Life Sciences 258 (2020) 118129

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Ulcerative colitis: Gut microbiota, immunopathogenesis and application of natural products in animal models

Roberto de Paula do Nascimento[a], Ana Paula da Fonseca Machado[a], Julio Galvez[b], Cinthia Baú Betim Cazarin[a], Mario Roberto Maróstica Junior[a,*]

[a] Universidade Estadual de Campinas (UNICAMP), Faculdade de Engenharia de Alimentos (FEA), Monteiro Lobato street, 80, 13083-862, Campinas, São Paulo, Brazil
[b] Universidad de Granada (UGR), Instituto de Investigación Biosanitaria de Granada (ibs.GRANADA), Centro de Investigación Biomédica, Departamento de Farmacología, 18071 Andaluzia, Granada, Spain

ARTICLE INFO

Keywords:
Inflammatory bowel diseases
Microbiota
Inflammation
Trinitrobenzene sulfonic acid
Oxazolone
Dextran sodium sulfate
Functional foods
Bioactive compounds
Natural products

ABSTRACT

Ulcerative colitis (UC) is an inflammatory bowel disease with increasing incidence in the world, especially in developing countries. Although knowledge of its pathogenesis has progressed over the last years, some details require clarification. Studies have highlighted the role of microbial dysbiosis and immune dysfunction as essential factors that may initiate the typical high-grade inflammatory outcome. In order to better understand the immunopathophysiological aspects of UC, experimental murine models are valuable tools. Some of the most commonly used chemicals to induce colitis are trinitrobenzene sulfonic acid, oxazolone and dextran sodium sulfate. These may also be used to investigate new ways of preventing or treating UC and therefore improving targeting in human studies. The use of functional foods or bioactive compounds from plants may constitute an innovative direction towards the future of alternative medicine. Considering the above, this review focused on updated information regarding the 1. gut microbiota and immunopathogenesis of UC; 2. the most utilized animal models of the disease and their relevance; and 3. experimental application of natural products, not yet tested in clinical trials.

1. Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) that occurs mostly in developed countries, such as those of Western Europe, the United States and New Zealand [1]. However, due to socio-economic development and westernization, since 1990, there has been an increase in cases of the disease in South American countries, such as Brazil [2]. Nowadays, the prevalence and annual incidence of UC may reach up to 505 and 58 cases per 100,000 people, respectively, depending on the region [3].

The etiology of the disease is still unclear; however, it is suggested that UC is a multifactorial disorder that includes four elements: microbiota, mucosal immunology, genetic predisposition and environmental factors (example: medication, food habits, smoking). Especially, it has been proposed that UC is a high-grade inflammatory response mediated by the immune system and that may be a consequence of microbial dysbiosis and disruption [4]. An increase in *Proteobacteria* and *Actinobacteria* microbial groups has been linked with the development of UC, as studies have shown [5,6]. In addition, some molecules, such as toll-like receptors (TLRs), IgG antibodies, nuclear factor kappa B (NF-κB) and pro-inflammatory cytokines, are commonly impaired in individuals with the disease, which may contribute to its progression [7]. UC affects mainly the rectum and colon, and can significantly worsen the quality of life and social ability of patients, due to common clinical signs, like body weight loss, diarrhea and rectal bleeding [8].

Studies with animals have been extensively conducted in order to discover new information regarding the immunopathophysiology of IBD, including UC, but also Crohn's disease (CD), another IBD with a high incidence worldwide [1]. The induction of colitis in murine through the use of chemical agents has been useful in those

Abbreviations: CD, Crohn's disease; COX-2, cyclo-oxygenase 2; CRC, colorectal cancer; CRP, C-reactive protein; DAI, Disease Activity Index; DSS, dextran sodium sulfate; EIM, extra-intestinal manifestation; IBD, inflammatory bowel disease; IEC, intestinal epithelial cells; IFN-γ, interferon gamma; IL, interleukin; ILC, innate lymphoid cells; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa B; NKT, natural killer T cells; OXA, oxazolone; pANCA, perinuclear anti-neutrophil cytoplasm antibody; SCFA, short chain fatty acids; TGF-β, transforming growth factor beta; Th, T-helper cell; TLR, Toll-like receptor; TNBS, trinitrobenzenesulfonic acid; TNF-α, tumor necrosis factor alpha; UC, ulcerative colitis

* Corresponding author.
E-mail addresses: jgalvez@ugr.es (J. Galvez), cbetim@unicamp.br (C.B.B. Cazarin), mmarosti@unicamp.br (M.R. Maróstica Junior).

https://doi.org/10.1016/j.lfs.2020.118129
Received 12 May 2020; Received in revised form 2 July 2020; Accepted 19 July 2020
Available online 25 July 2020

investigations, and especially, some of them are highly capable of reproducing the clinical, histopathological, and immunophysiological manifestations of UC [9]. Currently, the most commonly used chemical agents with better cost benefit are: 1. 2,4,6-trinitrobenzenesulfonic acid (TNBS), an acid intrarectally administered that can lead to both T-helper (Th) 1 and 2 cell-mediated responses in BALB/c mice; 2. Oxazolone (OXA), another haptenizing agent administered intrarectally to mice that can lead to UC-like colitis; and 3. dextran sodium sulfate (DSS), a salt given to mice via drinking water and capable of producing epithelial mucosa damage that more closely resembles UC [10].

Experimental mouse models also constitute valuable tools in the investigation of new ways of preventing or treating UC. The main treatment of UC is based on the use of aminosalicylates, corticosteroids, immunosuppressants and monoclonal antibodies. However, depending on the treatment, such therapies may present critical adverse effects [11,12]. Therefore, the study of functional foods, plants and bioactive compounds may be an innovative direction towards the future of alternative and/or complementary medicine.

In this review, we present an update on aspects of the gut microbiota and the immunopathogenesis of UC. Additionally, information about the most utilized animal models, and their application intending the discovery of new preventive or healing natural products will be shown. The study of such innovative products in animal models could potentially inspire the realization of clinical trials and application in the medical routine.

2. Gut microbiota

Patients with IBD usually present with dysbiosis, a condition characterized by an imbalance of beneficial and harmful population from microbiota [13]. Although there is still a debate in the literature on whether dysbiosis is the main causative factor or only a consequence of IBD, clear evidence shows the influence of specific bacteria on the modulation or impairment of the host's immunological response [14]. Some of the factors implicated in gut dysfunction of IBD include genetic and environmental aspects, to be discussed next.

The genetic implications of CD on microbiota, in comparison with UC, have been better investigated, especially those related to the *NOD2* gene [15]. However, studies with mice and humans have also been searching for answers regarding microbiota-related UC variants. Specifically, for UC, the following genes are implicated: *ATG16L1, LRRK2, MHCII, HLA, CARD9, CLEC7A, MUC5AC* and cytokine-related pathways (*IL-17, IL-22*). Alterations in the expression of variants related to mucus, like *MUC5AC*, appear to be relevant to determine peculiarities of UC development, since this may be the only factor not shared with CD [16]. Therefore, this parameter highlights the possible associated role of dysbiosis, mucus composition and epithelial barrier disruption in UC development.

Briefly, mucus is considered a barrier between the microbiota and the surface of the epithelium. It is mainly composed of mucins secreted by goblet cells that play an important role in the reconstitution and protection of the intestinal mucosa [17]. However, in patients with UC, there is an aberrant expression of mucin M1/MUC5AC [18], as well as altered patterns of glycosylation or diminished secretion of MUC2 [19,20], which may disturb the mucosal homeostasis. Therefore, a specific population of bacteria that binds to and degrades mucin glycans as a source of carbon [16] may have its abundance altered. A study by Png et al. [21] confirmed an alteration in mucolytic bacteria in individuals with UC. *Akkermancia muciniphila,* a species that may account for most part of the mucolytic ones, was found to be reduced, while the presence *of Ruminococcus torques* was significantly increased [21]. This shift may be a part of physiological changes in the mucous layer that could potentially lead to epithelial barrier breakdown and further activation of the immune response due to invasion and recognition of bacterial products [22]. Genetic disturbance that leads to dysbiosis and damage of the mucosal surface is not irreversible and can be modulated by environmental factors. However, it seems that this is mostly limited to infancy, a critical period in life for IBD prevention [23].

The influence of environmental factors on dysbiosis-driven UC is still largely unknown. Prospective cohort studies, like the Nurse Health Studies, aimed to investigate the association between environmental factors and the incidence of IBD. Surprisingly, results so far have shown that the food habits of an individual do not have a strong influence in the prevention or development of UC [24–26]. However, this is still conflicting, since some systematic reviews or meta-analyses published over the last decade indicated that different foods and dietary patterns play an important role in reducing or increasing the risk for UC. Additionally, randomized trials were also able to find interesting positive results on the effects of natural products on UC patients [27]. Based on these studies, it is also speculated that the protective or curative effects of diet on IBD are probably obtained by microbiota modulation. Diets, foods or compounds usually implicated in this manner include: Western and Mediterranean dietary patterns, proteins, digestible and non-digestible carbohydrates, polyunsaturated fatty acids and polyphenols [27].

The Western diet, rich in red meat, refined sugar and omega-6 fatty acids, and poor in fruit and vegetables has been markedly linked with lower microbial diversity and increased *Escherichia coli* invasiveness [28,29], which are features of patients with UC [30]. Additionally, a typical industrialized diet may also promote the reduction of beneficial bacteria, like *Bifidobacterium* species [31], which are set to induce remission in UC patients due to their anti-inflammatory effects [32–34]. In contrast, the consumption of a Mediterranean or rural agrarian diet is related to a healthy microbiome and a lower risk to develop UC [27,35].

A meal rich in animal protein, which is also one of the characteristics of the Western diet, may alone increase the risk for IBD [36]. A recent study using mice with DSS-induced colitis found that a diet rich in casein given preventively promoted pro-inflammatory responses related to changes in microbiota composition, like increases in *Streptococcus* and *Peptostreptococcus* [37]. Such genera have been found abundant in the fecal samples of populations with UC [38,39], indicating a possible role of a casein-rich diet in dysbiosis and increased UC risk, however, more studies are needed to confirm such associations. Studies in the literature had also shown a relation between regular consumption of red and processed meat and IBD development [40,41]. Since 1960, the consumption of meat has dramatically increased all over the world, especially in China and Latin American countries [42], and the incidence of UC is rising in newly industrialized cities [43]. Although poorly known, studies claim that sulfur metabolites from red meat and/or the formation of hydrogen sulfide from sulfate-reducing bacteria would be responsible for changes in microbiota, in association with the poor utilization of short-chain fatty acids (SCFAs) by enterocytes and the subsequent toxic damage to colonocytes [41,44]. The consumption of a high-protein in association with a low-carbohydrate diet may also promote negative changes in microbiota. This dietary pattern is said to culminate in reduced production of butyrate, the main SCFA that provides energy to colonocytes, being also essential against pro-inflammatory reactions [45]. In UC patients, the diminished production of butyrate and a decreased abundance of bacteria that generate it, like *Roseburia hominis* and *Faecalibacterium prausnitzii* [46], may be indicative that the consumption of a high-protein/carbohydrate ratio diet for long periods should be avoided for reasons of UC risk. This scenario suggests a high correlation between high animal protein consumption, especially red meat, dysbiosis and the development of UC.

Although a diet rich in total carbohydrates is essential, not any kind would be able to maintain a healthy individual status. In fact, a recent meta-analysis shows that the consumption of an additional 10 g/day of sucrose is directly related to UC [47]. This may happen because a high-sucrose diet, as animal studies demonstrate [48–50], is able to promote dysbiosis, followed by the release of lipopolysaccharide (LPS), a component of gram-negative bacteria, and increased gut permeability,

allowing the activation of immune response and the production of pro-inflammatory cytokines. One of the gram-negative bacteria phyla usually found in abundance in the microbiota of animals on a high-sugar diet [51] or in an obese population [52] is *Proteobacteria.* This phyla is also found to be increased in the microbiota of UC patients [38,53], which implies that diet factors capable of disturbing the abundance of *Proteobacteria* should be avoided in order to prevent the progression of inflammatory conditions. If sugar promotes dysbiosis, consumption of non-digestible carbohydrates, like fructooligosaccharides, for example, has an opposite effect [31]. The so-called "microbiota accessible carbohydrates" promote a reduction in *Clostridium* and *Enterococcus* species [54–56], previously said to be related to disease onset, and an increase in *Bifidobacteria* and *Lactobacilli* [57,58] genera and *Eubacterium rectale* [59,60] and *Roseburia* species [57,61], which are usually decreased in UC patients [30,62]. Consumption of fruit and vegetables, and therefore of a diet rich in dietary fibers, is also related to bacteria gene richness [63] and the production of SCFAs, such as acetate, butyrate and propionate, which possess anti-inflammatory-related actions and strengthen the epithelial mucosa barrier [64].

Finally, other studies testing omega-3 polyunsaturated fatty acids (PUFA) and polyphenols found interesting results in the modulation of microbiota and UC prevention by these compounds. For example, consumption of fish oil was able to increase the abundance of *Bifidobacterium* and *Roseburia* genera in healthy individuals [65]. Lack of the *Roseburia* genus is related to dysbiosis and the pathogenesis of UC [46], so prevention or treatment with omega-3 fatty acids may be an alternative to be considered. However, studies with animals are revealing that fish oil alone may not promote ameliorative effects in UC [66,67], strongly indicating that it should be in fact integrated with other sources of fat or diets, like olive oil [68], a balanced ratio of omega-6/omega-3 fatty acids [69,70] or in association with phenolic compounds, like curcumin [71]. Although still poorly studied, foods rich in or simply isolated polyphenols (example: algae, fungi, honey, propolis, resveratrol) could promote a healthy microbiota when given preventively to mice or rats with UC-like disease [72]. *Lactobacillus* species, which are found downregulated in relapsing UC patients [73], are one of the main bacteria increased after an intervention with polyphenols in animal models of UC [74–76]. *Lactobacillus* are related to a lower abundance of pathogenic bacteria and decreased inflammatory markers, like C-reactive protein (CRP) [77].

Considering previous information, it appears that a diet with fewer characteristics of a Western pattern, low in animal protein and sugar, rich in fruits and vegetables and balanced in fatty acids, could potentially prevent against dysbiosis and later UC development.

When already installed, UC causes important alterations in the microbiota composition of patients. These are characterized by changes in populations of not only bacteria, as mostly known, but also fungus and viral. Table 1 summarizes the main alterations found in the microbiota of UC patients in comparison with healthy subjects, according to studies in the last five years. Briefly, consistent data found that in UC, the populations of the following bacteria are increased: *Firmicutes, Actinobacteria* (phylum), *Bacteroides, Streptococcus* (genus), *Escherichia coli, Fusobacterium nucleatum (*species); and the following are decreased: *Bacteroidetes* (phylum), *Bifidobacterium, Blautia, Coprococcus, Lachnospira, Lactobacillus, Roseburia, Ruminnococus* (genus), *Akkermansia muciniphila, Bacteroides fragilis, Clostridium leptum, Eubacterium rectale, Faecalibacterium prausnitzi, Prevotella stercorea, Ruminococcus gnavus* (species). There are still conflicting data regarding some of these, due to differences in methodologies employed, populations studied and characteristics of patients (genetic background, disease severity, colon involvement, treatment). More studies are needed to clarify the composition of the microbiota.

3. Immunopathogenesis

As previously discussed, dysbiosis, which can be triggered by

Table 1
Significant alterations in microbiota of UC patients.

Microorganism (bacterium, fungus or virus)	Country (sample size)	Alteration	Reference
Bacterium			
Phylum			
Actinobacteria	Italy (82)	↑	[78]
	United Kingdom (11)	↑	[79]
Bacteroidetes	Germany/Lithuania/ India (30)	↑	[80]
	Italy (5)	↓	[81]
	Italy (82)	↓	[78]
	The Netherlands (pediatric, 41)	↓	[82]
	The Netherlands (107)	↑	[83]
Cyanobacteria	Italy (82)	↓	[78]
Firmicutes	Germany/Lithuania/ India (30)	↑	[80]
	Hong Kong (63)	↑	[84]
	Italy (82)	↑	[78]
	The Netherlands (107)	↓	[83]
	United Kingdom (11)	↑	[79]
Fusobactera	Italy (82)	↓	[78]
Proteobacteria	Germany/Lithuania/ India (30)	↓	[80]
	Italy (5)	↑	[81]
	The Netherlands (pediatric, 41)	↓	[82]
	The Netherlands (107)	↑	[83]
	United Kingdom (11)	↓	[79]
Tenericutes	The Netherlands (107)	↓	[83]
Verrucomicrobia	Italy (82)	↑	[78]
Class			
Betaproteobacteria	The Netherlands (107)	↑	[83]
Coriobacteriia	United Kingdom (11)	↑	[79]
Mollicutes	The Netherlands (107)	↓	[83]
Order			
Bacteroidales	The Netherlands (107)	↑	[83]
Family			
Actinomycetaceae	The Netherlands (107)	↓	[83]
Burkholderiaceae	United Kingdom (11)	↑	[79]
Christensenellaceae	The Netherlands (107)	↓	[83]
Coriobacteriaceae	The Netherlands (107)	↓	[83]
	United Kingdom (11)	↑	[79]
Dehalobacteriaceae	The Netherlands (107)	↓	[83]
Enterobacteriaceae	United Kingdom (11)	↓	[79]
Enterococcaceae	The Netherlands (107)	↑	[83]
Lachnospiraceae	China (63)	↓	[85]
Lactobacillaceae	The Netherlands (107)	↑	[83]
Methanobacteriaceae	The Netherlands (107)	↓	[83]
Mogibacteriaceae	The Netherlands (107)	↓	[83]
Porphyromonadaceae,	China (63)	↓	[85]

(*continued on next page*)

Table 1 (*continued*)

Microorganism (bacterium, fungus or virus)	Country (sample size)	Alteration	Reference
Prevotellaceae	United Kingdom (11)	↑	[79]
Pseudomonadaceae	Hong Kong (63)	↑	[84]
Rikenellaceae	United Kingdom (11)	↓	[79]
Ruminococcaceae	Hong Kong (63)	↑	[84]
Tannerellaceae	United Kingdom (11)	↓	[79]
Veillonellaceae	Hong Kong (63)	↑	[84]
Genus			
Actinomyces	Canada (19)	↑	[86]
Akkermansia	Czech Republic (32)	↓	[87]
Alistipes	China (8)	↓	[88]
Anaerofustis	Canada (19)	↑	[86]
Anaerostipes	China (8)	↓	[88]
Annaerococcus	Germany/Lithuania/ India (30)	↓	[80]
Atopobium	Finland (pediatric, 12)	↓	[89]
Bacteroides	China (28)	↑	[90]
	Finland (pediatric, 12)	↑	[89]
	Greece (20)	↑	[91]
	Italy (82)	↓	[78]
	USA (pediatric, 5)	↓	[92]
Bifidobacterium	Canada (19)	↑	[86]
	China (28)	↓	[90]
	Finland (pediatric, 12)	↓	[89]
Blautia	China (8)	↓	[88]
	Japan (48)	↓	[93]
	USA (pediatric, 5)	↓	[92,93]
Clostridium	China (8)	↓	[88]
	China (28)	↑	[90]
Coprococcus	China (8)	↓	[88]
	Czech Republic (32)	↓	[87]
	Hong Kong (63)	↑	[84]
Dialister	Italy (5)	↑	[81]
Dorea	China (63)	↓	[85]
Eggerthella	Canada (19)	↑	[86]
Enterococcus	China (63)	↑	[85]
Escherichia	Italy (82)	↑	[78]
Faecalibacterium	China (63)	↑	[85]
Faecalicoccus	Canada (19)	↑	[86]
Flavobacterium	Italy (82)	↓	[78]
Gemella	Canada (19)	↑	[86]
Gemmiger	Canada (19)	↓	[86]
Gordonibacter	Canada (19)	↓	[86]
Haemophilus	USA (pediatric, 5)	↑	[92]
Lachnospira	Canada (19)	↓	[86]
	China (8)	↓	[88]
Lactobacillus	China (28)	↓	[90]
	Finland (pediatric, 12)	↓	[89]
	Japan (48)	↑	[93]

Table 1 (*continued*)

