6) DSS + Borneol (3 mg/kg) (7) DSS + C.EDA (3.75 mg/kg) (8) DSS + C.EDA (7 mg/kg) (9) DSS + C.EDA (15 mg/kg)	Borneol → ↑ M2 polarization via JAK2-STAT3 signaling pathway *↓ M1 → infiltration *C. EDA → ↓ IL-1β, IL-6 and TNF-α *C. EDA → ↑ IL-10, M2 infiltration	
Xiaodong Zhu and colleague (2019)	DSS-induced colitis	Male C57BL/6 (B6) mice	1,25-Dihydroxyvitamin D	11 days	*N* = 6 mice in each group (1)Vehicle (2) DSS (3) DSS + VD (0.025 μg) (4) DSS2% + VD (0.05 μg) (5) DSS2% + VD (0.1 μg)	*↓ M1 polarization *↓TNF-α and IL-6 expression *↓IL-12 and IL-1β *↓ IRF5 phosphorylation *↑IL-10, ARG-I and IRF4 expressions	Not mentioned
Ae Sin Lee and colleague (2018)	DSS-induced colitis	Male C57BL/6 mice	COMP-angiopoietin-1	7 days	*N* = not mentioned (1) Adeno-virus-injected control group (2) COMP-Ang1-virus-injected control group (3) Adeno-virus-injected DSS administration group (4) COMP-Ang1-virus-injected DSS administration group	*↓Upregulation of IL-1β, IL-6 andTNF-α *↓Expression of M1 and M2 macrophage-related factors *↓Expression of VEGF-A,VEGF-C and VEGF-D	Not mentioned
Hongchen Zhang and Colleagues (2018)	DSS-induced colitis	Male C57BL/6 mice	*H. pylori*	5 times within 2 weeks	*N* = 10 mice in each group (1) Control (2) *H. pylori*-infected alone (3) DSS (4) *H. pylori*-infected + DSS	*↓Th17 and mRNA levels of IL-17A, IL-17F, and IL-21 *↑Treg and IL-10 *↑TGF-β; ↓ IL-6 and IL-23 *↑M2 macrophages	Not mentioned

Table 2 (continued)

References	Model of IBD	Type of animal	Treatment	Duration of treatment	No of animal and GP	Outcome	Adverse effects
Aliakbar Yousefi-Ahmadipour and Colleagues (2019)	TNBS-induced colitis	Male Wistar Rats	Combination therapy of mesenchymal stromal cells and sulfasalazine low dose (30 mg/kg)	Days 1 and 5 after inducing colitis	*N* = 6 mice in each group (1) Control (2) TNBS (3) Sulfasalazine (TNBS + sulfasalazine 30 mg/kg/day) (4) ASCs (TNBS + ASCs) (5) ASCs + sulfasalazine (TNBS + ASCs + sulfasalazine)	*↓Body weight loos, diarrhea, focal necrosis of the mucosa, erosion and sub mucosal edema *↑M1 → M2 *↓Expression TNF-α, IL-1, 1L-6, IL-7, IL-10 and TGF-β *↑Expression IL-10 and TGF-β *↑Expression ARG-I, TGF-β1 and IL-10 *↓MCP1 and CXCL9 *↓ NF-κB signaling *↑level of anti-apoptotic proteins *↑Treg cells *↓MPO	Not mentioned
Xiumei Che and colleagues (2018)	TNBS-induced colitis	Wild-type and MYD88-deficient mice	Guggulsterone (GGS)	4 days	*N* = not mentioned (1) Normal (2) GGS	*↓MMP-9 expression *↓NF-κB *↓Expression of macrophage inflammatory molecules *↓Modulation of M2 *Inhibition of infiltration of macrophages in inflamed colon	Not mentioned

DSS dextran sodium sulfate, *TNBS* 2,4,6-trinitrobenzene sulfonic acid, *NO* nitric oxide, *TNF* tumor necrosis factor, *TSG-6* TNF-a-stimulated protein/gene 6, *IFN* interferon, *IRF* interferon regulatory factor, *PGE2* prostaglandin E2, *ARG* arginase, *LP* lamina propria, *LPS* lipopolysaccharide, *ES* excretory/secretory, *MSC-Ex* extracts of MSCs, *ASCs* adipose tissue-derived MSCs, *IDO* indole amine 2,3-dioxygenase, *DTH* delayed type hypersensitivity, *MLNs* mesenteric lymph nodes, *17-HDPAn-6 n*-6 docosapentaenoic acid-derived (17S)-hydroxy-docosapentaenoic acid, *10,17-HDPAn-6* (10,17S)-dihydroxy-docosapentaenoic acid, *17-HDHA* 17(R/S)-hydroxy-docosahexaenoic acid, *SNX10* Sorting nexin 10, *WT* mice wild type, *VEGF* vascular endothelial growth factor, *LAB* lactic acid bacteria, *OXZ* oxazolone

2018). Another study demonstrated that berberine refined the 2,4,6-trinitrobenzene sulphonic acid (TNBS)-induced colitis in BALB/C mice, via controlling immune responses equilibrium. This alkaloid markedly attenuated colitis inflammation, both in local colon and sera, through inhibition of INF-γ, IL-1β, IL-17, IL-6, and TNF-α activities. Berberine accelerated the macrophages differentiation into the M1 and M2 cells, and also regulated the M1/M2 ratio. More importantly, berberine enhanced the p-signal transducers and activators of transcription 1 (STAT-1) and pSTAT3 expressions, consequently inhibited the Th1/Th17 differentiation, and restored the Th1/Th17/Treg balance. The splenic and colonic mRNA expression of IRF4/IRF5 was also elevated following berberine treatment. Concerning IBD, the prominent site of action for berberine was shown to be the innate immunity pathway (Li et al. 2015) (Table 2).

Baicalin

Baicalin was originally isolated from the root of Chinese herb Huangqin (*Scutellaria baicalensis* Georgi). Baicalin is the main active constitute of the plant with protective effect against inflammatory disorders such as IBD. In DSS-induced colic mice, baicalin modulated the macrophages polarization to the anti-inflammatory M2 phenotype. The levels of the anti-inflammatory cytokines such as interferon regulatory factor-4 (IRF-4) and IL-10 enhanced; nonetheless, the amount of M1-induced TNF-α and IL-23 reduced. Thus, baicalin could improve IBD through the polarization of macrophages into M2 phenotype (Zhu et al. 2016a) (Table 2).

Lupeol

In DSS-induced colitis mice, pentacyclic triterpene Lup_20 (29)_en_3β_ol (Lupeol) suppressed the TNF-α, IL-1β and IL-12 expressions, while upregulated the anti-inflammatory cytokine IL-10. Lupeol also downregulated CD68 and upregulated CD206, typical markers of M1 and M2 macrophages, meaning that lupeol can mediate IBD through inhibiting M1 and promoting M2 cells (Zhu et al. 2016b; Jang et al. 2014) (Table 2).

Genistein

Soy isoflavone 4′/5/7 trihydroxy isoflavone (genistein) inhibited both mucosal and systemic M1 macrophages (CD11b + CD11c) in the spleen, mesenteric lymph nodes (MLNs), colon, and lamina propria, and increased the M2 subpopulations of F4180 and CD206 in DSS-induced IBD mice. Genistein profoundly mediated the disease by disrupting the M1/M2 polarization, and also improved the body weight loss and the colon length. In LPS-induced macrophages, genistein inhibited the inflammatory response against the antibodies and hampered the NO and prostaglandin E2 pathways (Dia et al. 2008). Further, genistein caused a decreasing mark in TNF-α, IL-6, IL-1β, and monocyte chemoattractant protein-1 (MCP1) levels and increased the arginase-I expression, making it a proper candidate for colitis treatment either by downregulating cyclooxygenase-2 (COX-2) and myeloperoxidase (MPO), or by repressing the systemic inflammatory cytokines in mucosal organs (Abron et al. 2018) (Table 2).

Arctigenin

Arctigenin and its glycoside arctiin, the main compounds isolated from *Arctium lappa* seeds, were shown to inhibit the primary human T lymphocyte proliferation and in Chinese traditional, medicine is believed to act as anti-inflammatory agents (Tsai et al. 2011; Vemulpad and Jamie 2014). Arctigenin was found to improve the IBD scores, i.e., the body weight loss and the colon shortening. Further, this compound attenuated the inflammation via polarizing the M1–M2-like macrophages, and by suppressing the phosphatidylinositol-3-Kinase (PI3k) pathway. PI3k is an important regulator of M2–M1 polarization and the expression of different pro-inflammatory cytokines (Qiu et al. 2018; Tokuhira et al. 2015). Blockade of this pathway is a great choice to treat CD. In addition, arctigenin significantly suppressed the IL-1β, TNF-α and IL-6 expressions, while upregulated the IL-10 level in TNBS-induced colitis mice (Hyam et al. 2013; Tokuhira et al. 2015) (Table 2).