Microorganism (bacterium, fungus or virus)	Country (sample size)	Alteration	Reference
Megasphaera	China (8)	↓	[88]
Mogibacterium	Canada (19)	↓	[86]
Papillibacter	Germany/Lithuania/ India (30)	↓	[80]
Parabacteroides	China (63)	↓	[85]
Phascolarctobacterium	Czech Republic (32)	↓	[87]
Prevotella	Norway (23)	↑	[94]
Rikeneliaceae	China (63)	↓	[85]
Roseburia	China (8)	↓	[88]
	Czech Republic (32)	↓	[87]
Ruminococcus	Canada (19)	↓	[86]
	China (63)	↓	[85]
	USA (pediatric, 5)	↓	[92]
Sporobacter	Canada (19)	↓	[86]
Streptococcus	Canada (19)	↑	[86]
	China (63)	↑	[85]
	Italy (82)	↑	[78]
	USA (pediatric, 5)	↑	[92]
Sutterella	Italy (82)	↑	[78]
Thermaceae,	Hong Kong (63)	↑	[84]
Turicibacter	China (8)	↓	[88]
Veillonella	Italy (82)	↑	[78]
Species			
Acidaminococus intestini	Italy (82)	↑	[78]
Akkermansia muciniphila	Czech Republic (32)	↓	[87]
	Italy (5)	↓	[81]
	Italy (82)	↑	[78]
	Spain (23)	↓	[95]
	The Netherlands (pediatric, 41)	↓	[82]
Alistipes finegoldii	The Netherlands (pediatric, 41)	↓	[82]
Alistipes putredinis	The Netherlands (pediatric, 41)	↓	[82]
Alkaliphilus crotonatoxidans	Italy (82)	↓	[78]
Bacteroides thetaiotaomicron	Italy (82)	↓	[78]
Bacteroides acidifaciens	Italy (82)	↑	[78]
	USA (European/ South Asian, 30)	↓	[96]
Bacteroides caccae	Italy (82)	↓	[78]
Bacteroides denticanum	Italy (82)	↓	[78]
Bacteroides dorei	Italy (82)	↑	[78]
Bacteroides fragilis	Italy (5)	↑	[81]
	Japan (48)	↓	[93]
	The Netherlands (pediatric, 41)	↓	[82]
Bacteroides ovatus	USA (European/ South Asian, 30)	↓	[96]
Bacteroides uniformis	USA (European/ South Asian, 30)	↓	[96]
Bacteroides xilanisolvens	Italy (82)	↑	[78]
Bifidobacterium adolescentis	USA (European/ South Asian, 30)	↑	[96]
Bifidobacterium breve	Italy (82)	↑	[78]

(*continued on next page*)

Table 1 (*continued*)

Microorganism (bacterium, fungus or virus)	Country (sample size)	Alteration	Reference
Bilophila wadsworthia	Germany (pediatric, 6)	↓	[97]
	Italy (82)	↑	[78]
Butyricicoccus pullicaecorum	Czech Republic (32)	↓	[87]
Caloromator mitchelensis	Italy (82)	↓	[78]
Candidatus endobugula sertula	Italy (82)	↑	[78]
Clostridium colinum	Czech Republic (32)	↓	[87]
Clostridium difficile	Italy (5)	↓	[81]
Clostridium hathewayi	Japan (48)	↓	[93]
Clostridium leptum	Greece (20)	↓	[91]
	Japan (48)	↓	[93]
Clostridium oroticum	Japan (48)	↓	[93]
Clostridium perfringens	China (41)	↑	[98]
Clostridium ramosum	Germany (pediatric, 6)	↑	[97]
Collinsella intestinalis	Italy (82)	↑	[78]
Coprococcus catus	Czech Republic (32)	↓	[87]
Dorea formicigenerans	Japan (48)	↓	[93]
	USA (European/ South Asian, 30)	↑	[96]
Dysgonomonas nimpennyl	Italy (82)	↓	[78]
Escherichia albertii	Italy (82)	↑	[78]
Escherichia coli	China (28)	↑	[90]
	China (63)	↑	[85]
	Germany (pediatric, 6)	↑	[97]
	The Netherlands (pediatric, 41)	↑	[82]
Eubacterium rectale	Germany (pediatric, 6)	↓	[97]
	China (41)	↓	[98]
	Finland (pediatric, 12)	↓	[89]
Faecalibacterium prausnitzi	China (41)	↓	[98]
	Czech Republic (32)	↓	[87]
	Germany (pediatric, 6)	↓	[97]
	Greece (20)	↓	[91]
	Spain (23)	↓	[95]
	The Netherlands (pediatric, 41)	↑	[82]
	USA (European/ South Asian, 30)	↑	[96]
Fusicatenibacter saccharivorans	Japan (48)	↓	[93]
Fusobacterium nucleatum	Germany (pediatric, 6)	↑	[97]
	Italy (82)	↑	[78]
Lactobacillus mucosae	USA (European/ South Asian, 30)	↑	[96]
Mitsuokella multacida	USA (European/ South Asian, 30)	↑	[96]
Odoribacter splanchnicus	The Netherlands (pediatric, 41)	↓	[82]
Parabacteroides distasonis	Italy (82)	↓	[78]
Parabacteroides merdae	Italy (82)	↓	[78]
Pedobacter kwangyangensis	Italy (82)	↓	[78]
Phascolarctobacterium faecium	Italy (82)	↓	[78]
Prevotella copri	Italy (82)	↓	[78]

Table 1 (*continued*)

Microorganism (bacterium, fungus or virus)	Country (sample size)	Alteration	Reference
Prevotella shaii	Italy (82)	↑	[78]
Prevotella stercorea	Italy (82)	↓	[78]
	USA (European/ South Asian, 30)	↓	[96]
Prosthecobacter fluviatilis	Italy (82)	↑	[78]
Ruminococcus bromii	Italy (82)	↑	[78]
Ruminococcus flavefaciens	USA (European/ South Asian, 30)	↑	[96]
Ruminococcus gnavus	Czech Republic (32)	↓	[87]
	Germany (pediatric, 6)	↑	[97]
	Italy (5)	↓	[81]
	Japan (48)	↓	[93]
Serratia entomophila	Italy (82)	↑	[78]
Sphingobacterium shayense	Italy (82)	↓	[78]
Streptococcus vestibularis	Italy (82)	↑	[78]
Suterella wadsworthensis	Italy (82)	↓	[78]
Veillonella atypica	Italy (82)	↑	[78]
Veillonella denticariosi	Italy (82)	↑	[78]
Veillonella dispar	Italy (82)	↑	[78]
Veillonella montpellerensis	Italy (82)	↑	[78]
Veillonella parvula	USA (European/ South Asian, 30)	↑	[96]
Fungus			
Genus			
Aspergillus	China (14)	↑	[99]
Debaryomyces	USA (European/ South Asian, 30)	↑	[96]
Species			
Alternaria alternata	USA (European/ South Asian, 30)	↓	[96]
Aspergillus cibarius	USA (European/ South Asian, 30)	↓	[96]
Aspergillus flavus	USA (European/ South Asian, 30)	↓	[96]
Candida albicans	USA (European/ South Asian, 30)	↑	[96]
Candida sojae	USA (European/ South Asian, 30)	↓	[96]
Virus			
Order			
Caudovirales	Hong Kong (63)	↑	[84]
Family			
Anelloviridae	Hong Kong (63)	↑	[84]
Hepadnaviridae	Denmark (38)	↑	[100]
Microviridae	Hong Kong (63)	↑	[84]
Myovirida	Hong Kong (63)	↑	[84]
Pneumoviridae	Hong Kong (63)	↑	[84]
Podoviridae	Hong Kong (63)	↑	[84]
Polydnaviridae	Denmark (38)	↓	[100]
Tymoviridae	Denmark (38)	↓	[100]
Genus			
Coccolithovirus	Hong Kong (63)	↓	[84]
Lambdavirus	Hong Kong (63)	↑	[84]
Mimivirus	Hong Kong (63)	↑	[84]
Minivirus	Hong Kong (63)	↓	[84]

(*continued on next page*)

Table 1 (*continued*)

Microorganism (bacterium, fungus or virus)	Country (sample size)	Alteration	Reference
Orthopneumovirus	Hong Kong (63)	↑	[84]
Orthopoxvirus	Hong Kong (63)	↓	[84]
P1virus	Hong Kong (63)	↑	[84]
P22virus	Hong Kong (63)	↑	[84]
Phix174microvirus	Hong Kong (63)	↑	[84]
T4virus	Hong Kong (63)	↑	[84]
Species			
Chrysochromulina ericina virus	Hong Kong (63)	↑	[84]
Enterobacteria phage	Hong Kong (63)	↑	[84]
Escherichia phage	Hong Kong (63)	↑	[84]

Icon key: ↑: increased; ↓: decreased. Observations: 1. when not mentioned, studies utilized adults or a combination of adults and elderly for microbiota examination; 2. only the studies that discriminated between CD and UC were considered.

genetic and environmental factors, may be the main pathogenic factor of UC, since it can be associated with epithelial barrier function, contribute to the activation of proteins and cells of the immune system and propagate typical inflammatory responses. However, it is important to remember that immunological impairment may be the foremost factor responsible for the effects that lead to UC [4]. Therefore, more studies are needed to clarify this dubiety. Some of the most well-known components of the immune response that are related to UC pathogenesis, to be discussed next, include: TLRs, macrophages, neutrophils, innate lymphoid cells (ILCs), intestinal epithelial cells (IEC), IgG antibodies, pro-inflammatory cytokines and enzymes, NF-κB signaling pathway and Th2/Th9/Th17 adaptive immune responses [4] (Fig. 1).

TLRs may play an initial role in the pathology of UC. These receptors are expressed by dendritic cells for microbial recognition purposes, and they are essential for intestinal homeostasis and epithelial barrier function [101]. Polymorphism in TLR4 is observed in patients with UC, which could alter the susceptibility of these individuals to enteric infections and cause reduced tolerance to microbiota [102]. In fact, there is an abnormal increase in TLR4 expression in the colonocytes and in lamina propria of the intestine, which has been considered as one of the mechanisms for the activation of innate and adaptive immune responses [103,104]. LPS is one of the molecules involved in the activation of TLR4 [105] and its levels may be increased in the blood of patients with IBD [106].

The innate immune response of UC is characterized by a marked presence of neutrophils, macrophages, and dendritic cells. Neutrophils are one of the first cell types recruited during the active phase of the disease, which is increased in the blood and colon of patients. Some of the deleterious functions of this lymphocyte in UC include: impairment of epithelial barrier function, tissue destruction through oxidative and proteolytic damage, and release of inflammatory mediators [107,108]. Macrophages and dendritic cells, on the other hand, act in the uptake and processing of antigens, in addition to their subsequent presentation to T and B cells [109]. Recognition of molecular patterns associated with pathogens by macrophages and dendritic cells induces the activation of several signaling pathways, such as NF-κB, which results in increased production of acute pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α), interleukins (IL) (1β, 6, 8, 12, 18) and TNF-like cytokine 1A [103,110].

Innate lymphoid cells (ILCs), located near the intestinal epithelium, also play a role in UC. ILCs are important in resistance to and elimination of pathogens and maintenance of epithelial integrity, being able to produce several cytokines. However, stimuli from the altered microbiota and excess antigens may exacerbate the production of pro-inflammatory cytokines by ILCs and trigger and/or perpetuate inflammation in colon. High gene expression and/or tissue production of IL-17, IL-22, IL-23, and interferon gamma (IFN-γ) cytokines by ILCs may occur in these conditions [111,112]. Besides, IEC also appear to contribute to the production of cytokines, such as IL-18, IL-33, and IL-37, and in the activation of ILCs. Thus, the imbalance and excess cytokine levels produced by macrophages, dendritic cells, ILCs, and IEC contribute significantly to the loss of tight junctions function and IEC apoptosis, altering the integrity of the intestinal mucosa [113]. Components of the innate response induce the activation of the humoral and cellular response, which seems to be essential in the progression of inflammation at local and systemic levels [114].

Elevated amounts of IgM, IgA, and IgG antibodies have already been detected in patients with IBD [115]. Especially, IgG1 is increased in the blood of these individuals. This is an antibody that may target an epithelial protein called tropomyosin, which is part of the cytoskeleton of epithelium cells. In addition, UC patients also have increased serum levels of perinuclear anti-neutrophil cytoplasm antibody (pANCA), which is an autoantibody that can react with proteins located in granules, cytoplasm or the nuclear periphery of neutrophils. The production of IgG1 against tropomyosin and pANCA suggests that autoimmunity may play an important role in the course of UC [116,117].

As opposed to CD, which is characterized by a predominant Th1 response, in UC there is a higher activity of CD4+ Th2 lymphocytes. However, this response is considered atypical due to the abundant presence of non-classical natural killer T cells (NKT). These cells are activated through the presentation of a lipid antigen expressed through the CD1d receptor to T cells [118]. Activation of these NKT cells induces the production of great amounts of IL-13, which is a typical Th2-responsive cytokine capable of causing epithelial barrier damage, reducing the speed of mucosal repair, promoting changes in tight junctions and inducing the apoptosis of IEC [118]. Recent studies, however, have shown that patients with UC do not have high IL-13 levels and that treatment in humans with an anti-IL-13 antibody (Tralokinumab) does not reflect improvements in the clinical score [119,120].

Other findings support the predominance of the Th2 response in UC. Significant amounts of IL-5 producing Th2 cells [121] and increased expression of the GATA binding protein 3 have already been demonstrated in individuals with the disease [122]. Elevated levels of the anti-inflammatory cytokine IL-10 are also observed in the mucosa of patients [123]. This increase, however, is maybe not enough to effectively inhibit the inflammatory activity of monocytes and macrophages [124]. The anti-inflammatory cytokine IL-4, on the other hand, has its production decreased in the mucosa of patients [125]. This finding, associated with the most recent research regarding IL-13, indicates that UC may not exhibit all the characteristics of a Th2 response and that other cell types appear to exert influence in the course of the disease. In this sense, recent studies have evidenced meaningful participation of Th17, Th22, and Th9 cells, as well as cytokines related to their pathways [4,114,120].

Th17 cells appear to be involved in the pathogenesis of IBD, considering the recent genetic polymorphisms found in elements of its signaling pathway. Studies with humans reveal that the colon of patients with IBD has high amounts of cytokines produced by this cell type, such as IL-17A and IL-17F. These cytokines, in association with IL-21, also produced by Th17, would be responsible for the recruitment of neutrophils and increased regulation of pro-inflammatory cytokines, such as TNF, IL-1β, IL-6, and IL-8, which would result in deformation of the intestinal epithelium [126,127]. Also, Th17 cells would possibly be able to alter levels of regulatory elements of epithelial barrier function, such as Th22 and IL-22. In patients with UC, low levels of Th22 and IL-22 are found in the intestinal mucosa, and according to Leung et al. [128], they are probably related to important changes in the microbiota. Finally, with less evidence, studies also suggest the participation of Th9 cells, which could, together with IL-9, cause changes in epithelial barrier function and cellular repair. This cell type could

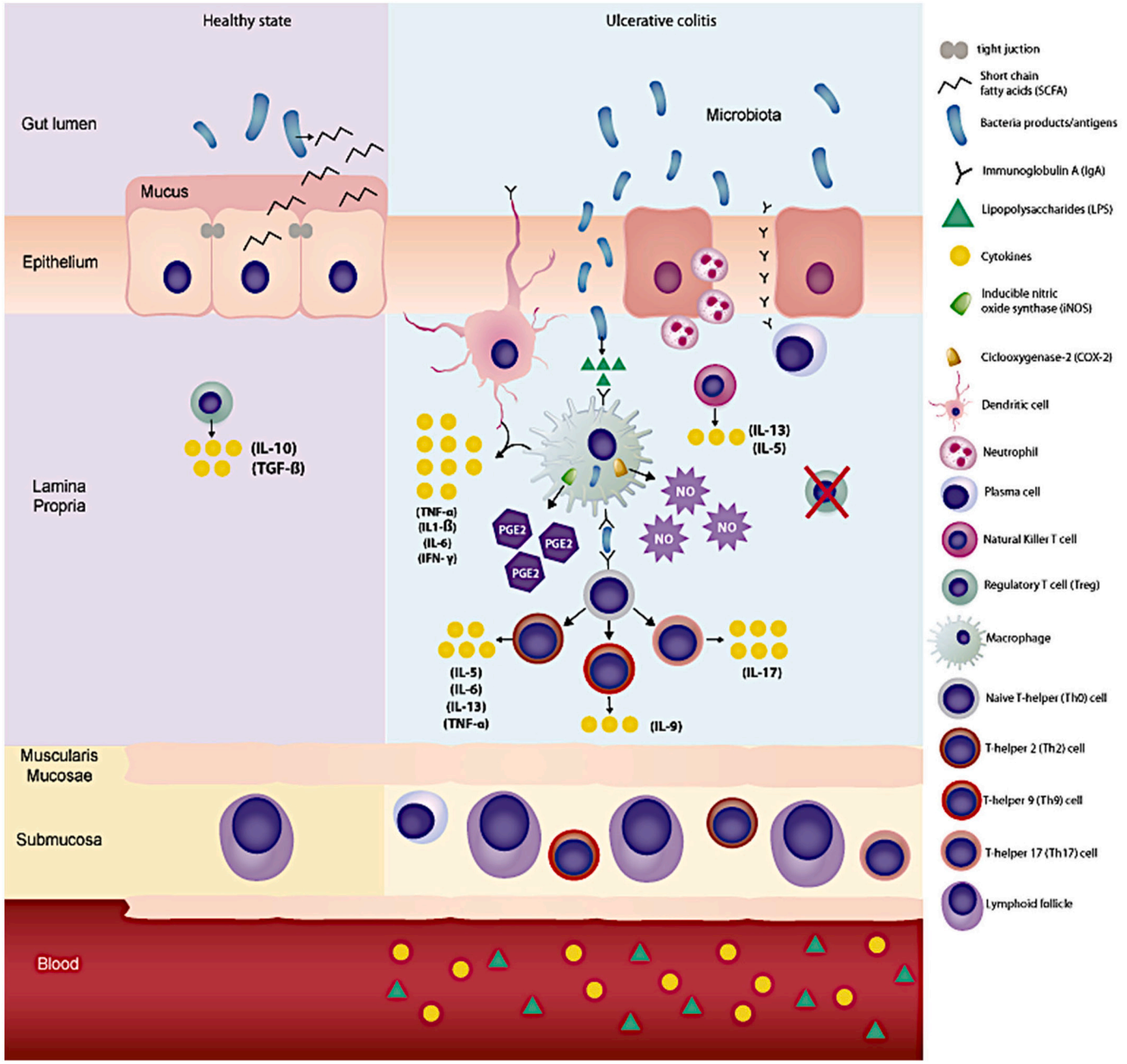

Fig. 1. Schematic drawing of the immune impairment of UC.
In UC, changes in microbiota could result in the exacerbation of the immune response (or vice versa), resulting in loss of mucosal integrity and mucus, tight junctions depletion, and low production of SCFA. The recognition of bacterial products, such as LPS, by dendritic cells and macrophages leads to the activation of intracellular factors and enzymes, such as inducible nitric oxide synthase (iNOS) and Ciclo-oxigenase-2 (COX-2), and the production/release of cytokines, free radicals, and prostaglandins. Neutrophils classically infiltrate the intestinal mucosa in the early stages of the inflammatory process. Antigen presentation to Th0 cells activates the cellular immune response, which is speculated to be characterized by a predominance of Th2 and NKT and its typical cytokines. Th9 and Th17 cell types also appear to be involved in the development of the disease, as well as plasma cells and IgA. T regulatory cells may be diminished in UC, which could impede the production of anti-inflammatory cytokines. In UC, the inflammatory process classically reaches mucosa and submucosa, not affecting muscular layers and serosa as in CD. High amounts of LPS and pro-inflammatory cytokines, especially TNF-α, can be found in patients with UC. Figure adapted and information from Ungaro et al. [4], Sahami et al. [132], Ordás et al. [133] and Rojo et al. [106]. Image created by Paula Januzzi Guedes, according to orientation of Roberto de Paula do Nascimento.

contribute to the development of UC, based on observations that animals without IL-9 production or its transcription factor PU.1, and treated with anti-IL-9, were protected from the disease [129].