4-Methoxylon Chocarpin

The root of *Abrus precatorius* is traditionally used to treat various inflammatory diseases. Triterpenoid saponins, alkaloids, flavonoids, steroidal compounds, and isoflavone are introduced as the main constitutes of the species. 4-methoxylonchocarpin (4-ML), an anti-inflammatory compound of *A. precatorius*, reduced the colon shortening and macroscopic scores in TNBS-induced colitis mice. It also suppressed the cell disruption and activation of TNBS-induced NF-κB, by preventing LPS binding to toll-like receptor-4 (TLR-4) of macrophages. Besides, 4-ML reduced the COX-2, iNOS, TNF-α, IL-1β, and IL-17 expressions, Th1/Th17 differentiation, M1 cells expression, and the polarization of M1 to M2. Therefore, 4-ML helps to control colitis, mainly through inhibiting LPS binding to TLR-4 of macrophages, and the M1 macrophages polarization (Jang et al. 2017) (Table 2).

Timosaponin AIII and Sarsasapogenin

Anemarrhena asphodeloides is a typical herbal medicine, containing furostanol and spirostal saponins, which are described to inhibit inflammation, and improve learning and memory in rats. The main constituents of the rhizome of *A. asphodeloides*, timosaponin AIII and its metabolite sarsasapogenin have been investigated against in vivo colitis model. Both compounds downregulated the LPS-stimulated COX-2 and iNOS, reduced the colon shortening, macroscopic scores, edema and the epithelial cells disruption. They also decreased the M1 cytokines (i.e. TNF-α, IL-1β, IL-6 and IL-17), and elevated the M2 anti-inflammatory cytokine IL-10. Timosaponin AIII and sarsasapogenin possessed their anti-inflammatory functions through inhibiting TLR-4, NF-κB, and MAPK signaling pathways, and by restoring the Th17/Treg balance. Of note, sarsasapogenin was found more potent than timosaponin AIII (Lim et al. 2015) (Table 2).

(+)-Borneol

Several in vivo and in vitro studies shown that Edaravone (a free radical scavenger compound) and Borneol (a natural bicyclic monoterpene), have substantial anti-inflammatory potentials. A combination of these compounds showed more efficacy than edaravone alone, when supplemented into DSS-induced colitis mice diet. Borneol and edaravone together enhanced the infiltration of M2 macrophages and cytokines, while abrogated the high levels of IL-1 via JAK2/STAT signaling pathway (Almeida et al. 2013; Zhang et al. 2017) (Table 2).

Guggulsterone (GGS)

Guggulsterone is a plant sterol isolated from the gum resin of *Commiphora mukul* tree with significant protective effect in IBD. In TNBS model of IBD, GGS modulated the IL-10 and TLR-4 signaling pathways, and the M2 markers such as CD206 and CD163 (Che et al. 2018) (Table 2).

Natural Products

n-6 Docosapentaenoic Acid-Derived (17s)-Hydroxy-docosapentaenoic Acid (10/17-HDPAn-6) and Docosahexaenoic Acid-Derived 17 (R/S)-Hydroxy-docosahexaenoic Acid (17-HDHA)

Both 10/17-HDPAn-6 and 17-HDHA are lipid products derived from omega-3 and omega-6. Omega-3 and omega-6 were proven to possess profound anti-inflammatory effects and play important roles in damaged tissues healing process. In DSS-induced colic mice, administration of 17-HDPAn-6, 10/17-HDPAn-6 and 17-HDHA, ameliorated the body weight loss, colon epithelial damage, macrophages infiltration and the Disease Activity Index (DAI), and also induced the phagocytosis activity (Chiu et al. 2012) (Table 2).

Sorting Nexin 10 (SNX10)

Sorting nexin 10 is a protein with great importance in endosomal trafficking, osteoclast maturation, regulation of macrophages polarization, and colitis progression. You et al. (2016) demonstrated that SNX10 reduced the weight loss, epithelial destruction, crypt loss in the colon, and improved the histological scores of acute colitis mice. Moreover, SNX10 restored colonic tissue damage by diminishing pro-inflammatory cytokines (i.e., IL-6, IL-12, IL-23, IL-1β and TNF-α). In addition, SNX10 promoted the polarization and population of M2 type and enhanced the anti-inflammatory cytokine IL-10 (You et al. 2016) (Table 2).