In summary, the exacerbation of the immune response (macrophages, neutrophils, Th2, Th9, Th17, pro-inflammatory cytokines), associated with defects in mucus and epithelial barrier function and alterations in microbiota may lead to the emergence of UC [4]. Over time, patients with UC may significantly increase the risk of getting colorectal cancer (CRC) [130], which is currently the second most deadly type of cancer in the world [131].

3.1. Endoscopic, histological and clinical changes

The typical inflammatory process of UC affects almost exclusively the final portion of the intestine, beginning in the rectum and advancing throughout the colon. According to the Montreal classification, UC

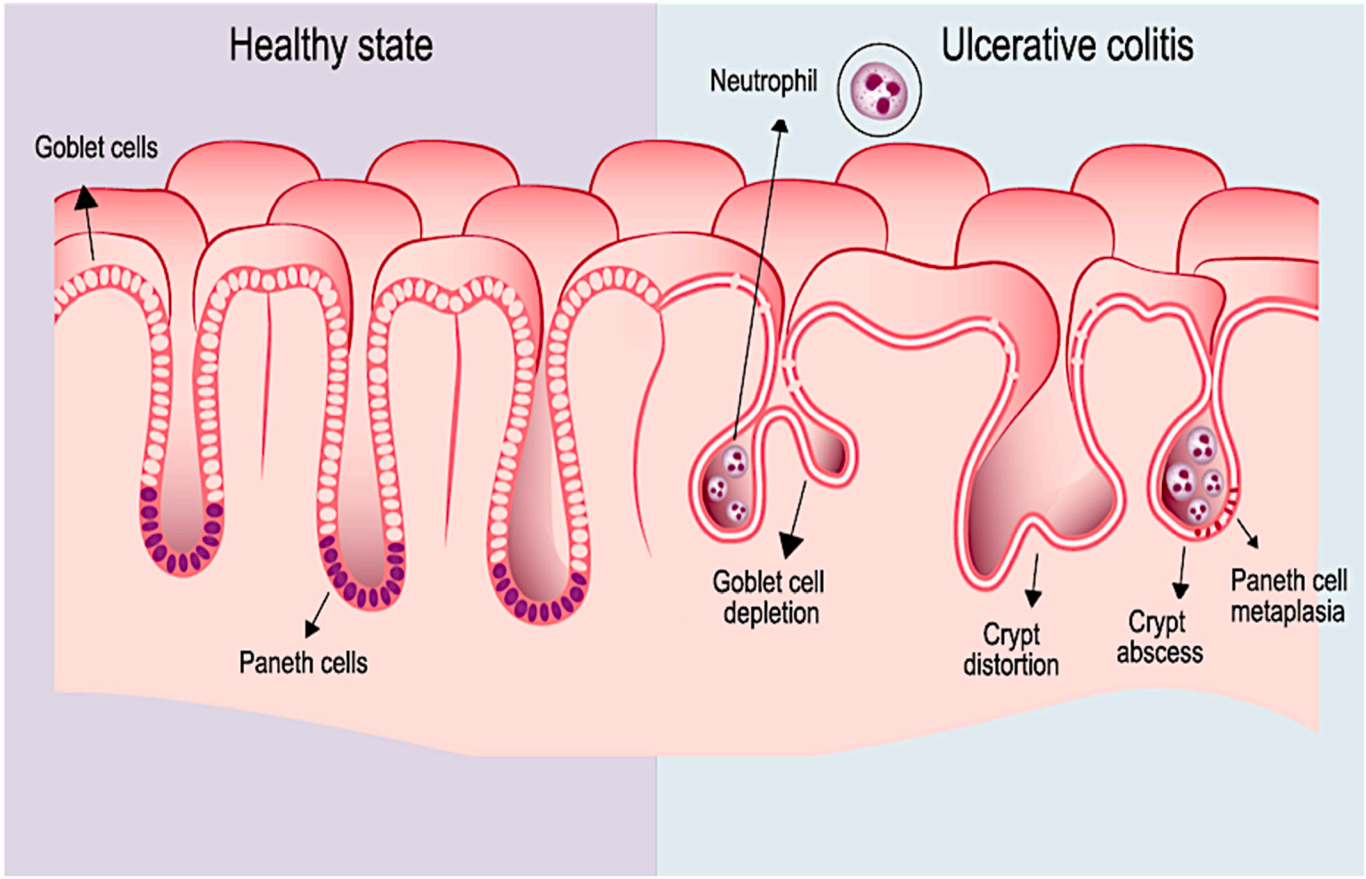

Fig. 2. Representative drawing of the changes in the colon of individuals with UC.
Some of the classic histological changes of human UC include goblet cell depletion, intestinal crypt distortion, intestinal crypt abscess and metaplasia of Paneth cells. Figure adapted from John Hopkins Medicine, Baltimore, USA (Link: https://www.hopkinsmedicine.org/gastroenterology_hepatology/_pdfs/small_large_intestine/ulcerative_colitis.pdf). Information based on Deroche, Xiao, Liu [135] and Magro et al. [136]. Image created by Paula Januzzi Guedes, according to orientation of Roberto de Paula do Nascimento.

patients may present proctitis (rectal involvement only), left-sided colitis (affects the rectum and sigmoid/descending colon), or extensive colitis (or pancolitis) (affects the entire colon) [134].

In general, the main endoscopic findings in patients in the active phase of UC are as follow: 1. diffuse and continuous inflammation, generally not sparing areas; 2. presence of ulcers and erosions; 3. occurrence of pseudopolyps due to the detachment of the mucosa and submucosa; 4. mucosal atrophy; 5. erythema, edema and loss of vascular pattern; and 6. tissue friability. On the other hand, the most important microscopic alterations are 1. irregularities in the architecture of intestinal crypts: shortening (presence of spaces between the bottom of the crypts and the upper layer of smooth muscle), abscesses (presence of neutrophils and formation of purulent exudate) and ramifications; 2. inflammation predominant in mucosa and submucosa, reaching, in more severe cases, deeper muscular layers; 3. abundant lymphoid aggregates in mucosa and submucosa: lymphocytes, neutrophils and eosinophils; 4. depletion of mucins and goblet cells in the epithelium; and 5. metaplasia of Paneth cell [135,136] (Fig. 2).

The typical histological alterations of UC cause significant symptoms in patients and may provoke a decrease in the quality of life of these individuals. The disease can alter the participation of patients in community activities, in the maintenance of friendships and the accomplishment of domestic services, as well as lead to incapacity at work. Studies reveal that a high disability at work is found in young individuals at the beginning of their professional life, and approximately up to 18% of UC patients receive disability pension due to the effects of the disease severity, drug therapy and/or history of surgery [8].

The main symptoms of UC in the active phase include: fecal urgency, several episodes on the same day of fluid pasty diarrhea, with or without rectal bleeding/mucus, and abdominal pains and cramps usually close to defecation. In addition, malaise, loss of appetite, pallor, muscle weakness, vomiting, loss of body weight, and fever are common [137,138]. These symptoms are often accompanied by anemia, iron deficiency, leukocytosis, thrombocytosis, and in severe cases, hypoalbuminemia, increased CRP, and high erythrocyte sedimentation rate [138]. Fecal calprotectin, a protein related to high concentrations of neutrophils, is also increased in feces of patients with IBD, and this characteristic differentiates common infections from IBD. Patients with high calprotectin values have a high chance of developing IBD, and higher values of this protein may indicate the presence of the disease in its active phase [4,139].

Patients with UC that do not undergo or respond to treatment can develop some complications. One of them is toxic megacolon, a condition characterized by colonic distension of at least 6 cm, accompanied by fever and leukocytosis and with a high risk of intestinal perforation and death [103]. The occurrence of intestinal obstructions, dysplasia and CRC are also possible complications. Patients who have UC for at least 20 years can increase the risk of CRC by up to 33%, so it is recommended that they are monitored frequently by colonoscopy [140].

4. Experimental investigation

4.1. Animal models

There are many IBD experimental models used to investigate the pathogenesis and to discover or understand mechanisms or pathways in

Table 2
Characteristics of trinitrobenzenesulfonic acid, oxazolone and dextran sodium sulfate-induced colitis models.

Chemical	Usage	Common strain	Model	Resemblance	Advantages	Weaknesses	References
TNBS	Dilution in ethanol (average: 40–50%); intrar. adm. (4–8 cm from anal verge) of up to 1 mL solution.	Wistar, Sprague-Dawley, SJL/J, C3HeJ	Acute: single adm. of 50–150 mg/kg.	Early stages of CD	1. Fast and low-cost. 2. None or low mortality.	1. Induction of Th1 and Th17 immune responses and not Th2. 2. It may not be an appropriate model of UC due to transmural damage and granuloma formation.	[10,143,144,147,157–159,180]
		BALB/c	Chronic: weekly adm. (2–7 weeks) of 50–185 mg/kg.	Advanced stages of CD or UC.	Investigation of an additional Th2 immune response and related cytokines.	1. No clear definition in the literature of this model, more studies needed. 2. It leans more towards a model of CD than UC, even in BALB/c, due to pathologic characteristics.	[10,143,144,147,157–159]
OXA	Cutaneous sensitization of 3% OXA (100–200 μL) dissolved in ethanol (100%) or a solution of acetone/olive oil (4:1) followed by an intrar. adm. of OXA five to eight days later.	C57BL/10 SJL/J BALB/c	Acute: a single adm. of 100–150 ul of OXA dissolved in 40–50% ethanol.	Advanced stages of UC.	Investigation of Th2 immune responses without the need of a chronic model that is time consuming.	High mortality rate.	[10,148,162,166,169,182]
			Chronic: three adm. of OXA every 14 days.	Chronic IBD.	Study of specific features of inflammation.	1. Lack of studies in the literature on this model. 2. Increased period of experiment.	[148]
DSS	Dilution in filtered water. Bottles of DSS should be changed for new ones every 3 days (at least).	C57BL/6, BALB/c, C3H/HeJ	Acute: 4–7 d. of DSS 2–5% plus up to 10 d. without DSS.	Early stages of UC.	Investigation of mechanisms of epithelial integrity, mucus composition and innate immune response.	Induction of Th1 and Th17 immune responses and not Th2.	[9,10,141,175–177]
			Chronic: 2–3 cycles of 5–7 d. of DSS 1–5% plus 5–10 d. without DSS.	Advanced stages of UC.	Investigation of responses from Th2 cells and related cytokines (IL-13/IL-5/IL-4).	1. High risk of mortality. 2. Increased period of experiment.	[9,10,141,176,177,183]
			Remission: 4–7 d. of DSS 2–5% plus 20–30 d. without DSS	UC patients in the remission phase.	Application of a model that may closely resemble the majority of UC patients who are in the remission phase.	1. No clear definition in the literature of this model, more studies needed. 2. Colitis may not be in full effect due to long recovery.	[184,185]
		BALB/c ICR	CRC: intrap. injection of a carcinogenic before DSS in drinking water.	UC patients with CRC or IBD that led to CRC.	1. Investigation of the role of inflammation in the development of CRC. 2. Opportunity of long exposure to foods or bioactive compounds in a prevention study.	1. High risk of mortality. 2. Long period of experiment 3. Stress for animals and researcher.	[186–188]

Abbreviations: adm.: administration; d.: days; intrap.: intraperitoneal; intrar.: intrarectal; CD: Crohn's disease; CRC: colorectal cancer; DSS: dextran sodium sulfate; IBD: inflammatory bowel disease; OXA: oxazolone; TNBS: trinitrobenzene sulfonic acid; UC: ulcerative colitis.

which drugs or foods act in the prevention and/or treatment of these diseases. The main inducible models of colitis include: 1. induction by chemicals or isolated compounds: TNBS, OXA, DSS, acetic acid, carrageenan, peptidoglycan A of streptococci and indomethacin; 2. genetically modified animals: *knockout* for IL-10 and MUC2, for example; and 3. CD4+ T cell transfer model in immunosuppressed animals [10,141,142]. Currently, TNBS, OXA and DSS in rodents are the most commonly used models of IBD-like colitis (Table 2), to be discussed next.

4.1.1. Trinitrobenzenesulfonic acid

First described in 1989 [143], intrarectal administration of TNBS dissolved in ethanol (Table 2) and given to rats, mice, guinea pigs or rabbits is capable of inducing IBD-like colitis. In this model, it is typical to find diffuse colonic inflammation characterized by increased leukocyte infiltrate, extensive ulceration and hyperemia [10]. Additionally, TNBS classically promotes the formation of macroscopic dark-brown necrotic lesions in parts of or in the whole colon of both rats and mice [144,145]. In the chronic model, which means at least two weekly administrations of TNBS, fibrosis may appear as a result of inflammation resolution [146]. Some of the clinical signs usually observed in animals include: bloody diarrhea, significant body weight loss (10% or more loss of initial body weight), fur piloerection and reduced movements [147]. In cases of strain resistant to the model or if researchers wish to obtain substantial colitis in mice without high mortality, some studies recommend [148] or perform [149] on mice a subcutaneous sensitization with TNBS days before the rectal administration. However, according to a systematic review by Silva, Pinto, Mateus [150], there is scant proof of its benefit and few authors to date have performed this step.

As for the mechanism of TNBS-induced colitis, the vehicle used in association with the acid is essential to the success of the model. Ethanol promotes the breakdown of the epithelial barrier, facilitating the infiltration and action of TNBS, which is responsible for haptenizing colonic proteins and allowing their recognition by the local immune system. Then, most commonly, Th1 cells are differentiated, releasing IFN-γ, which promotes activation and production of pro-inflammatory cytokines by macrophages, like TNF-α, IL-6 and IL-1β [151]. Additionally, production of high amounts of IL-17 in mice with chronic TNBS colitis [152] or an IL-23-driven Th17 response in rats in the acute model may also develop [153]. The cellular mechanism of action of TNBS is still uncertain, but according to a study by Cheon et al. [154], there is downregulation of calcium channels in association with upregulation of potassium ATP channels in the intestinal smooth muscle cells, which confers reduced colonic contractility and therefore may lead to instability in the region.

Recent studies consider also that the TNBS protocol mimics UC [155,156], probably due to its almost exclusive effect on the colon and because of ulcer formation. However, the immunophysiological behavior of TNBS-induced colitis appears to closely resemble CD due to the following observations: 1. the inflammation is predominantly characterized by Th1 type immune response with production of IL-12 cytokine; 2. some of the main features include transmural inflammation and formation of granulomas; and 3. the involvement of NOD2 gene, which is typically related to CD's genetic background [157]. Antoniou et al. [157] proposed that TNBS-induced colitis may also serve as a UC model when applied to BALB/c mice, since this strain is more susceptible to a Th2 immune response. In fact, BALB/c mice develop a mix of Th1 and Th2 responses when subjected to TNBS-induced chronic colitis, and additionally may develop fibrosis, which is a feature of end-stage of both UC and CD [158]. Considering this, its seems more appropriate to believe that the TNBS model, even in BALB/c mice, still has more characteristics of human CD, unless there is a blockage of Th1 immune response via IFN-γ or IL-12 cytokines [159]. Another option, which has less chance of error, is to simply consider TNBS-induced colitis a model of IBD.

4.1.2. Oxazolone

OXA, another haptenizing agent, was first used as a colitogenic in 1998 by Boirivant et al. [160]. Like TNBS, OXA is capable of inducing adaptive immune responses, but in a different way, since its main features are the production of Th2 cytokines, like IL-4 and IL-5 [160], and the abundance of NKT cells releasing IL-13 [161]. When administered to BALB/c mice, there is an even stronger direction towards a Th2 response [162], as previous knowledge has demonstrated. Therefore, by acting less like an IFN-γ and IL-12-driven Th1 response, this chemical would resemble more closely UC rather than CD (Table 2) [148]. Another difference from the TNBS model is that the effects of OXA are usually limited to distal colon [163]. However, colonic ulcerative necrosis is still present as an important macroscopic feature of haptenizing colitis agents [164]. In this regard, it seems appropriate to question the resemblance of TNBS and OXA-induced colitis models, since necrotic lesions may not represent the main histopathological characteristics of human IBD.

Microscopically, in a similar fashion to other chemical models of UC, like DSS, OXA causes mucosa bleeding, crypt abscesses, goblet cells depletion, bowel wall thickening and inflammation usually limited down to submucosa [165]. Clinically, depending on the protocol and strain utilized, the chemical may induce hunching, lethargy and a high Disease Activity Index (DAI) due to severe weight loss and soft stools [166]. Rectal bleeding may not be a common feature of this model, as occurs in DSS-induced colitis [148,167], since there is a lack of report from studies. Mortality due to OXA colitis may account for an average of 35–40% of animals, mice or rats, depending on the dose utilized [160,162,164,168]. In a recent study, Meroni et al. [169] also considered OXA, which was administered according to standard protocols, a model of sepsis, since results revealed a complete loss of mucosa, high mortality (65%), low body temperature and systemic high-grade inflammation reaching serum and spleen.

4.1.3. Dextran sodium sulfate

The DSS reagent remains the most common chemical inducer of UC in animals, and the inflammation caused by this compound is considered the most similar to the human disease [9,170].

DSS was first described in 1951 by Walton [171], who noted that this reagent had anticoagulant properties when at a higher molecular weight. However, it was only in 1985 that the first experimental study was published with the observation of its effects on the gastrointestinal tract [172]. The author assumed that sulfated polysaccharides, such as carrageenan, would be capable of promoting UC-like intestinal lesions, assuming that DSS could probably also be configured as a product for disease induction. DSS (molecular weight of 54 kDa and 19% of sulfur) at concentrations of 5 and 10% was added to the drinking water of Syrian hamsters, and the following effects of DSS consumption were observed for at least five days: bloody diarrhea and melena, infiltration of inflammatory cells in the colonic tissue, ulcers and erosions, crypt abscesses, mucosal congestion and alterations in the population of bacteria in the lumen [172]. From this research, a series of studies started using DSS for UC induction. It is now known that this reagent is the most widely chemical used in the world for induction of UC in rodents because of its wide availability, practicality, cost-effectiveness and the ability to reproduce some of the clinical, histological and immunophysiological aspects of UC [10].

The most likely mechanism of action for DSS concerns its ability to promote the rupture of the epithelial barrier. When carrying a highly negative charge, due to the presence of sulfated groups, DSS becomes toxic to the epithelium, inducing erosions that compromise epithelial barrier integrity and increase intestinal permeability [9]. Similarly, by penetrating the mucosa and altering its integrity, it would also act to facilitate the infiltration of bacteria and antigens into the lumen [142]. Although it is not fully understood, Laroui et al. [173] suggest that DSS enters the intestinal mucosa through its association with medium-chain fatty acids, leading to the fusion of this complex with the colonocyte

membrane. The presence of these vesicles in the cytoplasm may provoke changes in cellular signaling pathways and impairment of epithelial barrier function, causing alteration in tight junctions [173]. Moreover, it is known that the deleterious effects of DSS occur more frequently in the colon, which is probably related to the presence of water and electrolyte absorptive properties in a region with abundant microbiota [9].

Classically, consumption of DSS in rodents causes diarrhea, blood in the stool, and loss of body weight within 4 to 6 days. Because of the model's high lethality rate, it is advisable to monitor the DAI [174] to avoid the death of animals during the induction period. Photographs of the mouse's stool and anus may be taken in order to facilitate the monitoring of symptoms evolution and for posterior reliable blind evaluation [175]. During euthanasia, shortening of the colon and increased colon weight are typical macroscopic changes found. Some of the clinical signs and macroscopic modifications of this model are highly related to changes in microbiota, depletion of goblet cells and mucins, presence of ulcerations and erosions in the epithelial mucosa and extensive infiltration of lymphocytes and granulocytes. Other common alterations include: increased spleen weight and length, which may be associated with anemia, and increased volume of mesenteric lymph nodes [9,141,170,176,177].

Different responses can be achieved using the DSS model, depending on the period and frequency to which animals are exposed to the chemical (Table 2). By enabling its application in several sub models (acute, chronic, remission, CRC), DSS is possibly the most versatile reagent capable of inducing gut inflammation. The acute model of UC induced by DSS is currently one of the most widely used in studies. Besides being the most practical model, it is also responsible for providing findings of defects in the integrity of the epithelial barrier and the contribution of the innate immune response to UC. In fact, this model is typically characterized by changes in the expression of claudins and occlusive zonule proteins, depletion and/or structural alteration of mucins, epithelial degeneration, colonocyte necrosis and neutrophil infiltration in the lamina propria and submucosa. Additionally, there may be transepithelial migration of neutrophils to the intestinal mucosa (cryptitis), which eventually results in crypt abscesses [141,170,176,178]. Increased expression and/or production of TNF-α, IL-6, IL-17, and IL-8 has been reported in the colon and/or serum of mice [152]. The acute model can also be a useful tool in the study of dysbiosis in UC. The intake of DSS for a few days may cause changes in the luminal microbiota, especially in the genus *Clostridium* and family *Enterobacteriaceae,* which is in accordance with what was found in some individuals with the disease [179].