1,25-Dihydroxyvitamin D

1,25 Vitamin D (1,25VD) supplement may help to manage IBD via antibiosis anti-inflammatory effect, and by repairing the intestinal mucosal barrier (Li et al. 2018b). Vitamin D was shown to prevent M1 polarization in colitis patients. Further, this type of vitamin reduces the M1 secreted IL-6, 1L-12, IL-1β and TNF-α. Xiaodong Zhu et al. (2019) demonstrated that vitamin D can ameliorate IBD by restoring the macrophages and also by increasing the expression of IL-10 and arginase-I (Zhu et al. 2019) (Table 2).

Cartilage Oligomeric Matrix Protein (COMP)-Angiopoietin-1 (Ang1)

Ang1 is a secreted protein ligand of tyrosine kinase, playing a considerable role in vascular development (Davis et al. 1996; Yancopoulos et al. 2000). The N-terminal portion of Ang1 was replaced with the short coiled-coil domain of COMP to generate COMP-Ang1. In DSS-induced acute colitis model, COMP-Ang1 treatment improved the weight loss, and the clinical signs of colitis. In addition, COMP-Ang1 significantly decreased the density of lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1)-positive lymphatic vessels, restored the damaged colonic architecture, suppressed the immunoregulatory response, and decreased the M1/M2 infiltration into the inflamed colon, thereby, repressing the VEGF-C and D expressions (Lee et al. 2018) (Table 2).

Fibronectin Type III Domain Containing 4 (FNDC4)

Fibronectin type III domain containing 4 is a secreted factor sharing high homology with the exercise-associated

Table 3 In vitro studies targeting M1/M2 signaling pathway in IBD

References	Type of intervention to induce inflammation	Type of cell	Treatment	Duration of treatment	No of cell and GP	outcome	Adverse effects
Serge Dionne and Colleagues (2017)	LPS	Human monocytes	1.25 VD (a type of Vitamin D)	20 h	5×10^5 cell/ml	*M2 versus M1↑ *Inhibit the production of inflammatory cytokines by M1 and M2 *Production of TNF-α, IL-23P40, IL-12 and iNOS from M1 and M2 in CD patients↓ *Production of IL-10 by Mϕ in CD and control group↑ *Expression of MMP2 and CD-14 by M2↑	Not mentioned
Raymond A. Isidro and Colleagues (2014)	Monocytes were differentiated into M1 or M2 phenotype, stimulated by LPS, IFN-γ or IL-4	Human monocytes derived macrophage	VSL#3	11 days	5×10^5 cell/ml	*IL-1β, IL-23, IL-6 and IL-10↑ *Fibroblast-like M2↑ *Fibroblast-like Mϕ↓ *Granuloma-like aggregate of M1↓ *MDC secretion↓ *M2, Mϕ and anti-inflammatory cytokines↑	Not mentioned
Cheng-Ying Chiu and colleagues (2012)	Macrophage RAW 264.7 cells were incubated with *E. coli* K-12 bioparticles	Murine macrophage RAW 264.7 cells	1 μ M: 17-HDPAn-6, 10/17-HDPAn-6, 17-HDHA	2 h	1×10^5 cell/well	*↑ Differentiation of macrophages towards the M2 phenotype *↑ Phagocytosis activity *↓ mRNA levels TNF-α and iNOS *↑ mRNA levels of IL-1 receptor antagonist and the scavenger receptor type A *↓mRNA expression of M1cytokines *↓TNF-α secretion	No adverse effect

Table 3 (continued)

References	Type of intervention to induce inflammation	Type of cell	Treatment	Duration of treatment	No of cell and GP	outcome	Adverse effects
Supriya R. Hyam and colleagues (2013)	LPS	Macrophages	Arctigenin (10 and 20 μM)	20 h	0.5×10^6cells/well	*Suppress IKKβ phosphorylation and NF-κB activation *↓ TNF-α, IL-1β and IL-6 *↑ IL-10 *↓ LPS-induced P13K and AKT phosphorylation *↓ LPS-elevated IL-1β and TNF-α *↑LPS-reduced expression of IL-10 and CD204 *Attenuate LPS-translocated NF-kβ into the nucleus *↓ iNOS, COX-2 and NF-kβ	Not mentioned
Hyo-Min Jang and colleagues (2017)	LPS	Human monocytes	Methoxylonchocarpin (ML)	1 day	2×10^6 cell/well	*↓Expression of TNF *↓Activation of NF-κB in LPS-induced peritoneal macrophages *↓IL-6 expression *↓iNOS and COX-2 expressions *↓NF-κB translocation into the nucleus *↓LPS-induced phosphorylation of IRAK1, TAK1 and IKB *↓Binding of LPS to TLR-4	Not mentioned