4.2. Natural products

The precise etiology of UC is unknown and there is no specific causal treatment for this intestinal condition. That said, the main objectives of UC therapy are, first, to induce the reduction of symptoms during acute inflammation and, second, to control chronic inflammation, thereby preventing the spread and perpetuation of the inflammatory process [189,190]. With these objectives, one of the main strategies to effectively neutralize the exacerbated immune response is to interfere in various stages of the inflammatory cascade, mainly with the use of corticosteroids, aminosalicylates (sulfasalazine or mesalazine), immunosuppressants (azathioprine), and biological therapies (anti-TNF-α antibody infliximab). Unfortunately, these treatments are associated with potentially serious side effects, such as gastrointestinal problems (diarrhea and abdominal pain), anemia, hepatotoxicity, nephrotoxicity and hypersensitivity reactions, thus limiting their chronic use. In addition, when used for a prolonged period, these therapies may represent a high cost for patients. [189,191]. Considering that, the development of new drug treatments that combine efficacy and safety is an important goal in UC therapy.

Researchers in the field have been working hard in search of new therapeutic strategies through the application of natural products. Some examples include medicinal plants, bioactive/nutraceutical compounds of vegetable origin, animal and vegetable oils, micronutrients, prebiotics, probiotics and symbiotics. [189]. Some of the studies with animals show that these strategies may be valid for the prevention and treatment of UC. The ability to inhibit enzymes and modulate the intestinal microbiota, plus the antioxidant properties attributed to these products can justify their capacity to regulate the immune response and consequently reduce the severity of colitis [192]. Below we describe recent studies, not yet been tested in clinical trials, that have demonstrated the effectiveness of these natural products in experimental models of TNBS, OXA, and DSS. From these studies it will also be possible to note the relevance of these experimental models as tools to improve later clinical studies on UC.

Medicinal plants and nutraceuticals extracted from vegetables have been used in Asian medicine for at least 4000 years to treat a wide range of common diseases, including inflammatory diseases [191,193,194]. Their beneficial effects on UC have also been noticed in experimental models [195]. Some examples are described below.

Jia et al. [71] noted that curcumin, a natural phenolic product isolated from the rhizome of *Curcuma longa*, combined in the diet with fish oil (2% curcumin + 4% FO), enhanced the resolution of chronic inflammation, and suppressed NF-κB activation in the colon mucosa of C57BL/6 mice with DSS-induced colitis. Besides that, it was noted that this combination differentially modulated the expression of genes compared to fish oil administered alone, suggesting that dietary fatty acids and curcumin may interact in order to regulate mucosal homeostasis. In addition to this work, a recent study [196] showed that 0.2% w/w nanoparticle curcumin mixed in a normal diet to mice significantly improved experimental colitis via modulation of the gut microbial structure and expansion of regulatory T cells, thus indicating that this form of intervention could be a new natural candidate as a therapeutic option for the treatment of UC in humans.

Another example of nutraceutical is capnoidine, a compound extracted from the medicinal plant *Corydalis dubia* of the Himalayan mountains, which afforded protection against TNBS-induced colitis in C57BL/6 mice [197]. The animals treated with capnoidine (50 μg/mouse) showed a significant improvement in clinical symptoms (body weight, mobility, piloerection and stool consistency), in the profile of inflammatory cytokines, expression of NF-κB and histological inflammation in the colon.

Gallic acid, a phenolic compound widely used by traditional Asian medicine, and also Western medicine, has also shown promising effects against experimental UC [195]. This phenolic is present in several natural products such as leaves, nuts, citrus fruit and grapes. The results obtained by Zhu et al. [198] showed that the administration of pure gallic acid in dosages of 20, 40 and 60 mg/kg significantly increased the expressions of IL-4 and IL-10 while decreasing the expressions of IL-1, IL-6, IL-12, IL-17, IL-23, transforming growth factor beta (TGF-β) and TNF-α in BALB/c mice with TNBS-induced colitis. Furthermore, western blot analysis has shown that this polyphenol can efficiently suppress the NF-κB signaling pathway.

Other phytochemicals such as quercetin [199–201], rutin [202,203] and proanthocyanidin [204,205] have been widely reported in the literature for their ability to alleviate inflammation, injury to tissue and the symptoms associated with UC. In addition to these, a wide range of natural products has been applied as an alternative therapy for UC [189,191,195]. In order to not make this topic too extensive, we have summarized in Table 3 some works recently published in the literature that show promising effects of other nutraceuticals, especially those belonging to the class of polyphenols, in the prevention and treatment of chemically-induced UC in rodents.

Similarly, different plant extracts have been proposed as having beneficial effects on intestinal inflammation. Thus, tea is one of the most popular beverages consumed worldwide, being an interesting source of bioactive compounds that can help promote intestinal health

Table 3
Experimental models of colitis and main results observed after treatment with natural products.

Experimental model	Animal	Induction	Nutraceutical	Prevention or treatment	Main results	References
TNBS	Male BALB/c mice	1 mg of TNBS in 100 μL of 50% ethanol (v/v)	Tauroursodeoxy-cholate	Tauroursodeoxychola-te (20, 40 and 60 mg/kg b.w.) and Sulfasalazine (500 mg/kg b.w.) were administered by gavage for 7 consecutive days.	Treatment significantly improved body weight change and decreased the macroscopic and histopathological scores. The colonic tissue levels of IL-1β, IFN-γ and TNF-α were significantly reduced in the treated groups.	[238]
TNBS	Male Wistar rats	10 mg of TNBS in 0.25 mL of 50% ethanol (v/v)	Grape peel powder	Grape peel powder (12.4 mg phenolics/animal/day) and Mesalamine by gavage (25 mg/animal/day) for 7 consecutive days.	Grape peel powder recovered Glutathione levels and Glutathione-related enzyme activities. Grape peel, insoluble fiber and fiber-bound polyphenols prevented the increase of caspase-3 mRNA.	[239]
TNBS	Male C57BL/6 mice	TNBS (in 5% of volumes) at a dose of 100 mg/kg b.w.	Flavonoids (naringenin, nobiletin and hesperetin)	Flavonoids (40 mg/kg b.w./day) and Balsalazide (1 g/kg b.w./day) were administered orally for 7 and 3 days before and after TNBS treatment.	The results showed that flavonoids alleviated body weight loss and colon shortness, decreased DAI score, and up-regulated claudin-2, occludin and zona occludens-1 expression significantly.	[240]
TNBS	Male BALB/c mice	TNBS in 50% ethanol (v/v)	Gallic acid	Gallic acid (20, 40 and 60 mg/kg b.w.) and Sulphasalazine were administered twice a day for another 7 days by intragastric injection.	The results showed that administration of gallic acid significantly increased the expressions of IL-4, and IL-10, while down-regulating IL-1, IL-6, IL-12, IL-17, IL-23, TGF-β and TNF-α expressions compared with a model control group.	[198]
TNBS	Male BALB/c mice	1 mg of TNBS in 0.1 mL of 50% ethanol (v/v)	Taurocholate	Experimental animals were treated with taurocholate (20, 40 and 60 mg/kg b.w./day) and Sulfasalazine (500 mg/kg b.w./day) for 7 consecutive days. The drugs were given orally once a day and were suspended in saline.	The activity accumulation of myeloperoxidase and the colonic tissue levels of IL-1β, IFN-γ and TNF-α were decreased with administration of taurocholate. Furthermore, the treatment significantly inhibited body weight loss, improved colonic weight and length, and decreased macroscopic and histopathological scores.	[241]
TNBS	Male BALB/c mice	2 mg of TNBS dissolved in 40% ethanol (v/v)	Norisoboldine	Norisoboldine (20 and 40 mg/kg b.w.) and 5-aminosalicylic acid (200 mg/kg b.w.) were orally administered with a volume of 0.2 mL for 7 consecutive days.	Norisoboldine significantly reduced expressions of cleaved IL-1β and cleaved Caspase-1. It ameliorated TNBS-induced colitis in mice by inhibiting NLRP3 inflammasome activation.	[242]
TNBS	Male BALB/c mice	4 mg of TNBS in 0.1 mL of 30% ethanol (v/v)	Chlorogenic acid	20 mg/kg b.w. of Chlorogenic acid were orally (150 μL) and intracolonically (100 μL) administered twice a day.	Chlorogenic acid reduced neutrophil infiltration and inhibition of NF-κB-dependent pathways. Moreover, it reduced the hydrogen peroxide level in the colon tissue, suppressed secretions of IL-6 and decreased myeloperoxidase activity.	[243]
TNBS	Male Sprague Dawley rats	5% (w/v) of TNBS in ethanol	Paeonol (aeonol-loaded self-microemulsion)	Tauroursodeoxychola-te (100 and 200 mg/kg b.w.), Sodium carboxylmethyl cellulose solution (0.5%; 10 mL/kg b.w.) and Sulphasalazine (500 mg/kg b.w.) were intragastrically administered for 7 consecutive days.	Paeonol reduced the levels of IL-17, IL-6 and TGF-β1. This work has provided a new promising topical drug candidate for the clinical treatment of colitis and a favorable formulation strategy for the development of insoluble bioactive components extracted from Chinese herbs.	[244]
TNBS	Male Wistar rats	10 mg of TNBS dissolved in 0.25 mL of 50% ethanol (v/v)	*Aronia melanocarpa* fruit juice (rich in phenolic compounds, mainly proanthocyanin-dins, flavonoids and phenolic acids)	The juice (2.5, 5 and 10 mL/kg b.w.) and Sulfasalazine (400 mg/kg b.w.) were orally administered for 14 days.	The juice improved the macroscopic and microscopic signs of colitis and prevented against the increase of colonic thiobarbituric acid reactive substances. Regarding different indices, the effect of the juice was comparable or even higher than that of sulfasalazine.	[245]
TNBS	Male Wistar rats	10 mg of TNBS dissolved in 0.25 mL of 50% ethanol (v/v)	Aqueous extract of *Passiflora edulis* leaves (source of vitexin, isovitexin and isoorientin)	1100 μg/mL of the extract were ingested for 14 consecutive days.	The consumption of the extract decreased the level of pro-inflammatory cytokines in colon tissue, especially by reducing IL-1β five-fold and TNF-α two-fold compared to the control group.	[246]

(*continued on next page*)

Table 3 (*continued*)

Experimental model	Animal	Induction	Nutraceutical	Prevention or treatment	Main results	References
OXA	Male BALB/c mice and male Wistar rats	Presensitization): 0.2 mL of a 1% or 3% (w/v) solution of OXA in 100% ethanol. Induction: 0.15 mL of OXA solution in 50% ethanol.	Nerol	Nerol (10–300 mg/kg b.w.) and sulfasalazine (100 mg/kg b.w.) were given orally once a day for 8 consecutive days (24 h after colitis induction and once during the subsequent 7 days).	Nerol showed antinociceptive effects and reduced the levels of the inflammatory cytokines IL-13 and TNF-α. It also decreased pathological alterations and prevented against gastric damage.	[247]
OXA	BALB/c mice	Presensitization: 0.2 mL OXA solution (3% mass ratio and 99% ethanol as solvent). Induction: 0.15 mL 1% OXA solution (50% mass ratio and ethanol as the solvent).	Kudingcha polyphenols extract	The extract (250 and 500 mg/kg b.w.) and sulfasalazine (500 mg/kg b.w.) were given 2 mL once a day for 26 days.	The extract significantly increased the activity of glutathione and the level of IL-2. It reduced the activities of myeloperoxidase, nitric oxide, malondialdehyde and the level of IL-10 in mice with colitis. The results of qPCR assay show that the extract can significantly improve the expression of antioxidant enzymes and decrease the expression of IL-8 and chemokine CXCR2.	[248]
OXA and DSS	BALB/c mice and C57BL6 mice	150 μL of OXA solution with concentration of 7.5 mg/mL in 40% ethanol. 2.5% DSS for 4 consecutive days.	Apple procyanidins	Procyanidins (0.1%, 0.3% or 1%) were administered via drinking water for 14 days.	Procyanidins increased the proportions of TCRγδ and TCRαβ-CD8αα T cells and suppressed IFN-γ synthesis in stimulated intraepithelial lymphocytes. In addition, it also inhibited phorbol 12-myristate 13-acetate-induced secretion of IL-8 in intestinal epithelial cells.	[249]
DSS	Male BALB/C mice	3% DSS dissolved in drinking water for 7 consecutive days.	Palmatine	Palmatine (10, 40 and 100 mg/kg b.w.) and Sulphasalazine (200 mg/kg b.w.) were administered once a day.	The levels of myeloperoxidase, IL-1β, TNF-α and the number of F4/80 + cells in colon of DSS mice were remarkably decreased by palmatine. Moreover, it significantly prevented body weight loss and colonic shortening and reduced the disease activity index and histopathologic score.	[250]
DSS	Female C57BL/6NCrljOri mice	2% DSS dissolved in drinking water for 5 consecutive days.	Krill oil-incorporated liposomes	Liposomes were given to mice by gavage at a dose corresponding to 300 μmole/kg as a total lipid mixture for 9 days.	Oral administration of Krill oil-incorporated liposomes reduced the production of pro-inflammatory cytokines like TNF-α, IL-6, and the systemic level of endotoxin; and slightly reduced the macroscopic signs of the disease.	[222]
DSS	Male C57BL/6 mice	Water supplemented with 2.5% DSS for two 5-day cycles	Turanose	AIN-93G diet in which 25% and 50% of the sucrose were replaced with turanose. Diet given for 2 weeks.	In colon tissues, reductions were observed in micro RNA (miR)-21 expression, histone acetylation, expression of pro-inflammatory cytokines and phosphorylation of extracellular signal-regulated kinase and signal transducer and activator of transcription 3. Turanose improved disease activity index scores, colon length, histopathological features, and myeloperoxidase activity.	[251]
DSS	Female C57BL/6J mice	DSS was dissolved in drinking water to 2% and administered for 9 days	Daucosterol	Daucosterol was orally administered 3 times every week at 10 mg/kg b.w. in 0.5% carboxymethylcellulose solution. For pre-treatment, daucosterol was administered for 2 weeks prior to DSS treatment.	Daucosterol reduced DSS-induced production of reactive oxygen species, infiltration of macrophages, and expression of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β. Furthermore, it increased natural killer cell activity and inhibited excessive antibody IgA levels in mice with DSS-induced colitis.	[252]
DSS	Male C57BL/6 mice	3% (w/v) DSS dissolved in drinking water for 7 days	Peanut shell extract	Peanut shell extract (200 and 400 mg/kg b.w.) and Sulfasalazine (50 mg/kg b.w.) were administered daily via an intragastric route for 14 days.	The extract alleviated colon shortening, body weight loss, DAI, and colon injury score. These physiological improvements were validated by reduced levels of pro-inflammatory cytokines and infiltrating macrophage accumulation in the inflamed colon.	[253]
DSS	Female BALB/c mice	3% (w/v) DSS in drinking water	Nanoparticle curcumin	Nanoparticle curcumin (0.2% w/w) was administered once a day for 7 consecutive days.	Curcumin nanoparticles suppressed mRNA expression and NF-κB activation in colonic epithelial cells. The treatment increased the	[196]

(*continued on next page*)

Table 3 (*continued*)

Experimental model	Animal	Induction	Nutraceutical	Prevention or treatment	Main results	References
					abundance of butyrate-producing bacteria, the levels of fecal butyrate and the expansion of regulatory T cells in the colonic mucosa.	
DSS	Female C57BL/6 mice	2% DSS in drinking water over 7 days	Aqueous extract of *Inonotus obliquus*	The extract (50 and 100 mg/kg b.w.) was administered twice a day for 7 days before and during DSS administration for a total of 14 days.	The extract markedly attenuated DSS-induced iNOS levels and myeloperoxidase accumulation in colon tissues, demonstrating its suppressive effect on infiltration of immune cells. In addition, the extract significantly inhibited mRNA expression of pro-inflammatory cytokines induced by DSS in colon tissues.	[254]
DSS	Male BALB/c mice	3% (w/v) DSS in drinking water for 7 consecutive days	Compound sophorae decoction (a Chinese medicinal formula composed of six Chinese herbs)	Sophorae decoction (7.28 g/kg b.w.) and mesalazine (0.52 g/kg b.w.) were given orally once a day for one week.	The administration of the compound sophorae decoction reduced the level of inflammatory factors (IL-1β, TNF-α) and also decreased the proportions of Th17 cells in spleen and the expression of IL-17A, signal transducer and activator of transcription 3 and IL-6 in colonic tissues	[255]
DSS	Male C57BL/6 mice	3% (w/v) DSS in drinking water for 5 consecutive days	Rape bee pollen extract	Rape bee pollen extract (21.2 g/kg b.w. and 10.6 g/kg b.w.) was administered for 14 consecutive days.	The extract ameliorated colon shortening, spleen enlargement and colon weight. It inhibited the activities of related inflammatory cytokines. Additionally, the extract altered the gut microbial structure of mice.	[256]
DSS	Female BALB/c mice	5% DSS for 7 consecutive days	Alginate/chitosan microcapsules containing IL-1Ra (Alg/Chi/IL-1Ra microcapsule)	Alg/Chi/IL-1Ra microcapsules (1 mg/kg b.w.), Alg/Chi/BSA microcapsules (1 mg/kg b.w.), and unencapsulated IL-1Ra (1 mg/kg b.w.) were intragastrically administered once a day for 8 days.	DAI evaluation, colon length, colon tissue morphology, histologic damage scores and relative protein concentrations (Myeloperoxidase, TNF-α and IL-1β) demonstrated that the microcapsules alleviated DSS-induced colitis in mice.	[257]
DSS	Male C57BL6 mice	2.5% DSS for 10 consecutive days	Dried apple peel powder	Powder (200 or 400 mg/kg b.w.) was administered by gavage for 10 days pre- and 1 day post-colitis induction.	Apple powder reduced infiltration of inflammatory cells and concomitantly displayed a potential for counteracting inflammation and oxidative stress. Moreover, it partially restored mitochondrial abnormalities related to size, density, redox homeostasis, ATP synthesis, apoptosis and regulatory mitochondrial transcription factors.	[258]

Abbreviations: b.w.: body weight; v/v: volume/volume; w/v: weight/volume; DAI: Disease Activity Index; DSS: dextran sodium sulfate; IFN-γ: interferon y; IL: interleukin; iNOS: inducible nitric oxide synthase; NF-κB: nuclear factor kappa B; OXA: oxazolone; TNBS: trinitrobenzene sulfonic acid; TNF-α: Tumor necrosis factor alpha.

[206,207]. Many studies conducted over the past three decades have shown that green tea has numerous benefits due to its polyphenol content [206]. Although green tea consists of more than 2000 components, regarding UC, interest is focused on (−)-*epi*-gallocatechin-3-gallate (EGCG), (−)-*epi*-gallocatechin and (−)-*epi*-catechin, all with powerful antioxidant properties. Although there is a clinical study [208] in which a product rich in EGCG was tested in patients with mild to moderate UC, it is noteworthy that studies utilizing extracts concentrated in other catechins have not yet been carried out in humans with IBD. Therefore, further animal testing using green tea extracts or compounds is still needed to clarify certain metabolic mechanisms that catechins may influence and to define dosages that are surely non-toxic [209,210]. Studies with rodents using TNBS [211,212] and DSS [213,214] models have shown that the use of polyphenols from green tea alleviated clinical symptoms such as bloody diarrhea, weight and colon loss [211,212], colonic shortening, hemorrhage, ulcers, edema, gastrointestinal permeability, and neutrophil infiltration [213]. The experiments also revealed that the compounds prevented against acute colitis by inhibiting the production of TNF-α and IL-6, as well as reactive oxygen species through a mechanism that involves the inhibition of NF-κB. [211]. In addition, treatment with green tea compounds had a significantly lower impact on the tissue concentration of malondialdehyde, the final product of lipid peroxidation, indicating an improvement in animal health [213,214]. Increased activity of antioxidant enzymes such as superoxide dismutase and glutathione peroxidase was also observed [213].

Grapes, plum, cherry and berries such as blueberry, strawberry, blackberry and raspberry are other rich sources of bioactive compounds, such as phenolic acids, flavonoids and, mainly, anthocyanins, which have shown a positive effect on UC improvement due to their antioxidant and anti-inflammatory properties [206,215]. Blueberry extract rich in anthocyanins (1 or 10%) and dry blueberry (20% in the diet, 11.2% of anthocyanins) reduced the colonic inflammation scores of DSS-induced colitis and the production of IFN-γ and IL-6 from mesenteric lymph node cells. Oral administration of both also resulted in an improvement of acute and chronic colitis. Moreover, both prevented against apoptosis induced by inflammation in epithelial cells [216]. The lyophilized black raspberry diet (5 or 10%) given to C57BL/6J mice with DSS-induced colitis reduced ulceration, acute injury and shortening of the colon, and provided reduced levels of TNF-α and IL-1β in the colonic tissue. The treatment also suppressed COX-2 levels, with a concomitant decrease in prostaglandin E2 in plasma [217]. Finally, the study by Marchi et al. [218] shows that concentrated grape juice reduces the expression of iNOS, TNF-α and COX-2 and decreases DNA damage in Wistar rats with TNBS-induced colitis. All of these studies demonstrate a potent anti-inflammatory effect of red berries during colonic injury in chemically-induced UC models, thus supporting their possible therapeutic or preventive roles against colitis.

Oils of vegetable and animal origin are also dietary components highly investigated in recent times, and studies suggest that they have a wide range of therapeutic applications and may exhibit beneficial effects on IBD [206,219]. Epidemiological observations revealed a low incidence of IBD in Eskimos, whose diet is rich in fish oil, and also in populations living in the Mediterranean region, who use olive oil as a typical ingredient in their diets [191,219,220]. The protective role of these oils is the result of their specific composition, including high proportions of monounsaturated fatty acids (such as oleic acid for seed oils), balanced presence of polyunsaturated fatty acids (such as omega-3 fatty acids for fish oil) and/or other secondary components, such as α-tocopherol and phenolic compounds [191,219,220]. The results obtained from the research carried out by Jia et al. [71] indicated that fish oil combined with curcumin had the ability to modulate colonic cytokinetics and gene expression in DSS-treated rodents, as previously mentioned. Another interesting association is fish oil plus a standard therapy for UC. From this study, Mbodji et al. [221] observed that omega-3 fatty acids plus 5-aminosalicylic acid significantly reduced the inflammatory response in rats with TNBS-induced colitis by lowering NF-κB activation and inducing peroxisome proliferator-activated receptor-γ expression. Besides that, the results showed that this combination was more effective than a higher dose of 5-aminosalicylic acid alone, thus indicating that the use of omega-3 fatty acids in association with 5-aminosalicylic acid may reduce the dose of the standard therapy. Krill oil, a marine-derived oil rich in omega-3 fatty acids, incorporated in liposomes at a concentration of 300 μmole/kg, has also proven to be an effective nanovehicle to ameliorate the inflammatory responses of DSS-induced UC in C57BL/6NCrljOri mice [222]. Oral administration of krill oil-incorporated liposomes suppressed the production of TNF-α, IL-16 and the systemic levels of endotoxin, and slightly reduced the macroscopic signs of the disease [222]. Finally, the study by Balaha et al. [223] showed that garlic oil administrated in doses of 25, 50 and 100 mg/kg/day attenuated tissue injury in the DSS-induced acute colitis model, by relieving oxidative stress, suppressing pro-inflammatory cytokines levels and the activity of myeloperoxidase. Furthermore, it improved the macroscopic and microscopic changes in the colonic mucosa in a dose-dependent manner. From these findings, it is notable that some oils of vegetable and animal origin, rich in unsaturated fatty acids, are very promising natural products to be used in UC therapy.

Some micronutrients found in foods, such as ascorbic acid, vitamin D, vitamin E, α-tocopherol, biotin, selenium and zinc have been proven to act as exogenous antioxidant defenses for IBD [191,195]. For this reason, supplements or foods rich in these nutrients have been widely applied in animals and humans in an attempt to prevent or alleviate against the oxidative stress generated by UC acute and chronic inflammation [191,195]. Recently, Sang et al. [224] noted that the treatment with selenium (2 μg/g body weight) restored the levels of IL-10, in addition to reducing IFN-γ and IL-17A. Therapy with biotin (1 mmol/L), a water-soluble vitamin indispensable to human health, improved the expression of inflammatory cytokines and reduced intestinal impermeability and the activation of NF-κB. Besides that, it also improved the DAI, the healing process and fecal levels of calprotectin [225]. These meetings suggest that some micronutrients may have therapeutic potential to prevent and treat colitis in mice and patients with UC.

In recent years, growing interest in the hypothesis that intestinal dysbiosis may result in immune impairment associated with UC and other intestinal diseases has resulted in several studies with probiotics, prebiotics and symbiotics [220]. Probiotic bacteria can be defined as living microorganisms that, when administered in adequate amounts, provide a benefit to the health of the host [191]. Studies related to intestinal inflammation have demonstrated anti-inflammatory effects and an improvement in clinical markers as a result of the use of probiotics, in particular VSL#3, *E. coli* Nissle 1917, and strains of the genera *Bifidobacterium* and/or *Lactobacillus* [226]. Probiotics are said to be capable of modifying the microbiota, replacing harmful microbes with useful ones [219,227–229]. In an animal model, it was recently observed by Lorén et al. [230] that the probiotic formula I3.1 (*Lactobacillus plantarum* - CECT7484, CECT7485) normalized the levels of the cytokine IL-6 and significantly increased the histological score. Besides that, the administration of I3.1 prevented against excessive weight loss and reduced the severity of the disease in the DSS-induced colitis. Probiotics such as *Saccharomyces boulardii* (5×10^9 colony-forming units) also inhibited DSS-induced colitis in rodents, by modifying the colonic expression of different inflammatory markers, the epithelial integrity of proteins and by increasing bacterial diversity, thus ameliorating dysbiosis [227]. Treatment of rats with OXA-induced colitis using *Lactobacillus acidophilus* (1×10^7 colony-forming units/mL/day oral for 14 days) combined with olsalazine (60 mg/kg/day oral for 14 days) offered a more significant reduction in the serum levels of TNF-α, IL-6, and CRP, and in the DAI, when compared to animals treated only with *Lactobacillus acidophilus* or olsalazine [231]. Based on such results, the authors concluded that L. *acidophilus* could be recommended as adjuvant therapy in combination with olsalazine to

achieve a more effective treatment for UC [231]. Although several studies indicate the therapeutic potential of probiotics in UC therapy, a recent study [232] proved that high doses of *Lactococcus lactis* subsp. lactis JCM5805 (15 and 20 mg) had harmful effects by increasing the death rate of mice and worsening the disease trough pro-inflammatory cytokines. More studies testing different probiotic formulas for UC therapy are needed.

Prebiotics are mainly complex carbohydrates (oligosaccharides and polysaccharides) derived from fruit, vegetables, cereals and grains that are not metabolized in the stomach or small intestine, but are fermented in the colon, leading to the growth of useful bacteria and consequent improvement of its metabolic activity [207]. For example, the konjac oligosaccharide exhibited its prebiotic properties in the TNBS-colitis model in rats, promoting the growth of *Lactobacilli* and *Bifidobacteria* and the production of SCFAs. In addition, its administration reduced the levels of malondialdehyde, the production of pro-inflammatory markers in the colon, including TNF-α and IL-6, and the inhibition of iNOS and COX-2 [233]. In mice with acetic acid-induced colitis, the oral administration of oligosaccharides (100, 500 and 1000 mg/kg) from *Gracilaria fisheri*, a red seaweed, was capable of improving gastrointestinal dysmotility and gut dysbiosis by modulating *Enterobacteria* populations and SCFAs concentration [234].

Many studies are proving that the administration of prebiotics together with probiotics has an even more potent effect in IBD than when applied separately. For example, the results found by Ocón et al. [235] showed that the prebiotic compound AHCC (active hexose-correlated compound), when combined with the probiotic *Bifidobacterium longum* BB536, improves the intestinal inflammatory activity of mice with TNBS-induced colitis compared to those treated with AHCC or *Bifidobacterium longum* BB536 separately. This improvement was demonstrated by changes in body weight gain, colonic weight and length ratio, myeloperoxidase activity and iNOS expression. Recently, Ivanovska et al. [236] also observed improvement in colonic damage, a decline in myeloperoxidase enzyme activity and an increase in the *Lactobacillus* count in feces of animals that received a symbiotic formula (*Lactobacillus casei* plus oligofructose-enriched inulin).

Finally, it is important to emphasize that despite the possible positive effects of therapeutic strategies using natural products on intestinal health, more studies are needed to better understand the mechanisms of action responsible for these effects, and mainly to reach dosages that are not toxic to humans and animals [214,215,237]. For example, experimental animal studies and epidemiological research have shown that high doses of certain nutraceuticals, especially phenolic compounds, can cause liver and kidney dysfunction and negatively modulate the digestion of macronutrients [214,237]. These side effects arise from the fact that polyphenols can also act as pro-inflammatory substances. From this, dosage limits of compounds/nutraceutical products should be investigated for the treatment of UC and other intestinal diseases. The accumulated evidence on the toxicity of phytochemicals reminds us of popular expressions such as “nothing in excess is good” and “more than enough is too much” [237].

5. Conclusions

The dilemma regarding the main causative factor of UC, if by dysbiosis or immune dysfunction, is still a major puzzle for researchers. However, information regarding the pathogenesis of UC has progressed substantially over the last 20 years, especially due to new findings regarding microbiota composition, food habits and their associative relation to disease onset. Studies with rodents are one of the main tools responsible for this progress and although experimental models of colitis are not a perfect fit, they make it possible to understand several pathway mechanisms underlying colonic inflammation. Additionally, chemically-induced models of colitis, like TNBS, OXA and DSS, have been established as indispensable tools for research on new preventive or healing natural products. The positive effects of bioactive compounds, such as polyphenols, dietary fibers, essential fatty acids, vitamins and symbiotics in models of colonic inflammation suggest that the obligation of a single common drug-based therapy for UC may not last for many years.

Authors' contribution

RPN, APFM – wrote the manuscript
JG, CBBC, MRMJ – revised the manuscript
All authors read and approved the final version of the manuscript

Declaration of competing interest

None.

Acknowledgments

Special thanks to 1. Paula Januzzi Guedes, a self-employed design professional responsible for creating the original images of this article; and 2. Red Iberomericana de Alimentos Autoctonos Subutilizados (ALSUB-CYTED, 118RT0543). This study was partly funded by 1. *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES)* – Finance Code 001; 2. *Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)* - Process 140812/2019-9, 403328/2016-0 and 301496/2019-6; and 3. *Fundação de Amparo à Pesquisa do Estado de São Paulo* – Process 2017/23657-6, 2015/50333-1, 2018/11069-5 and 2015/13320-9.

References

[1] N.A. Molodecky, I.S. Soon, D.M. Rabi, W.A. Ghali, M. Ferris, G. Chernoff, E.I. Benchimol, R. Panaccione, S. Ghosh, H.W. Barkema, G.G. Kaplan, Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review, Gastroenterology 142 (2012) 46–54.e42, https://doi.org/10.1053/j.gastro.2011.10.001.
[2] C.R. Victoria, L.Y. Sassaki, H.R.D.C. Nunes, Incidence and prevalence rates of inflammatory bowel diseases, in midwestern of São Paulo State, Brazil, Arq. Gastroenterol. (2009), https://doi.org/10.1590/S0004-28032009000100009.
[3] S.C. Ng, H.Y. Shi, N. Hamidi, F.E. Underwood, W. Tang, E.I. Benchimol, R. Panaccione, S. Ghosh, J.C.Y. Wu, F.K.L. Chan, J.J.Y. Sung, G.G. Kaplan, Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies, Lancet 390 (2017) 2769–2778, https://doi.org/10.1016/S0140-6736(17)32448-0.
[4] R. Ungaro, S. Mehandru, P.B. Allen, L. Peyrin-biroulet, J. Colombel, Ulcerative colitis, Lancet 389 (2017), https://doi.org/10.1016/S0140-6736(16)32126-2.
[5] A.D. Kostic, R.J. Xavier, D. Gevers, The microbiome in inflammatory bowel disease: current status and the future ahead, Gastroenterology 146 (2014) 1489–1499, https://doi.org/10.1053/j.gastro.2014.02.009.
[6] M. Zhang, B. Liu, Y. Zhang, H. Wei, Y. Lei, L. Zhao, Structural shifts of mucosa-associated lactobacilli and Clostridium leptum subgroup in patients with ulcerative colitis, J. Clin. Microbiol. 45 (2007) 496–500, https://doi.org/10.1128/JCM.01720-06.
[7] F. Fava, S. Danese, Intestinal microbiota in inflammatory bowel disease: friend of foe? World J. Gastroenterol. (2011), https://doi.org/10.3748/wjg.v17.i5.557.
[8] K. Büsch, A. Sonnenberg, N. Bansback, Impact of inflammatory bowel disease on disability, Curr. Gastroenterol. Rep. 16 (2014), https://doi.org/10.1007/s11894-014-0414-0.
[9] B. Chassaing, J.D. Aitken, M. Malleshappa, M. Vijay-Kumar, Dextran sulfate sodium (DSS)-induced colitis in mice, Curr. Protoc. Immunol. 104 (2014), https://doi.org/10.1002/0471142735.im1525s104 Unit 15.25.
[10] P.K. Randhawa, K. Singh, N. Singh, A.S. Jaggi, A review on chemical-induced inflammatory bowel disease models in rodents, Korean J. Physiol. Pharmacol. (2014), https://doi.org/10.4196/kjpp.2014.18.4.279.
[11] S. Chul Park, Y. Tae Jeen, Current and emerging biologics for ulcerative colitis, Gut Liver 9 (2015) 18–27, https://doi.org/10.5009/gnl14226.
[12] L.P. McLean, R.K. Cross, Adverse events in IBD: to stop or continue immune suppressant and biologic treatment, Expert Rev. Gastroenterol. Hepatol. (2014), https://doi.org/10.1586/17474124.2014.881715.
[13] Z.H. Shen, C.X. Zhu, Y.S. Quan, Z.Y. Yang, S. Wu, W.W. Luo, B. Tan, X.Y. Wang, Relationship between intestinal microbiota and ulcerative colitis: mechanisms and clinical application of probiotics and fecal microbiota transplantation, World J. Gastroenterol. (2018), https://doi.org/10.3748/wjg.v24.i1.5.
[14] J.J. Kim, M.S. Shajib, M.M. Manocha, W.I. Khan, Investigating intestinal inflammation in DSS-induced model of IBD, J. Vis. Exp. (2012) 1–6, https://doi.org/10.3791/3678.
[15] M.L. Lauro, J.M. Burch, C.L. Grimes, The effect of NOD2 on the microbiota in