Table 3 (continued)

References	Type of intervention to induce inflammation	Type of cell	Treatment	Duration of treatment	No of cell and GP	outcome	Adverse effects
Su-Min Lim and colleagues (2015)	LPS	Peritoneal macrophages and splenocytes	Timosaponin AIII and sarsasapogenin	3 days	1×10^6 cells/well	*↓Expression of inflammatory mediators *↓NF-κB activation and translocation *↓MAPK signaling pathway *↓Phosphorylation of IRAK1, TAK1, IKB-α and P56 in LPS-stimulated peritoneal macrophages *↓IL-17 + T cell population *Restoring Th17/Treg cell balance	Not mentioned
Xiumei Che and colleagues (2018)	LPS	(1) Bone marrow derived macrophage (BMDM) of female mice (2) HT-29 cells (3) RAW 264.7 macrophages (4) L 929 cells	Guggulsterone	1 h	Not mentioned	*↓ Hyper activation of macrophage by attenuating TREM-1 *↓ NF-κB and AP-1 *↓ Activation of NF-κB	Not mentioned

MDC macrophage-derived chemokine

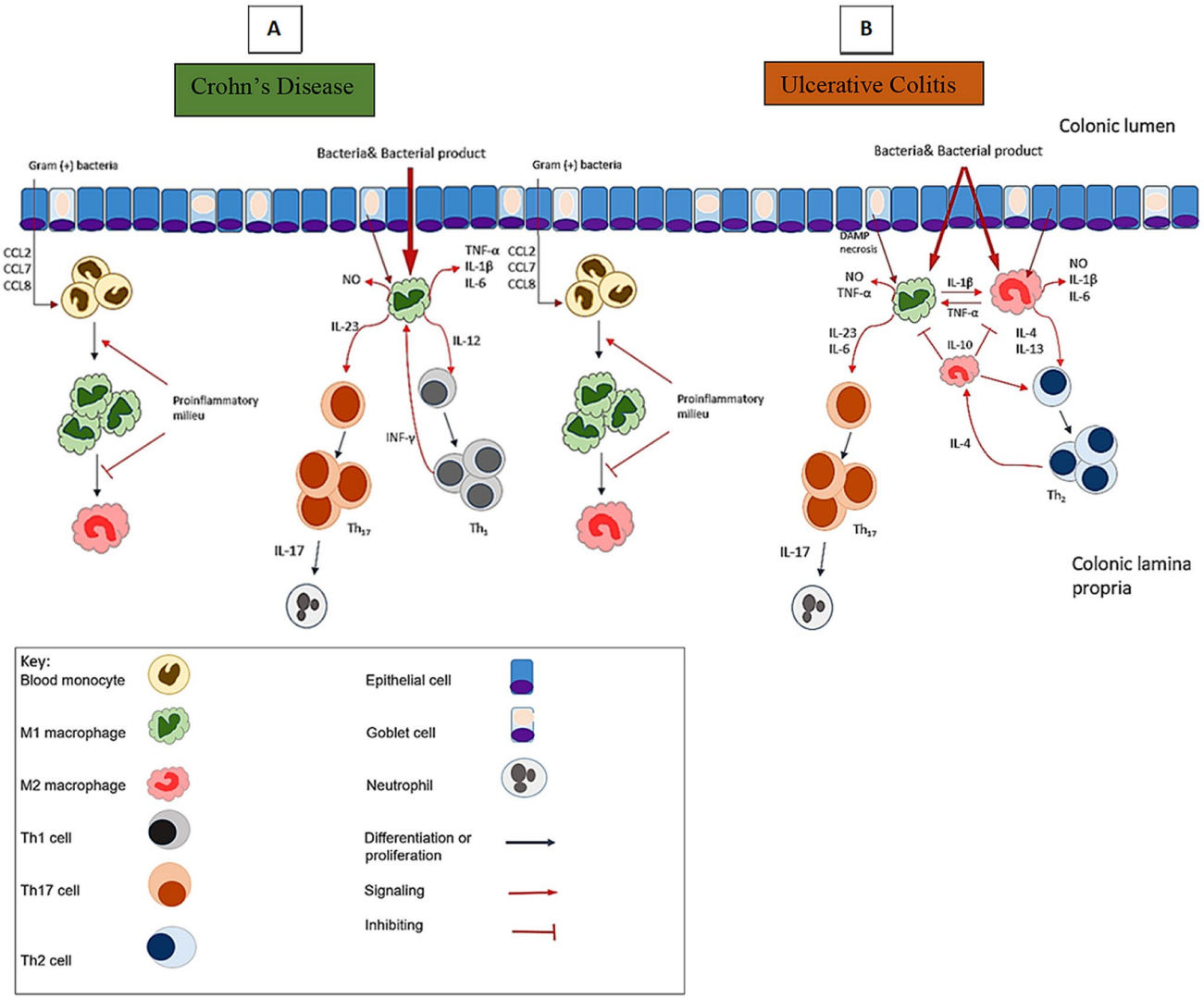

Fig. 1 **a** Inflammatory pathway in Crohn's disease. **b** Inflammatory pathway in ulcerative colitis

myokine irisin (FNDC5), which is upregulated in several mouse models of inflammation. Administration of recombinant FNDC4 in mouse model of colitis reduced the IBD severity through downregulation of classical M1 and M2, partly via STAT pathway in basal state (Bosma et al. 2016) (Table 2).

Living Organisms

Lactobacillus plantarum

Lactic acid bacteria (LAB) are safe microorganisms that ameliorate the inflammatory diseases and are frequently distributed in gut microbiota. Jang et al. reported that *L. plantarum* CLP-0611 is beneficial for IBD, through changing the polarization of M1 pro-inflammatory macrophages to M2 anti-inflammatory cells by means of IL-10, arginase-I, and CD206 inhibition (Jang et al. 2014) (Table 2).

Lactobacillus brevis G-101

Lactobacillus brevis G-101 down-regulated the TNF-α, IL-1β, IL-6, nuclear factor kappa-β (NF-κB), and AP1 expressions in TNBS-induced colitic mice. Besides, the bacteria amended the inflammatory markers (i.e., shortening of the colon, increase of MPO activity and pro-inflammatory cytokines). *L. brevis G-101* also suppressed the TLR-4-linked NF-κB, mitogen-activated protein kinase (MAPK), and AKT pathways (Jang et al. 2014). The bacteria promoted the polarization of M1 macrophages to M2-like macrophages (Jang et al. 2013) (Table 2).

Lactobacillus plantarum CLP-0611

In colitis mice, CLP-0611 modulated the disease by suppressing TLR-4 linked to NF-κB and MAPK signaling, and increased the M1 to M2 polarization. CLP-0611 considerably stimulated the M2-induced cytokine IL-10, arginase-I, and CD206 (Jang et al. 2013, 2014) (Table 2).

Helicobacter pylori

Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium and an important risk factor for gastritis. A number of studies suggested that there is an inverse effect between *H. pylori* and IBD, where the bacteria can ameliorate the disease. *H. pylori* colonization increased the TGFβ and decreased IL-6 and IL-23 in DSS model of IBD. Moreover, *H. pylori* colonization significantly enhanced M2 macrophages, representing protective effect against chronic colitis through balancing Th17/Treg and escalation of M2 phenotype (Zhang et al. 2018) (Table 2).

Cell Therapies

Mesenchymal Stem Cells-Exosomes (MSC-EX)

Intraperitoneally, administration of human umbilical cord mesenchymal stem cells (hUC-MSCs) extract reduced colitis, DAI, and the histological colitis scores in mice model of colitis. MSC-EX changed the macrophages functional phenotypes from M1 to M2, by decreasing the levels of MCP1, chemokine (C-X-C motif) ligand 9 (CXCL9), and iNOS (Song et al. 2017) (Table 2).

Human Adipose Tissue-Derived from Mesenchymal Stem Cells (hAT-MSC)

One of the familiar secretory factors valid for the anti-inflammatory activity is the TNF-α-induced gene/protein 6 (TSG-6), a mediator of inflammatory responses in IBD (Tang et al. 2009). TSG-6 is a key factor influencing the MSC immunemodulatory properties. The therapeutic benefit of adipose tissue-derived (cAT)-MSC produced TNF-α-induced TSG-6 was reported in DSS-induced IBD mice (Danchuk et al. 2011).