Crohn's disease, Curr. Opin. Biotechnol. (2016), https://doi.org/10.1016/j.copbio.2016.02.028.
[16] L.J. Cohen, J.H. Cho, D. Gevers, H. Chu, Genetic factors and the intestinal microbiome guide development of microbe-based therapies for inflammatory bowel diseases, Gastroenterology (2019), https://doi.org/10.1053/j.gastro.2019.03.017.
[17] W. Fries, S. Comunale, Ulcerative Colitis: Pathogenesis, (2011), pp. 1373–1382.
[18] M.-E. Forgue-Lafitte, B. Fabiani, P.P. Levy, N. Maurin, J.-F. Fléjou, J. Bara, Abnormal expression of M1/MUC5AC mucin in distal colon of patients with diverticulitis, ulcerative colitis and cancer, Int. J. Cancer 121 (2007) 1543–1549, https://doi.org/10.1002/ijc.22865.
[19] J.M.H. Larsson, H. Karlsson, J.G. Crespo, M.E.V. Johansson, L. Eklund, H. Sjövall, G.C. Hansson, Altered O-glycosylation profile of MUC2 mucin occurs in active ulcerative colitis and is associated with increased inflammation, Inflamm. Bowel Dis. (2011), https://doi.org/10.1002/ibd.21625.
[20] B.J.W. Van Klinken, J.W.G. Van Der Wal, A. Einerhand, H.A. Büller, J. Dekker, Sulphation and secretion of the predominant secretory human colonic mucin MUC2 in ulcerative colitis, Gut (1999), https://doi.org/10.1136/gut.44.3.387.
[21] C.W. Png, S.K. Lindén, K.S. Gilshenan, E.G. Zoetendal, C.S. McSweeney, L.I. Sly, M.A. McGuckin, T.H.J. Florin, Mucolytic bacteria with increased prevalence in IBD mucosa augment in vitro utilization of mucin by other bacteria, Am. J. Gastroenterol. (2010), https://doi.org/10.1038/ajg.2010.281.
[22] M.E.V. Johansson, J.K. Gustafsson, J. Holmen-Larsson, K.S. Jabbar, L. Xia, H. Xu, F.K. Ghishan, F.A. Carvalho, A.T. Gewirtz, H. Sjovall, G.C. Hansson, Bacteria penetrate the normally impenetrable inner colon mucus layer in both murine colitis models and patients with ulcerative colitis, Gut (2014), https://doi.org/10.1136/gutjnl-2012-303207.
[23] R.S. Blumberg, Environment and genes: what is the interaction? Dig. Dis. 34 (2016) 20–26, https://doi.org/10.1159/000442920.
[24] M.D. Kappelman, Environmental factors and inflammatory bowel disease: elusive or nonexistent? Inflamm. Bowel Dis. 19 (2013) 548–549, https://doi.org/10.1097/MIB.0b013e318281ce99.
[25] A.T. Chan, Inflammatory bowel disease findings from the nurses' health study I and II, Gastroenterol. Hepatol. 11 (2015) 767–769.
[26] A.N. Ananthakrishnan, H. Khalili, G.G. Konijeti, L.M. Higuchi, P. De Silva, J.R. Korzenik, C.S. Fuchs, W.C. Willett, J.M. Richter, A.T. Chan, A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis, Gastroenterology (2013), https://doi.org/10.1053/j.gastro.2013.07.050.
[27] R. Reddavide, O. Rotolo, M.G. Caruso, E. Stasi, M. Notarnicola, C. Miraglia, A. Nouvenne, T. Meschi, G.L. De' Angelis, F. Di Mario, G. Leandro, The role of diet in the prevention and treatment of inflammatory bowel diseases, Acta Biomed 89 (2018) 60–75, https://doi.org/10.23750/abm.v89i9-S.7952.
[28] A. Zhernakova, A. Kurilshikov, M.J. Bonder, E.F. Tigchelaar, M. Schirmer, T. Vatanen, Z. Mujagic, A.V. Vila, G. Falony, S. Vieira-Silva, J. Wang, F. Imhann, E. Brandsma, S.A. Jankipersadsing, M. Joossens, M.C. Cenit, P. Deelen, M.A. Swertz, R.K. Weersma, E.J.M. Feskens, M.G. Netea, D. Gevers, D. Jonkers, L. Franke, Y.S. Aulchenko, C. Huttenhower, J. Raes, M.H. Hofker, R.J. Xavier, C. Wijmenga, J. Fu, Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity, Science (80-.) (2016), https://doi.org/10.1126/science.aad3369.
[29] M. Martinez-Medina, J. Denizot, N. Dreux, F. Robin, E. Billard, R. Bonnet, A. Darfeuille-Michaud, N. Barnich, Western diet induces dysbiosis with increased e coli in CEABAC10 mice, alters host barrier function favouring AIEC colonisation, Gut (2014), https://doi.org/10.1136/gutjnl-2012-304119.
[30] R. Pittayanon, J.T. Lau, G.I. Leontiadis, F. Tse, Y. Yuan, M. Surette, P. Moayyedi, Differences in gut microbiota in patients with vs without inflammatory bowel diseases: a systematic review, Gastroenterology (2019), https://doi.org/10.1053/J.GASTRO.2019.11.294.
[31] R.K. Singh, H.W. Chang, D. Yan, K.M. Lee, D. Ucmak, K. Wong, M. Abrouk, B. Farahnik, M. Nakamura, T.H. Zhu, T. Bhutani, W. Liao, Influence of diet on the gut microbiome and implications for human health, J. Transl. Med. (2017), https://doi.org/10.1186/s12967-017-1175-y.
[32] H. Tamaki, H. Nakase, S. Inoue, C. Kawanami, T. Itani, M. Ohana, T. Kusaka, S. Uose, H. Hisatsune, M. Tojo, T. Noda, S. Arasawa, M. Izuta, A. Kubo, C. Ogawa, T. Matsunaka, M. Shibatouge, Efficacy of probiotic treatment with Bifidobacterium longum 536 for induction of remission in active ulcerative colitis: a randomized, double-blinded, placebo-controlled multicenter trial, Dig. Endosc. (2016), https://doi.org/10.1111/den.12553.
[33] M. Pilarczyk Zurek, M. Zwolinska Wcisło, T. Mach, K. Okon, P. Adamski, P.B. Heczko, A.M. Cichonska, G. Stefanski, M. Strus, Influence of Lactobacillus and Bifidobacterium combination on the gut microbiota, clinical course, and local gut inflammation in patients with ulcerative colitis: a preliminary, single-center, open-label study, J. Probiotics Heal. (2017), https://doi.org/10.4172/2329-8901.1000163.
[34] H. Ishikawa, I. Akedo, T. Otani, Y. Umesaki, R. Tanaka, A. Imaoka, Randomized controlled trial of the effect of bifidobacteria-fermented milk on ulcerative colitis, J. Am. Coll. Nutr. (2003), https://doi.org/10.1080/07315724.2003.10719276.
[35] C. De Filippo, D. Cavalieri, M. Di Paola, M. Ramazzotti, J.B. Poullet, S. Massart, S. Collini, G. Pieraccini, P. Lionetti, Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa, Proc. Natl. Acad. Sci. U. S. A. (2010), https://doi.org/10.1073/pnas.1005963107.
[36] P. Jantchou, S. Morois, F. Clavel-Chapelon, M.C. Boutron-Ruault, F. Carbonnel, Animal protein intake and risk of inflammatory bowel disease: the E3N prospective study, Am. J. Gastroenterol. (2010), https://doi.org/10.1038/ajg.2010.192.
[37] K. Kostovcikova, S. Coufal, N. Galanova, A. Fajstova, T. Hudcovic, M. Kostovcik, P. Prochazkova, Z.J. Zakostelska, M. Cermakova, B. Sediva, M. Kuzma, H. Tlaskalova-Hogenova, M. Kverka, Diet rich in animal protein promotes pro-inflammatory macrophage response and exacerbates colitis in mice, Front. Immunol. (2019), https://doi.org/10.3389/fimmu.2019.00919.
[38] H.-Q. Ma, T.-T. Yu, X.-J. Zhao, Y. Zhang, H.-J. Zhang, Fecal microbial dysbiosis in Chinese patients with inflammatory bowel disease, World J. Gastroenterol. 24 (2018) 1464–1477, https://doi.org/10.3748/wjg.v24.i13.1464.
[39] Y.-L. Zhang, L.-T. Cai, J.-Y. Qi, Y.-Z. Lin, Y.-C. Dai, N. Jiao, Y.-L. Chen, L. Zheng, B.-B. Wang, L.-X. Zhu, Z.-P. Tang, R.-X. Zhu, Gut microbiota contributes to the distinction between two traditional Chinese medicine syndromes of ulcerative colitis, World J. Gastroenterol. 25 (2019) 3242–3255, https://doi.org/10.3748/wjg.v25.i25.3242.
[40] M.E. Spehlmann, A.Z. Begun, E. Saroglou, F. Hinrichs, U. Tiemann, A. Raedler, S. Schreiber, Risk factors in German twins with inflammatory bowel disease: results of a questionnaire-based survey, J. Crohn's Colitis (2012), https://doi.org/10.1016/j.crohns.2011.06.007.
[41] S.L. Jowett, C.J. Seal, M.S. Pearce, E. Phillips, W. Gregory, J.R. Barton, M.R. Welfare, Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study, Gut (2004), https://doi.org/10.1136/gut.2003.024828.
[42] H.C.J. Godfray, P. Aveyard, T. Garnett, J.W. Hall, T.J. Key, J. Lorimer, R.T. Pierrehumbert, P. Scarborough, M. Springmann, S.A. Jebb, Meat consumption, health, and the environment, Science (2018), https://doi.org/10.1126/science.aam5324.
[43] G. Cui, A. Yuan, A systematic review of epidemiology and risk factors associated with Chinese inflammatory bowel disease, Front. Med. (2018), https://doi.org/10.3389/fmed.2018.00183.
[44] E.A. Magee, C.J. Richardson, R. Hughes, J.H. Cummings, Contribution of dietary protein to sulfide production in the large intestine: an in vitro and a controlled feeding study in humans, Am. J. Clin. Nutr. (2000), https://doi.org/10.1093/ajcn/72.6.1488.
[45] D.C.M. Rapozo, C. Bernardazzi, H.S.P. De Souza, Diet and microbiota in inflammatory bowel disease: the gut in disharmony, World J. Gastroenterol. (2017), https://doi.org/10.3748/wjg.v23.i12.2124.
[46] K. Machiels, M. Joossens, J. Sabino, V. De Preter, I. Arijs, V. Eeckhaut, V. Ballet, K. Claes, F. Van Immerseel, K. Verbeke, M. Ferrante, J. Verhaegen, P. Rutgeerts, S. Vermeire, A decrease of the butyrate-producing species roseburia hominis and faecalibacterium prausnitzii defines dysbiosis in patients with ulcerative colitis, Gut (2014), https://doi.org/10.1136/gutjnl-2013-304833.
[47] F. Wang, J. Feng, Q. Gao, M. Ma, X. Lin, J. Liu, J. Li, Q. Zhao, Carbohydrate and protein intake and risk of ulcerative colitis: systematic review and dose-response meta-analysis of epidemiological studies, Clin. Nutr. (2017), https://doi.org/10.1016/j.clnu.2016.10.009.
[48] C. Kong, R. Gao, X. Yan, L. Huang, H. Qin, Probiotics improve gut microbiota dysbiosis in obese mice fed a high-fat or high-sucrose diet, Nutrition (2019), https://doi.org/10.1016/j.nut.2018.10.002.
[49] T. Sen, C.R. Cawthon, B.T. Ihde, A. Hajnal, P.M. DiLorenzo, C.B. de La Serre, K. Czaja, Diet-driven microbiota dysbiosis is associated with vagal remodeling and obesity, Physiol. Behav. (2017), https://doi.org/10.1016/j.physbeh.2017.02.027.
[50] M. Laffin, R. Fedorak, A. Zalasky, H. Park, A. Gill, A. Agrawal, A. Keshteli, N. Hotte, K.L. Madsen, A high-sugar diet rapidly enhances susceptibility to colitis via depletion of luminal short-chain fatty acids in mice, Sci. Rep. (2019), https://doi.org/10.1038/s41598-019-48749-2.
[51] M.H. Do, E. Lee, M.-J. Oh, Y. Kim, H.-Y. Park, High-glucose or -fructose diet cause changes of the gut microbiota and metabolic disorders in mice without body weight change, Nutrients 10 (2018), https://doi.org/10.3390/nu10060761.
[52] E.O. Méndez-Salazar, M.G. Ortiz-López, M.D.L.Á. Granados-Silvestre, B. Palacios-González, M. Menjivar, Altered gut microbiota and compositional changes in firmicutes and proteobacteria in Mexican undernourished and obese children, Front. Microbiol. (2018), https://doi.org/10.3389/fmicb.2018.02494.
[53] S. Michail, M. Durbin, D. Turner, A.M. Griffiths, D.R. Mack, J. Hyams, N. Leleiko, H. Kenche, A. Stolfi, E. Wine, Alterations in the gut microbiome of children with severe ulcerative colitis, Inflamm. Bowel Dis. (2012), https://doi.org/10.1002/ibd.22860.
[54] R. Rogier, T.H.A. Ederveen, H. Wopereis, A. Hartog, J. Boekhorst, S.A.F.T. Van Hijum, J. Knol, J. Garssen, B. Walgreen, M.M. Helsen, P.M. Van Der Kraan, P.L.E.M. Van Lent, F.A.J. Van De Loo, S. Abdollahi-Roodsaz, M.I. Koenders, Supplementation of diet with non-digestible oligosaccharides alters the intestinal microbiota, but not arthritis development, in IL-1 receptor antagonist deficient mice, PLoS One (2019), https://doi.org/10.1371/journal.pone.0219366.
[55] A. Marcobal, M. Barboza, J.W. Froehlich, D.E. Block, J.B. German, C.B. Lebrilla, D.A. Mills, Consumption of human milk oligosaccharides by gut-related microbes, J. Agric. Food Chem. (2010), https://doi.org/10.1021/jf9044205.
[56] Z. Liu, X. Lin, G. Huang, W. Zhang, P. Rao, L. Ni, Prebiotic effects of almonds and almond skins on intestinal microbiota in healthy adult humans, Anaerobe (2014), https://doi.org/10.1016/j.anaerobe.2013.11.007.
[57] A. Jefferson, K. Adolphus, The effects of intact cereal grain fibers, including wheat bran on the gut microbiota composition of healthy adults: a systematic review, Front. Nutr. (2019), https://doi.org/10.3389/fnut.2019.00033.
[58] A. Costabile, A. Klinder, F. Fava, A. Napolitano, V. Fogliano, C. Leonard, G.R. Gibson, K.M. Tuohy, Whole-grain wheat breakfast cereal has a prebiotic effect on the human gut microbiota: a double-blind, placebo-controlled, crossover study, Br. J. Nutr. (2008), https://doi.org/10.1017/S0007114507793923.
[59] A. Venkataraman, J.R. Sieber, A.W. Schmidt, C. Waldron, K.R. Theis, T.M. Schmidt, Variable responses of human microbiomes to dietary supplementation with resistant starch, Microbiome (2016), https://doi.org/10.1186/s40168-016-0178-x.

[60] A.W. Walker, J. Ince, S.H. Duncan, L.M. Webster, G. Holtrop, X. Ze, D. Brown, M.D. Stares, P. Scott, A. Bergerat, P. Louis, F. McIntosh, A.M. Johnstone, G.E. Lobley, J. Parkhill, H.J. Flint, Dominant and diet-responsive groups of bacteria within the human colonic microbiota, ISME J (2011), https://doi.org/10.1038/ismej.2010.118.
[61] I. Martínez, J.M. Lattimer, K.L. Hubach, J.A. Case, J. Yang, C.G. Weber, J.A. Louk, D.J. Rose, G. Kyureghian, D.A. Peterson, M.D. Haub, J. Walter, Gut microbiome composition is linked to whole grain-induced immunological improvements, ISME J (2013), https://doi.org/10.1038/ismej.2012.104.
[62] S.L. Zhang, S.N. Wang, C.Y. Miao, Influence of microbiota on intestinal immune system in ulcerative colitis and its intervention, Front. Immunol. (2017), https://doi.org/10.3389/fimmu.2017.01674.
[63] A. Cotillard, S.P. Kennedy, L.C. Kong, E. Prifti, N. Pons, E. Le Chatelier, M. Almeida, B. Quinquis, F. Levenez, N. Galleron, S. Gougis, S. Rizkalla, J.M. Batto, P. Renault, J. Doré, J.D. Zucker, K. Clément, S.D. Ehrlich, H. Blottière, M. Leclerc, C. Juste, T. De Wouters, P. Lepage, C. Fouqueray, A. Basdevant, C. Henegar, C. Godard, M. Fondacci, A. Rohia, F. Hajduch, J. Weissenbach, E. Pelletier, D. Le Paslier, J.P. Gauchi, J.F. Gibrat, V. Loux, W. Carré, E. Maguin, M. Van De Guchte, A. Jamet, F. Boumezbeur, S. Layec, Dietary intervention impact on gut microbial gene richness, Nature (2013), https://doi.org/10.1038/nature12480.
[64] D.L. Topping, P.M. Clifton, Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides, Physiol. Rev. (2001), https://doi.org/10.1152/physrev.2001.81.3.1031.
[65] H. Watson, S. Mitra, F.C. Croden, M. Taylor, H.M. Wood, S.L. Perry, J.A. Spencer, P. Quirke, G.J. Toogood, C.L. Lawton, L. Dye, P.M. Loadman, M.A. Hull, A randomised trial of the effect of omega-3 polyunsaturated fatty acid supplements on the human intestinal microbiota, Gut (2018), https://doi.org/10.1136/gutjnl-2017-314968.
[66] G. Arslan, K. Erichsen, A.M. Milde, L. Helgeland, T. Bjørkkjær, L. Frøyland, A. Berstad, No protection against DSS-induced colitis by short-term pretreatment with seal or fish oils in rats, Integr. Med. Insights. (2007), https://doi.org/10.1177/117863370700200004.
[67] N. Bosco, V. Brahmbhatt, M. Oliveira, F.P. Martin, P. Lichti, F. Raymond, R. Mansourian, S. Metairon, C. Pace-Asciak, V. Bastic Schmid, S. Rezzi, D. Haller, J. Benyacoub, Effects of increase in fish oil intake on intestinal eicosanoids and inflammation in a mouse model of colitis, Lipids Health Dis. (2013), https://doi.org/10.1186/1476-511X-12-81.
[68] D. Camuesco, J. Gálvez, A. Nieto, M. Comalada, M.E. Rodríguez-Cabezas, A. Concha, J. Xaus, A. Zarzuelo, Dietary olive oil supplemented with fish oil, rich in EPA and DHA (n-3) polyunsaturated fatty acids, attenuates colonic inflammation in rats with DSS-induced colitis, J. Nutr. (2005), https://doi.org/10.1093/jn/135.4.687.
[69] K. Vieira de Barros, G. Gomes de Abreu, R.A.N. Xavier, C.A. Real Martinez, M.L. Ribeiro, A. Gambero, P. de Oliveira Carvalho, V.L.F. Silveira, Effects of a high fat or a balanced omega 3/omega 6 diet on cytokines levels and DNA damage in experimental colitis, Nutrition 27 (2011) 221–226, https://doi.org/10.1016/j.nut.2009.11.014.
[70] C. Charpentier, R. Chan, E. Salameh, K. Mbodji, A. Ueno, M. Coëffier, C. Guérin, S. Ghosh, G. Savoye, R. Marion-Letellier, Dietary n-3 PUFA may attenuate experimental colitis, Mediat. Inflamm. (2018), https://doi.org/10.1155/2018/8430614.
[71] Q. Jia, I. Ivanov, Z.Z. Zlatev, R.C. Alaniz, B.R. Weeks, E.S. Callaway, J.S. Goldsby, L.A. Davidson, Y.-Y. Fan, L. Zhou, J.R. Lupton, D.N. McMurray, R.S. Chapkin, Dietary fish oil and curcumin combine to modulate colonic cytokinetics and gene expression in dextran sodium sulphate-treated mice, Br. J. Nutr. 106 (2011) 519–529, https://doi.org/10.1017/S0007114511000390.
[72] A.K. Singh, C. Cabral, R. Kumar, R. Ganguly, H.K. Rana, A. Gupta, M.R. Lauro, C. Carbone, F. Reis, A.K. Pandey, Beneficial effects of dietary polyphenols on gut microbiota and strategies to improve delivery efficiency, Nutrients (2019), https://doi.org/10.3390/nu11092216.
[73] S.J. Ott, S. Plamondon, A. Hart, A. Begun, A. Rehman, M.A. Kamm, S. Schreiber, Dynamics of the mucosa-associated flora in ulcerative colitis patients during remission and clinical relapse, J. Clin. Microbiol. (2008), https://doi.org/10.1128/JCM.01512-08.
[74] M. Jayachandran, J. Xiao, B. Xu, A critical review on health promoting benefits of edible mushrooms through gut microbiota, Int. J. Mol. Sci. (2017), https://doi.org/10.3390/ijms18091934.
[75] K. Wang, Z. Wan, A. Ou, X. Liang, X. Guo, Z. Zhang, L. Wu, X. Xue, Monofloral honey from a medical plant, Prunella Vulgaris, protected against dextran sulfate sodium-induced ulcerative colitis via modulating gut microbial populations in rats, Food Funct. (2019), https://doi.org/10.1039/c9fo00460b.
[76] M. Larrosa, M.J. Yanéz-Gascón, M.V. Selma, A. Gonzáles-Sarrías, S. Toti, J.J. Cerón, F. Tomás-Barberán, P. Dolara, J.C. Espín, Effect of a low dose of dietary resveratrol on colon microbiota, inflammation and tissue damage in a DSS-induced colitis rat model, J. Agric. Food Chem. 57 (2009) 2211–2220.
[77] X. Tzounis, A. Rodriguez-Mateos, J. Vulevic, G.R. Gibson, C. Kwik-Uribe, J.P.E. Spencer, Prebiotic evaluation of cocoa-derived flavanols in healthy humans by using a randomized, controlled, double-blind, crossover intervention study, Am. J. Clin. Nutr. (2011), https://doi.org/10.3945/ajcn.110.000075.
[78] M.L. Santoru, C. Piras, A. Murgia, V. Palmas, T. Camboni, S. Liggi, I. Ibba, M.A. Lai, S. Orrù, S. Blois, A.L. Loizedda, J.L. Griffin, P. Usai, P. Caboni, L. Atzori, A. Manzin, Cross sectional evaluation of the gut-microbiome metabolome axis in an Italian cohort of IBD patients, Sci. Rep. (2017), https://doi.org/10.1038/s41598-017-10034-5.
[79] M.T. Alam, G.C.A. Amos, A.R.J. Murphy, S. Murch, E.M.H. Wellington, R.P. Arasaradnam, Microbial imbalance in inflammatory bowel disease patients at different taxonomic levels, Gut Pathog 12 (1) (2020), https://doi.org/10.1186/s13099-019-0341-6.
[80] A. Rehman, P. Rausch, J. Wang, J. Skieceviciene, G. Kiudelis, K. Bhagalia, D. Amarapurkar, L. Kupcinskas, S. Schreiber, P. Rosenstiel, J.F. Baines, S. Ott, Geographical patterns of the standing and active human gut microbiome in health and IBD, Gut (2016), https://doi.org/10.1136/gutjnl-2014-308341.
[81] L.R. Lopetuso, V. Petito, C. Graziani, E. Schiavoni, F. Paroni Sterbini, A. Poscia, E. Gaetani, F. Franceschi, G. Cammarota, M. Sanguinetti, L. Masucci, F. Scaldaferri, A. Gasbarrini, Gut microbiota in health, diverticular disease, irritable bowel syndrome, and inflammatory bowel diseases: time for microbial marker of gastrointestinal disorders, Dig. Dis. (2017), https://doi.org/10.1159/000477205.
[82] T.G.J. De Meij, E.F.J. De Groot, C.F.W. Peeters, N.K.H. De Boer, C.M.F. Kneepkens, A. Eck, M.A. Benninga, P.H.M. Savelkoul, A.A. Van Bodegraven, A.E. Budding, Variability of core microbiota in newly diagnosed treatment-naïve paediatric inflammatory bowel disease patients, PLoS One (2018), https://doi.org/10.1371/journal.pone.0197649.
[83] F. Imhann, A. Vich Vila, M.J. Bonder, J. Fu, Di. Gevers, M.C. Visschedijk, L.M. Spekhorst, R. Alberts, L. Franke, H.M. Van Dullemen, R.W.F. Ter Steege, C. Huttenhower, G. DIjkstra, R.J. Xavier, E.A.M. Festen, C. Wijmenga, A. Zhernakova, R.K. Weersma, Interplay of host genetics and gut microbiota underlying the onset and clinical presentation of inflammatory bowel disease, Gut (2018), https://doi.org/10.1136/gutjnl-2016-312135.
[84] T. Zuo, X.J. Lu, Y. Zhang, C.P. Cheung, S. Lam, F. Zhang, W. Tang, J.Y.L. Ching, R. Zhao, P.K.S. Chan, J.J.Y. Sung, J. Yu, F.K.L. Chan, Q. Cao, J.Q. Sheng, S.C. Ng, Gut mucosal virome alterations in ulcerative colitis, Gut (2019), https://doi.org/10.1136/gutjnl-2018-318131.
[85] Y.L. Zhang, L.T. Cai, J.Y. Qi, Y.Z. Lin, Y.C. Dai, N. Jiao, Y.L. Chen, L. Zheng, B.B. Wang, L.X. Zhu, Z.P. Tang, R.X. Zhu, Gut microbiota contributes to the distinction between two traditional Chinese medicine syndromes of ulcerative colitis, World J. Gastroenterol. (2019), https://doi.org/10.3748/wjg.v25.i25.3242.
[86] J.D. Forbes, C.Y. Chen, N.C. Knox, R.A. Marrie, H. El-Gabalawy, T. De Kievit, M. Alfa, C.N. Bernstein, G. Van Domselaar, A comparative study of the gut microbiota in immune-mediated inflammatory diseases - does a common dysbiosis exist? Microbiome (2018), https://doi.org/10.1186/s40168-018-0603-4.
[87] L. Bajer, M. Kverka, M. Kostovcik, P. Macinga, J. Dvorak, Z. Stehlikova, J. Brezina, P. Wohl, J. Spicak, P. Drastich, Distinct gut microbiota profiles in patients with primary sclerosing cholangitis and ulcerative colitis, World J. Gastroenterol. (2017), https://doi.org/10.3748/wjg.v23.i25.4548.
[88] G.L. Chen, Y. Zhang, W.Y. Wang, X.L. Ji, F. Meng, P.S. Xu, N.M. Yang, F.Q. Ye, X.C. Bo, Partners of patients with ulcerative colitis exhibit a biologically relevant dysbiosis in fecal microbial metacommunities, World J. Gastroenterol. (2017), https://doi.org/10.3748/wjg.v23.i25.4624.
[89] J. Maukonen, K.L. Kolho, M. Paasela, J. Honkanen, P. Klemetti, O. Vaarala, M. Saarela, Altered fecal microbiota in paediatric inflammatory bowel disease, J. Crohns. Colitis. (2015), https://doi.org/10.1093/ecco-jcc/jjv147.
[90] W. Zhong, X. Lu, H. Shi, G. Zhao, Y. Song, Y. Wang, J. Zhang, Y. Jin, S. Wang, Distinct microbial populations exist in the mucosa-associated microbiota of diarrhea predominant irritable bowel syndrome and ulcerative colitis, J. Clin. Gastroenterol. 53 (2019) 660–672, https://doi.org/10.1097/MCG.0000000000000961.
[91] Z.H. Shen, C.X. Zhu, Y.S. Quan, Z.Y. Yang, S. Wu, W.W. Luo, B. Tan, X.Y. Wang, Relationship between intestinal microbiota and ulcerative colitis: mechanisms and clinical application of probiotics and fecal microbiota transplantation, World J. Gastroenterol. 24 (2018) 5–14, https://doi.org/10.3748/wjg.v24.i1.5.
[92] M.A. Fernandes, S.G. Verstraete, T.G. Phan, X. Deng, E. Stekol, B. LaMere, S.V. Lynch, M.B. Heyman, E. Delwart, Enteric virome and bacterial microbiota in children with ulcerative colitis and Crohn disease, J. Pediatr. Gastroenterol. Nutr. (2019), https://doi.org/10.1097/MPG.0000000000002140.
[93] K. Takeshita, S. Mizuno, Y. Mikami, T. Sujino, K. Saigusa, K. Matsuoka, M. Naganuma, T. Sato, T. Takada, H. Tsuji, A. Kushiro, K. Nomoto, T. Kanai, A single species of clostridium subcluster XIVa decreased in ulcerative colitis patients, Inflamm. Bowel Dis. (2016), https://doi.org/10.1097/MIB.0000000000000972.
[94] C. Olbjørn, M.C. Småstuen, E. Thiis-Evensen, B. Nakstad, M.H. Vatn, J. Jahnsen, P. Ricanek, S. Vatn, A.E.F. Moen, T.M. Tannæs, J.C. Lindstrøm, J.D. Söderholm, J. Halfvarson, F. Gomollón, C. Casén, M.K. Karlsson, R. Kalla, A.T. Adams, J. Satsangi, G. Perminow, Fecal microbiota profiles in treatment-naïve pediatric inflammatory bowel disease – associations with disease phenotype, treatment, and outcome, Clin. Exp. Gastroenterol. (2019), https://doi.org/10.2147/CEG.S186235.
[95] M. Lopez-Siles, N. Enrich-Capó, X. Aldeguer, M. Sabat-Mir, S.H. Duncan, L.J. Garcia-Gil, M. Martinez-Medina, Alterations in the abundance and co-occurrence of Akkermansia muciniphila and Faecalibacterium prausnitzii in the colonic mucosa of inflammatory bowel disease subjects, Front. Cell. Infect. Microbiol. (2018), https://doi.org/10.3389/fcimb.2018.00281.
[96] J.S. Mar, B.J. Lamere, D.L. Lin, S. Levan, M. Nazareth, U. Mahadevan, S.V. Lynch, Disease severity and immune activity relate to distinct interkingdom gut microbiome states in ethnically distinct ulcerative colitis patients, MBio (2016), https://doi.org/10.1128/mBio.01072-16.
[97] R.L. Knoll, K. Forslund, J.R. Kultima, C.U. Meyer, U. Kullmer, S. Sunagawa, P. Bork, S. Gehring, Gut microbiota differs between children with inflammatory bowel disease and healthy siblings in taxonomic and functional composition: a metagenomic analysis, Am. J. Physiol. - Gastrointest. Liver Physiol. (2017), https://doi.org/10.1152/ajpgi.00293.2016.