In a study by Song et al. (2018), TSG-6 positively manipulated the body weight loss, and shortening of the colon length, and also extended the bowel wall thickening. TSG-6 also reduced the colonic inflammatory responses and apoptosis via suppression of TNF-α and IL-6, while upregulated the IL-10 expression. M1–M2 transformation, increased M2 cells, M2 markers, human mannose receptor CD206, and arginase-I were stated to be the main mechanisms underlying the suppression of IBD by TSG-6 (Choi et al. 2011; Lee et al. 2009; Song et al. 2018) (Table 2).

Bone Marrow Cell-Derived Innate M2 Macrophages (BM1M-M2MS)

In an experiment, BMIMs were differentiated into M2 macrophages. Then, BMIM-M2MS were intravenously transplanted into a typical Th2-mediated inflammatory oxazolone (OXZ)-induced colitis model. As a result, BMIM-M2Ms elevated the expression of IL-4 and IL-1β cytokines, indicating that BMIM-M2Ms transplantation improved the intestinal inflammation and mucosal damage (Cheng et al. 2017) (Table 2).

Combination Therapy of Mesenchymal Stromal Cells and Sulfasalazine

In colitis patients, a combination therapy of mesenchymal stromal cells and low dose of sulfasalazine caused significant changes in amount of M1 and M2 cytokines. This therapeutic approach decreased the markers related to M1 macrophages such as CXCL9 and MPC1, while increased the M2 markers including arginase-I, TGF-β, and IL-10. Sulfasalazine and mesenchymal stromal cells profoundly mediated the disease by decreasing the body weight lost, diarrhea, focal necrosis of the mucosa erosion and sub-mucosal edema (Yousefi-Ahmadipour et al. 2019) (Table 2).

In Vitro Studies

Plant Extracts and Phytochemicals

Arctigenin

In LPS-stimulated peritoneal macrophages, arctigenin potently suppressed the NF-κB activation, inhibited the expression of pro-inflammatory cytokines IL-1β, IL-6 and TNF-α, whereas increased the expression of cytokine IL-10 and CD204. Additionally, arctigenin elevated the M2 macrophages markers and prevented the M1 polarization to M2-like macrophages (Hyam et al. 2013) (Table 3).

(+)-Borneol

The combination of borneol and edaravone had minor effects on M1 macrophages polarization. This combination increased the M2 cells population through the JAK2/STAT3 pathway (Zhang et al. 2017) (Table 3).

Timosaponin AIII and Sarsasapogenin

Timosaponin AIII and sarsasapogenin were shown to inhibit the inflammatory mediator's expressions, suppressed the NF-κB activation, and decreased the phosphorylation of

IRAK1, TAK1, IKBα, and P65 in LPS-stimulated peritoneal macrophages. They also downregulated the MAPK signaling and the translocation of NF-κB into the nuclei. This treatment decreased the IL-17$^+$ T-cell population and restored the balance of Th17/Treg cells, suggesting that timosaponin AIII and sarsasapogenin could inhibit the differentiation of splenic CD4$^+$ T cells into the Th17 cells in vitro (Lim et al. 2015) (Table 3).

Guggulsterone (GGS)

GGS blocked the TLR via triggering the receptor expressed on myeloid cells 1 (TREM-1) -expressing intestinal macrophages excitation. GGs also enhanced M1 to M2 transition by increasing IL-10 and suppressing the TREM-1. GGS hyper activated the macrophages by TREM-1 moderation and reducing the NF-κB and AP-1 levels (Che et al. 2018) (Table 3).

Natural Products

1,25 Vitamin D

Peripheral blood monoclonal cells (PBMCs) of CD patients were supplemented with 1,25VD. 1,25VD reduced the TNF-α, IL-23P40, IL-12 and iNOS levels, and inhibited the inflammatory cytokines production by M1 and M2. 1,25VD upregulated M2-induced MMP2 and CD-14 expressions, enhanced M2 cells, and increased the IL-10 level. It was proved that 1,25VD strengthened the phagocytic and chemotaxis aspects of the MΦ macrophages, yet exerted an inhibitory effect on pro-inflammatory cytokines productions. (Dionne et al. 2017). Similarly, Zhu et al. exhibited that in peripheral blood monoclonal cells, 1,25(OH)2D3 caused LPS-induced M1 transformation to the M2 subset, suppressed the TNF-α, and IL-6 expression, and interferon regulatory factor 5 (IRF5) phosphorylation, and enhanced the IL-10, arginase-1, VDR, and IRF4 expressions (Zhu et al. 2019) (Table 3).