[98] K.Y. Li, J.L. Wang, J.P. Wei, S.Y. Gao, Y.Y. Zhang, L.T. Wang, G. Liu, Fecal microbiota in pouchitis and ulcerative colitis, World J. Gastroenterol. (2016), https://doi.org/10.3748/wjg.v22.i40.8929.

[99] X. Qiu, J. Ma, C. Jiao, X. Mao, X. Zhao, M. Lu, K. Wang, H. Zhang, Alterations in the mucosa-associated fungal microbiota in patients with ulcerative colitis, Oncotarget 8 (2017) 107577–107588, https://doi.org/10.18632/oncotarget.22534.

[100] F. Ungaro, L. Massimino, F. Furfaro, V. Rimoldi, L. Peyrin-Biroulet, S. D'Alessio, S. Danese, Metagenomic analysis of intestinal mucosa revealed a specific eukaryotic gut virome signature in early-diagnosed inflammatory bowel disease, Gut Microbes (2019), https://doi.org/10.1080/19490976.2018.1511664.

[101] E. Cario, D.K. Podolsky, Differential Alteration in Intestinal Epithelial Cell Expression of Toll-like Receptor 3 (TLR3) and TLR4 in Inflammatory Bowel Disease, vol. 68, (2000), pp. 7010–7017.

[102] X. Shen, R. Shi, H. Zhang, K. Li, Y. Zhao, R. Zhang, The toll-like receptor 4 D299G and T399I polymorphisms are associated with Crohn's disease and ulcerative colitis: a meta-analysis, Digestion (2010), https://doi.org/10.1159/000260417.

[103] S. Danese, C. Fiocchi, Ulcerative colitis, N. Engl. J. Med. (2011), https://doi.org/10.1056/NEJMra1102942.

[104] M. Hausmann, S. Kiessling, S. Mestermann, G. Webb, T. Spöttl, T. Andus, J. Schölmerich, H. Herfarth, K. Ray, W. Falk, G. Rogler, Toll-like receptors 2 and 4 are up-regulated during intestinal inflammation, Gastroenterology (2002), https://doi.org/10.1053/gast.2002.33662.

[105] E. Cario, Toll-like receptors in inflammatory bowel diseases: a decade later, Inflamm. Bowel Dis. (2010), https://doi.org/10.1002/ibd.21282.

[106] Ó.P. Rojo, A.L. San Román, E.A. Arbizu, A.D.L.H. Martínez, E.R. Sevillano, A.A. Martínez, Serum lipopolysaccharide-binding protein in endotoxemic patients with inflammatory bowel disease, Inflamm. Bowel Dis. (2007), https://doi.org/10.1002/ibd.20019.

[107] H.S.P. De Souza, C. Fiocchi, Immunopathogenesis of IBD, Nat. Publ. Gr 13 (2015) 13–27, https://doi.org/10.1038/nrgastro.2015.186.

[108] J.C. Brazil, N.A. Louis, C.A. Parkos, The role of polymorphonuclear leukocyte trafficking in the perpetuation of inflammation during inflammatory bowel disease, Inflamm. Bowel Dis. (2013), https://doi.org/10.1097/MIB.0b013e318281f54e.

[109] D.H. Kim, J.H. Cheon, Pathogenesis of inflammatory bowel disease and recent advances in biologic therapies, Immune Netw (2017), https://doi.org/10.4110/in.2017.17.1.25.

[110] A. Kaistha, J. Levine, Inflammatory bowel disease: the classic gastrointestinal autoimmune disease, Curr. Probl. Pediatr. Adolesc. Health Care. (2014), https://doi.org/10.1016/j.cppeds.2014.10.003.

[111] E. Van Der Gracht, S. Zahner, M. Kronenberg, When Insult Is Added to Injury: Cross Talk between ILCs and Intestinal Epithelium in IBD, vol. 2016, (2016), https://doi.org/10.1155/2016/9765238.

[112] A. Geremia, C.V. Arancibia-cárcamo, M.P.P. Fleming, N. Rust, B. Singh, N.J. Mortensen, S.P.L. Travis, F. Powrie, IL-23 – Responsive Innate Lymphoid Cells Are Increased in Inflammatory Bowel Disease, vol. 208, (2011), pp. 1127–1133, https://doi.org/10.1084/jem.20101712.

[113] R. Okamoto, M. Watanabe, Role of epithelial cells in the pathogenesis and treatment of inflammatory bowel disease, J. Gastroenterol. (2016), https://doi.org/10.1007/s00535-015-1098-4.

[114] M.F. Neurath, Cytokines in inflammatory bowel disease, Nat. Rev. Immunol. (2014), https://doi.org/10.1038/nri3661.

[115] F. Takahashi, K.M. Das, Isolation and Characterization of a Colonic Autoantigen Specifically Recognized by Colon Tissue-bound Immunoglobulin G from Idiopathic Ulcerative Colitis, vol. 76, (1985), pp. 311–318.

[116] X. Geng, L. Biancone, Hui Hui Dai, J.J.C. Lin, N. Yoshizaki, A. Dasgupta, F. Pallone, K.M. Das, Tropomyosin isoforms in intestinal mucosa: production of autoantibodies to tropomyosin isoforms in ulcerative colitis, Gastroenterology (1998), https://doi.org/10.1016/S0016-5085(98)70310-5.

[117] S. Bhagat, K.M. Das, A shared and unique peptide in the human colon, eye, and joint detected by a monoclonal antibody, Gastroenterology (1994), https://doi.org/10.1016/0016-5085(94)90066-3.

[118] I.J. Fuss, F. Heller, M. Boirivant, F. Leon, M. Yoshida, S. Fichtner-Feigl, Z. Yang, M. Exley, A. Kitani, R.S. Blumberg, P. Mannon, W. Strober, Nonclassical CD1d-restricted NK T cells that produce IL-13 characterize an atypical Th2 response in ulcerative colitis, J. Clin. Invest. (2004), https://doi.org/10.1172/JCI19836.

[119] S. Danese, G. Fiorino, L. Peyrin-Biroulet, E. Lucenteforte, G. Virgili, L. Moja, S. Bonovas, Biological agents for moderately to severely active ulcerative colitis, Ann. Intern. Med. (2014), https://doi.org/10.7326/M13-2403.

[120] P. Biancheri, A. Di Sabatino, F. Ammoscato, F. Facciotti, F. Caprioli, R. Curciarello, S.S. Hoque, A. Ghanbari, I. Joe-Njoku, P. Giuffrida, L. Rovedatti, J. Geginat, G.R. Corazza, T.T. Macdonald, Absence of a role for interleukin-13 in inflammatory bowel disease, Eur. J. Immunol. (2014), https://doi.org/10.1002/eji.201343524.

[121] I.J. Fuss, M.F. Neurath, M. Boirivant, C. Fiocchi, W. Strober, Disparate CD4 + lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease, Shock (1997), https://doi.org/10.1097/00024382-199703001-00528.

[122] J.B. Seidelin, M. Coskun, P.H. Kvist, T.L. Holm, K. Holgersen, O.H. Nielsen, IL-33 promotes GATA-3 polarization of gut-derived T cells in experimental and ulcerative colitis, J. Gastroenterol. (2014), https://doi.org/10.1007/s00535-014-0982-7.

[123] S. Melgar, M.M.W. Yeung, A. Bas, G. Forsberg, O. Suhr, Å. Öberg, S. Hammarström, Å. Danielsson, M.L. Hammarström, Over-expression of interleukin 10 in mucosal T cells of patients with active ulcerative colitis, Clin. Exp. Immunol. (2003), https://doi.org/10.1046/j.1365-2249.2003.02268.x.

[124] G. Roda, M. Marocchi, A. Sartini, E. Roda, Cytokine networks in ulcerative colitis, Ulcers (2011), https://doi.org/10.1155/2011/391787.

[125] G.A. West, T. Matsuura, A.D. Levine, J.S. Klein, C. Fiocchi, Interleukin 4 in inflammatory bowel disease and mucosal immune reactivity, Gastroenterology (1996), https://doi.org/10.1053/gast.1996.v110.pm8964392.

[126] T. Kobayashi, S. Okamoto, T. Hisamatsu, N. Kamada, H. Chinen, R. Saito, M.T. Kitazume, A. Nakazawa, A. Sugita, K. Koganei, K. Isobe, T. Hibi, IL23 differentially regulates the Th1/Th17 balance in ulcerative colitis and Crohn's disease, Gut (2008), https://doi.org/10.1136/gut.2007.135053.

[127] L. Rovedatti, T. Kudo, P. Biancheri, M. Sarra, C.H. Knowles, D.S. Rampton, G.R. Corazza, G. Monteleone, A. Di Sabatino, T.T. MacDonald, Differential regulation of interleukin 17 and interferon γ production in inflammatory bowel disease, Gut (2009), https://doi.org/10.1136/gut.2009.182170.

[128] J.M. Leung, M. Davenport, M.J. Wolff, K.E. Wiens, W.M. Abidi, M.A. Poles, I. Cho, T. Ullman, L. Mayer, P. Loke, IL-22-producing CD4 + cells are depleted in actively inflamed colitis tissue, Mucosal Immunol. (2014), https://doi.org/10.1038/mi.2013.31.

[129] K. Gerlach, Y. Hwang, A. Nikolaev, R. Atreya, H. Dornhoff, S. Steiner, H.A. Lehr, S. Wirtz, M. Vieth, A. Waisman, F. Rosenbauer, A.N.J. McKenzie, B. Weigmann, M.F. Neurath, T H 9 cells that express the transcription factor PU.1 drive T cell-mediated colitis via IL-9 receptor signaling in intestinal epithelial cells, Nat. Immunol. (2014), https://doi.org/10.1038/ni.2920.

[130] J.K. Triantafillidis, G. Nasioulas, P.A. Kosmidis, Colorectal cancer and inflammatory bowel disease: epidemiology, risk factors, mechanisms of carcinogenesis and prevention strategies, Anticancer Res. 29 (2009) 2727–2737.

[131] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (2018) 394–424, https://doi.org/10.3322/caac.21492.

[132] S. Sahami, I.A. Kooij, S.L. Meijer, G.R. Van Den Brink, C.J. Buskens, A.A. Te Velde, The link between the appendix and ulcerative colitis: clinical relevance and potential immunological mechanisms, Am. J. Gastroenterol. (2016), https://doi.org/10.1038/ajg.2015.301.

[133] I. Ordás, L. Eckmann, M. Talamini, D.C. Baumgart, W.J. Sandborn, Ulcerative colitis, Lancet (2012), https://doi.org/10.1016/S0140-6736(12)60150-0.

[134] J. Satsangi, M.S. Silverberg, S. Vermeire, J.F. Colombel, The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications, Gut (2006), https://doi.org/10.1136/gut.2005.082909.

[135] T.C. DeRoche, S.Y. Xiao, X. Liu, Histological evaluation in ulcerative colitis, Gastroenterol. Rep. (2014), https://doi.org/10.1093/gastro/gou031.

[136] F. Magro, C. Langner, A. Driessen, A. Ensari, K. Geboes, G.J. Mantzaris, V. Villanacci, G. Becheanu, P.B. Nunes, G. Cathomas, W. Fries, A. Jouret-Mourin, C. Mescoli, G. de Petris, C.A. Rubio, N.A. Shepherd, M. Vieth, R. Eliakim, European consensus on the histopathology of inflammatory bowel disease, J. Crohn's Colitis (2013), https://doi.org/10.1016/j.crohns.2013.06.001.

[137] L.M. Delmondes, M.O. Nunes, A.R. Azevedo, M.M. de S. Oliveira, L.E.R. Coelho, J. da R. Torres-Neto, Clinical and sociodemographic aspects of inflammatory bowel disease patients, Gastroenterol. Res. (2015), https://doi.org/10.14740/gr649w.

[138] K. Conrad, D. Roggenbuck, M.W. Laass, Diagnosis and classification of ulcerative colitis, Autoimmun. Rev. (2014), https://doi.org/10.1016/j.autrev.2014.01.028.

[139] J. Guardiola, T. Lobatón, L. Rodríguez-Alonso, A. Ruiz-Cerulla, C. Arajol, C. Loayza, X. Sanjuan, E. Sánchez, F. Rodríguez-Moranta, Fecal level of calprotectin identifies histologic inflammation in patients with ulcerative colitis in clinical and endoscopic remission, Clin. Gastroenterol. Hepatol. (2014), https://doi.org/10.1016/j.cgh.2014.06.020.

[140] E.R. Kim, D.K. Chang, Colorectal cancer in inflammatory bowel disease: the risk, pathogenesis, prevention and diagnosis, World J. Gastroenterol. 20 (2014) 9872–9881, https://doi.org/10.3748/wjg.v20.i29.9872.

[141] A.M. Westbrook, A. Szakmary, R.H. Schiestl, Mouse models of intestinal inflammation and cancer, Arch. Toxicol. (2016), https://doi.org/10.1007/s00204-016-1747-2.

[142] P. Kiesler, I.J. Fuss, W. Strober, Experimental models of inflammatory bowel diseases, Med. Hyg. (Geneve) (2001), https://doi.org/10.1016/j.jcmgh.2015.01.006.

[143] G.P. Morris, P.L. Beck, M.S. Herridge, W.T. Depew, M.R. Szewczuk, J.L. Wallace, Hapten-induced model of chronic inflammation and ulceration in the rat colon, Gastroenterology 96 (1989) 795–803, https://doi.org/10.1016/0016-5085(89)90904-9.

[144] A.P.R. Paiotti, R.A. Neto, P. Marchi, R.M. Silva, V.L. Pazine, J. Noguti, M.M. Pastrelo, A.P.B. Gollücke, S.J. Miszputen, D.A. Ribeiro, The anti-inflammatory potential of phenolic compounds in grape juice concentrate (G8000™) on 2,4,6-trinitrobenzene sulphonic acid-induced colitis, Br. J. Nutr. (2013), https://doi.org/10.1017/S000711451300007X.

[145] C.S. De Almeida, V. Andrade-Oliveira, N.O.S. Câmara, J.F. Jacysyn, E.L. Faquim-Mauro, Crotoxin from Crotalus durissus terrificus is able to down-modulate the acute intestinal inflammation in mice, PLoS One (2015), https://doi.org/10.1371/journal.pone.0121427.

[146] S. Fichtner-Feigl, W. Strober, E.K. Geissler, H.J. Schlitt, Cytokines mediating the induction of chronic colitis and colitis-associated fibrosis, Mucosal Immunol. (2008), https://doi.org/10.1038/mi.2008.41.

[147] H. Mi, F. Bin Liu, H.W. Li, J.T. Hou, P.W. Li, Anti-inflammatory effect of Chang-An-Shuan on TNBS-induced experimental colitis in rats, BMC Complement. Altern. Med. (2017), https://doi.org/10.1186/s12906-017-1794-0.