17-HDPA *n*-6 and 17-HDHA

In murine macrophage RAW 264 cells, 17-HDPAn, 10, 17-HDPAn-6 or 17-HDHA activated M1/M2 polarization by inducing the differentiation towards M2 phenotype. In cell culture condition, the compounds increased the M2 chemokine IL-1 receptor antagonist and the scavenger receptor type 1, while depressed the mRNA expression of M1 cytokines such as TNF-α and iNOS (Chiu et al. 2012) (Table 3).

Living Microorganisms

Vsl#3

VSL#3 is a probiotic mixture of 8 different strains composed of *Bifidobacterium longum*, *B. infantis*, *B. breve*, *L. acidophilus*, *L. casei*, *L. delbrueckii* ssp. *bulgaricus, L. plantarum,* and *Streptococcus salivarus* ssp. *Thermophiles* mesalcurr (Connell et al. 2018). VSL#3 exposure to M1 and M2 macrophages led to a significant decline of pro-inflammatory cytokines and chemokines secretions and, in contrast, induced a remarked increase in secretion of anti-inflammatory cytokines and chemokines, regardless of the polarization status. M1, M2, and M_Φ macrophages exposed to VSL#3 secreted higher levels of certain anti-inflammatory factors like IL-1β, IL-23, IL-6, and IL-10. VSL#3 also reduced macrophage-derived chemokine (MDC) secretion (Isidro and Appleyard 2016; Isidro et al. 2014) (Table 3).

Conclusion

Even though IBD is a prevalent gastrointestinal inflammatory disease, the inciting etiology has yet to be elucidated. The significance of macrophages infiltration and activation has been associated with IBD. Following inflammation, a set of immune responses changes the body's homeostasis to a direction that stimulates the macrophages invasion and induces various inflammatory targets. Several important regulators such as STAT, and TLRs mediate the macrophages polarization. In addition, a number of microRNAs has been identified which are able to mediate the expression of effective regulators that determine the ratio of M1/M2 cells (Li et al. 2018a). A number of transcription factors have also been involved in the regulation of M1/M2 equilibrium. For instance, IRF5 stimulates M1 polarization (Krausgruber et al. 2011), although STAT6, C/EBPb, and IRF4 upregulate the M2-associated genes (Ruffell et al. 2009; Satoh et al. 2010). Imbalanced macrophages polarization leads to the promotion of the IBD progression and symptoms, as well as the secretion of specific cytokines and/or chemo-kinases, depending on the percentage of the inflammatory M1 and anti-inflammatory M2 macrophages. Based on the type of cytokine that macrophages produce, receptor expression, and effector function, they act as either pro-inflammatory or immunoregulatory factors. The proportion of cytokines within the mucosal microenvironment determines the macrophages polarization. M1 macrophages produce pro-inflammatory cytokines including IL-1β, IL-6, IL-12, and TNF-α, which contributes in host defense against microorganisms. In contrast, M2 cells suppress the pro-inflammatory responses, mediate anti-inflammatory cytokines/actions, and also contribute in wound healing and scavenging activities. In lamina

propria of IBD subjects, inflammatory M1 macrophages invade the intestinal tissues, disrupt the tight junction proteins, induce epithelial cell apoptosis, and impair the epithelial barrier, resulting in intestinal inflammation (Lissner et al. 2015; Cosín-Roger et al. 2013; Steinbach and Plevy, 2013). In contrast, M2 macrophages accelerate inflammation resolution, tissue repairing and remodeling during wound healing by upregulation of several mediators, particularly IL-10. Several studies demonstrated that the defect in M2 polarization or its associated cytokines leads to increased severity of colitis; whereas, adoptive transferring of regulatory T cells or M2 macrophages or inducing M2 polarization was shown to attenuate experimental colitis (Hunter et al. 2010; Zhu et al. 2014). Herein, we reported that several natural products ranging from living microorganisms to plant phytochemicals are able to shift the M1/M2 ratio positively toward controlling IBD. Overall, these natural components reduce the inflammatory mediator's productions, while promoting the anti-inflammatory cytokines. However, considerable improvement has been achieved in this manner; yet, many other issues should be clarified such as the mechanisms of macrophage polarization, the signaling pathways underlying the macrophages functions, and the pathological alterations. There is a lack of clinical trials on the correlation between M1 and M2 macrphages pathways and IBD, thereby, requiring future studies in this area.

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