[148] S. Wirtz, V. Popp, M. Kindermann, K. Gerlach, B. Weigmann, S. Fichtner-Feigl, M.F. Neurath, Chemically induced mouse models of acute and chronic intestinal inflammation, Nat. Protoc. (2017), https://doi.org/10.1038/nprot.2017.044.

[149] S.C. Bischoff, R. Mailer, O. Pabst, G. Weier, W. Sedlik, Z. Li, J.J. Chen, D.L. Murphy, M.D. Gershon, Role of serotonin in intestinal inflammation: knockout of serotonin reuptake transporter exacerbates 2,4,6-trinitrobenzene sulfonic acid colitis in mice, Am. J. Physiol. - Gastrointest. Liver Physiol. (2009), https://doi.org/10.1152/ajpgi.90685.2008.
[150] Pinto Silva, Mateus, preclinical study in vivo for new pharmacological approaches in inflammatory bowel disease: a systematic review of chronic model of TNBS-induced colitis, J. Clin. Med. (2019), https://doi.org/10.3390/jcm8101574.
[151] W. Strober, B.R. Lúdvíksson, I.J. Fuss, The pathogenesis of mucosal inflammation in murine models of inflammatory bowel disease and Crohn disease, Ann. Intern. Med. (1998), https://doi.org/10.7326/0003-4819-128-10-199805150-00009.
[152] P. Alex, N.C. Zachos, T. Nguyen, L. Gonzales, T.E. Chen, L.S. Conklin, M. Centola, X. Li, Distinct cytokine patterns identified from multiplex profiles of murine DSS and TNBS-induced colitis, Inflamm. Bowel Dis. (2009), https://doi.org/10.1002/ibd.20753.
[153] İ. Karaboga, S. Demirtas, T. Karaca, Investigation of the relationship between the TH17/IL-23 pathway and innate-adaptive immune system in TNBS-induced colitis in rats, Iran, J. Basic Med. Sci. 20 (2017) 870–879, https://doi.org/10.22038/ijbms.2017.9108.
[154] G.J. Cheon, Y. Cui, D.S. Yeon, S.C. Kwon, B.G. Park, Mechanisms of motility change on trinitrobenzenesulfonic acid-induced colonic inflammation in mice, Korean J. Physiol. Pharmacol. (2012), https://doi.org/10.4196/kjpp.2012.16.6.437.
[155] Y. Ni, M. Liu, H. Yu, Y. Chen, Y. Liu, S. Chen, J. Ruan, A. Da, Y. Zhang, T. Wang, Desmethylbellidifolin from Gentianella acuta ameliorate TNBS-induced ulcerative colitis through antispasmodic effect and anti-inflammation, Front. Pharmacol. (2019), https://doi.org/10.3389/fphar.2019.01104.
[156] S.S. Sadar, N.S. Vyawahare, S.L. Bodhankar, Ferulic acid ameliorates tnbs-induced ulcerative colitis through modulation of cytokines, oxidative stress, inos, cox-2, and apoptosis in laboratory rats, EXCLI J. (2016), https://doi.org/10.17179/excli2016-393.
[157] E. Antoniou, G.A. Margonis, A. Angelou, A. Pikouli, P. Argiri, I. Karavokyros, A. Papalois, E. Pikoulis, The TNBS-induced colitis animal model: an overview, Ann. Med. Surg. (2016), https://doi.org/10.1016/j.amsu.2016.07.019.
[158] S. Fichtner-Feigl, I.J. Fuss, J.C. Preise, W. Strober, A. Kitani, Treatment of murine Th1- and Th2-mediated inflammatory bowel disease with NF-κB decoy oligonucleotides, J. Clin. Invest. (2005), https://doi.org/10.1172/JCI24792.
[159] T. Dohi, K. Fujihashi, H. Kiyono, C.O. Elson, J.R. McGhee, Mice deficient in Th1- and Th2-type cytokines develop distinct forms of hapten-induced colitis, Gastroenterology (2000), https://doi.org/10.1053/gast.2000.16500.
[160] M. Boirivant, I.J. Fuss, A. Chu, W. Strober, Oxazolone colitis: a murine model of T helper cell type 2 colitis treatable with antibodies to interleukin 4, J. Exp. Med. (1998), https://doi.org/10.1084/jem.188.10.1929.
[161] F. Heller, I.J. Fuss, E.E. Nieuwenhuis, R.S. Blumberg, W. Strober, Oxazolone colitis, a Th2 colitis model resembling ulcerative colitis, is mediated by IL-13-producing NK-T cells, Immunity (2002), https://doi.org/10.1016/S1074-7613(02)00453-3.
[162] R. Kojima, S. Kuroda, T. Ohkishi, K. Nakamaru, S. Hatakeyama, Oxazolone-induced colitis in BALB/C mice: a new method to evaluate the efficacy of therapeutic agents for ulcerative colitis, J. Pharmacol. Sci. 96 (2004) 307–313, https://doi.org/10.1254/JPHS.FP0040214.
[163] W. Wu, F. Wang, X. Gao, T. Niu, X. Zhu, X. Yan, H. Chen, Synergistic effect of κ-carrageenan on oxazolone-induced inflammation in BALB/c mice, BMC Gastroenterol. 16 (2016) 1–13, https://doi.org/10.1186/s12876-016-0459-7.
[164] M. Lagranderie, C. Kluge, H. Kieferbiasizzo, M. Abolhassani, M. Nahori, C. Fitting, M. Huerre, A. Bandeira, H. Bercovier, G. Marchal, Mycobacterium bovis Bacillus Calmette-Guérin killed by extended freeze-drying reduces colitis in mice, Gastroenterology 141 (2011) 642–652.e4, https://doi.org/10.1053/j.gastro.2011.05.002.
[165] J. Yang, J. Zhao, T. Nakaguchi, H. Gregersen, Biomechanical changes in oxazolone-induced colitis in BALB/C mice, J. Biomech. (2009), https://doi.org/10.1016/j.jbiomech.2009.01.028.
[166] X. Wang, F. Fan, Q. Cao, Modified Pulsatilla decoction attenuates oxazolone-induced colitis in mice through suppression of inflammation and epithelial barrier disruption, Mol. Med. Rep. (2016), https://doi.org/10.3892/mmr.2016.5358.
[167] J.A. Jiminez, T.C. Uwiera, G.D. Inglis, R.R.E. Uwiera, Animal models to study acute and chronic intestinal inflammation in mammals, Gut Pathog (2015), https://doi.org/10.1186/s13099-015-0076-y.
[168] L. Zhang, N. Cao, Y. Wang, Y. Wang, C. Wu, X. Cheng, C. Wang, Improvement of oxazolone-induced ulcerative colitis in rats using andrographolide, Molecules 25 (2019), https://doi.org/10.3390/molecules25010076.
[169] E. Meroni, N. Stakenborg, P.J. Gomez-Pinilla, G. De Hertogh, G. Goverse, G. Matteoli, S. Verheijden, G.E. Boeckxstaens, Functional characterization of oxazolone-induced colitis and survival improvement by vagus nerve stimulation, PLoS One 13 (2018) 1–19, https://doi.org/10.1371/journal.pone.0197487.
[170] D.D. Eichele, K.K. Kharbanda, Dextran sodium sulfate colitis murine model: an indispensable tool for advancing our understanding of inflammatory bowel diseases pathogenesis, World J. Gastroenterol. (2017), https://doi.org/10.3748/wjg.v23.i33.6016.
[171] K. Walton, Experiments with dextran sulphate as an anticoagulant, J. R. Soc. Med. (1951), https://doi.org/10.1177/003591575104400710.
[172] T. Ohkusa, Production of experimental ulcerative colitis in hamsters by dextran sulfate sodium and change in intestinal microflora, Nippon Shokakibyo Gakkai Zasshi (1985), https://doi.org/10.11405/nisshoshi1964.82.1327.
[173] H. Laroui, S.A. Ingersoll, H.C. Liu, M.T. Baker, S. Ayyadurai, M.A. Charania, F. Laroui, Y. Yan, S.V. Sitaraman, D. Merlin, Dextran sodium sulfate (DSS) induces colitis in mice by forming nano-lipocomplexes with medium-chain-length fatty acids in the colon, PLoS One 7 (2012) e32084, , https://doi.org/10.1371/journal.pone.0032084.
[174] L.A. Dieleman, M.J.H.J. Palmen, H. Akol, E. Bloemena, A.S. Peña, S.G.M. Meuwissen, E.P. Van Rees, Chronic experimental colitis induced by dextran sulphate sodium (DSS) is characterized by Th1 and Th2 cytokines, Clin. Exp. Immunol. (1998), https://doi.org/10.1046/j.1365-2249.1998.00728.x.
[175] R. de P. do Nascimento, A.V. Lima, L.M. Oyama, A.P.R. Paiotti, L. Cardili, C.A.R. Martinez, J.A. Pereira, M.F. Silva, I.C. Garofolo, V.L.F. Silveira, L.C. Caperuto, Extra-virgin olive oil and flaxseed oil have no preventive effects on DSS-induced acute ulcerative colitis, Nutrition (2020) 110731, https://doi.org/10.1016/J.NUT.2020.110731.
[176] M. Perše, A. Cerar, Dextran sodium sulphate colitis mouse model: traps and tricks, J. Biomed. Biotechnol. 2012 (2012), https://doi.org/10.1155/2012/718617.
[177] S. Wirtz, C. Neufert, B. Weigmann, M.F. Neurath, Chemically induced mouse models of intestinal inflammation, Nat. Protoc. (2007), https://doi.org/10.1038/nprot.2007.41.
[178] I.B. Renes, J.A. Boshuizen, D.J.P.M. Van Nispen, N.P. Bulsing, H.A. Büller, J. Dekker, A.W.C. Einerhand, Alterations in Muc2 biosynthesis and secretion during dextran sulfate sodium-induced colitis, Am. J. Physiol. - Gastrointest. Liver Physiol. (2002), https://doi.org/10.1152/ajpgi.00229.2001.
[179] P.M. Munyaka, M.F. Rabbi, E. Khafipour, J.E. Ghia, Acute dextran sulfate sodium (DSS)-induced colitis promotes gut microbial dysbiosis in mice, J. Basic Microbiol. 56 (2016) 986–998, https://doi.org/10.1002/jobm.201500726.
[180] R.S. Parra, A.H. Lopes, E.U. Carreira, M.R. Feitosa, F.Q. Cunha, S.B. Garcia, T.M. Cunha, J.J.R. Da Rocha, O. Féres, Hyperbaric oxygen therapy ameliorates TNBS-induced acute distal colitis in rats, Med. Gas Res. (2015), https://doi.org/10.1186/s13618-015-0026-2.
[182] T. Liu, Y. Shi, J. Du, X. Ge, X. Teng, L. Liu, E. Wang, Q. Zhao, Vitamin D treatment attenuates 2,4,6-trinitrobenzene sulphonic acid (TNBS)-induced colitis but not oxazolone-induced colitis, Sci. Rep. 6 (2016) 1–10, https://doi.org/10.1038/srep32889.
[183] N. Taghipour, M. Molaei, N. Mosaffa, M. Rostami-Nejad, H.A. Aghdaei, A. Anissian, P. Azimzadeh, M.R. Zali, An experimental model of colitis induced by dextran sulfate sodium from acute progresses to chronicity in C57BL/6: correlation between conditions of mice and the environment, Gastroenterol. Hepatol. from Bed to Bench (2016), https://doi.org/10.22037/ghfbb.v1i9.868.
[184] S. Sánchez-Fidalgo, A. Cárdeno, M. Sánchez-Hidalgo, M. Aparicio-Soto, C.A. De la Lastra, Dietary extra virgin olive oil polyphenols supplementation modulates DSS-induced chronic colitis in mice, J. Nutr. Biochem. (2013), https://doi.org/10.1016/j.jnutbio.2012.11.008.
[185] S. Sánchez-Fidalgo, L. Sánchez De Ibargüen, A. Cárdeno, C. Alarcón De La Lastra, Influence of extra virgin olive oil diet enriched with hydroxytyrosol in a chronic DSS colitis model, Eur. J. Nutr. (2012), https://doi.org/10.1007/s00394-011-0235-y.
[186] M. De Robertis, E. Massi, M.L. Poeta, S. Carotti, S. Morini, L. Cecchetelli, E. Signori, V.M. Fazio, The AOM/DSS murine model for the study of colon carcinogenesis: from pathways to diagnosis and therapy studies, J. Carcinog. 10 (2011) 9, https://doi.org/10.4103/1477-3163.78279.
[187] B. Parang, C.W. Barrett, C.S. Williams, AOM/DSS model of colitis-associated Cancer, Methods Mol. Biol. 1422 (2016) 297–307, https://doi.org/10.1007/978-1-4939-3603-8_26.
[188] Y.J. Choi, Y.J. Choi, N. Kim, R.H. Nam, S. Lee, H.S. Lee, H.-N. Lee, Y.-J. Surh, D.H. Lee, Açaí berries inhibit colon tumorigenesis in azoxymethane/dextran sulfate sodium-treated mice, Gut Liver 11 (2017) 243–252, https://doi.org/10.5009/gnl16068.
[189] T. Vezza, A. Rodríguez-Nogales, F. Algieri, M.P. Utrilla, M.E. Rodriguez-Cabezas, J. Galvez, Flavonoids in inflammatory bowel disease: a review, Nutrients. 8 (2016) 1–22, https://doi.org/10.3390/nu8040211.
[190] D. Camuesco, M. Comalada, M.E. Rodrı, A. Nieto, M.D. Lorente, A. Concha, A. Zarzuelo, J. Ga, The intestinal anti-inflammatory effect of quercitrin is associated with an inhibition in iNOS expression, Br. J. Pharmacol. (2004) 908–918, https://doi.org/10.1038/sj.bjp.0705941.
[191] F.A. Moura, K.Q. de Andrade, J.C.F. dos Santos, O.R.P. Araújo, M.O.F. Goulart, Antioxidant therapy for treatment of inflammatory bowel disease: does it work? Redox Biol. 6 (2015) 617–639, https://doi.org/10.1016/j.redox.2015.10.006.
[192] I. Balmus, A. Ciobica, A. Trifan, C. Stanciu, The implications of oxidative stress and antioxidant therapies in inflammatory bowel disease: clinical aspects and animal models, Saudi J. Gastroenterol. 22 (2016) 3–17, https://doi.org/10.4103/1319-3767.173753.
[193] H. Hanai, K. Sugimoto, Curcumin has bright prospects for the treatment of inflammatory bowel disease, Curr. Pharm. Des. 15 (2009) 2087–2094, https://doi.org/10.2174/138161209788489177.
[194] M.S. Baliga, J. Nandhini, F. Emma, M.V. Venkataranganna, P. Venkatesh, R. Fayad, Indian medicinal plants and spices in the prevention and treatment of ulcerative colitis, Bioact. Food as Diet. Interv. Liver Gastrointest. Dis (2013) 173–185, https://doi.org/10.1016/B978-0-12-397154-8.00188-3.
[195] S.Y. CAO, S.J. YE, W.W. WANG, B. WANG, T. ZHANG, Y.Q. PU, Progress in active compounds effective on ulcerative colitis from Chinese medicines, Chin. J. Nat. Med. 17 (2019) 81–102, https://doi.org/10.1016/S1875-5364(19)30012-3.
[196] M. Ohno, A. Nishida, Y. Sugitani, K. Nishino, O. Inatomi, M. Sugimoto, M. Kawahara, A. Andoh, Nanoparticle curcumin ameliorates experimental colitis via modulation of gut microbiota and induction of regulatory T cells, PLoS One 12 (2017) e0185999, , https://doi.org/10.1371/journal.pone.0185999.
[197] C. Shepherd, P. Giacomin, S. Navarro, C. Miller, A. Loukas, P. Wangchuk, A medicinal plant compound, capnoidine, prevents the onset of inflammation in a

mouse model of colitis, J. Ethnopharmacol. 211 (2018) 17–28, https://doi.org/10.1016/j.jep.2017.09.024.
[198] L. Zhu, P.Q. Gu, H. Shen, Gallic acid improved inflammation via NF-κB pathway in TNBS-induced ulcerative colitis, Int. Immunopharmacol. 67 (2019) 129–137, https://doi.org/10.1016/j.intimp.2018.11.049.
[199] M. Shigeshiro, S. Tanabe, T. Suzuki, Dietary polyphenols modulate intestinal barrier defects and inflammation in a murine model of colitis, J. Funct. Foods 5 (2013) 949–955, https://doi.org/10.1016/j.jff.2013.02.008.
[200] I. Castangia, A. Nácher, C. Caddeo, V. Merino, O. Díez-Sales, A. Catalán-Latorre, X. Fernàndez-Busquets, A.M. Fadda, M. Manconi, Therapeutic efficacy of quercetin enzyme-responsive nanovesicles for the treatment of experimental colitis in rats, Acta Biomater. 13 (2015) 216–227, https://doi.org/10.1016/j.actbio.2014.11.017.
[201] B. Guven, M. Can, O. Piskin, B.G. Aydin, K. Karakaya, O. Elmas, B. Acikgoz, Flavonoids protect colon against radiation induced colitis, Regul. Toxicol. Pharmacol. 104 (2019) 128–132, https://doi.org/10.1016/j.yrtph.2019.03.006.
[202] K.H. Kwon, A. Murakami, T. Tanaka, H. Ohigashi, Dietary rutin, but not its aglycone quercetin, ameliorates dextran sulfate sodium-induced experimental colitis in mice: attenuation of pro-inflammatory gene expression, Biochem. Pharmacol. 69 (2005) 395–406, https://doi.org/10.1016/j.bcp.2004.10.015.
[203] C. Mascaraque, R. López-Posadas, M.J. Monte, I. Romero-Calvo, A. Daddaoua, M. González, E. Martínez-Plata, M.D. Suárez, R. González, J.J.G. Marín, A. Zarzuelo, O. Martínez-Augustin, F. Sánchez de Medina, The small intestinal mucosa acts as a rutin reservoir to extend flavonoid anti-inflammatory activity in experimental ileitis and colitis, J. Funct. Foods 13 (2015) 117–125, https://doi.org/10.1016/j.jff.2014.12.041.
[204] L.H. Maurer, C.B.B. Cazarin, A. Quatrin, N.M. Minuzzi, E.L. Costa, J. Morari, L.A. Velloso, R.F. Leal, E. Rodrigues, V.C. Bochi, M.R.M. Júnior, T. Emanuelli, Grape peel powder promotes intestinal barrier homeostasis in acute TNBS-colitis: a major role for dietary fiber and fiber-bound polyphenols, Food Res. Int. 123 (2019) 425–439, https://doi.org/10.1016/j.foodres.2019.04.068.
[205] Y. Wang, B. Ge, X. Yang, J. Zhai, L. Yang, X. Wang, X. Liu, J. Shi, Y. Wu, Proanthocyanidins from grape seeds modulates the nuclear factor-kappa B signal transduction pathways in rats with TNBS-induced recurrent ulcerative colitis, Int. Immunopharmacol. 11 (2011) 1620–1627, https://doi.org/10.1016/j.intimp.2011.05.024.
[206] A. Saxena, K. Kaur, S. Hegde, F.M. Kalekhan, M.S. Baliga, R. Fayad, Dietary agents and phytochemicals in the prevention and treatment of experimental ulcerative colitis, J. Tradit. Complement. Med. 4 (2014) 203–217, https://doi.org/10.4103/2225-4110.139111.
[207] N.K.R. Ghattamaneni, S.K. Panchal, L. Brown, Nutraceuticals in rodent models as potential treatments for human inflammatory bowel disease, Pharmacol. Res. 132 (2018) 99–107, https://doi.org/10.1016/j.phrs.2018.04.015.
[208] G. Dryden, A. Lam, K. Beatty, H. Qazzaz, C. Mcclain, A pilot study to evaluate the safety and efficacy of an oral dose of (−)-epigallocatechin-3-gallate–rich Polyphenon E in patients with mild to moderate ulcerative colitis, Inflamm. Bowel Dis. 19 (2013) 1904–1912, https://doi.org/10.1097/MIB.0b013e31828f5198.
[209] H. Inoue, S. Akiyama, M. Maeda-Yamamoto, A. Nesumi, T. Tanaka, A. Murakami, High-dose green tea polyphenols induce nephrotoxicity in dextran sulfate sodium-induced colitis mice by down-regulation of antioxidant enzymes and heat-shock protein expressions, Cell Stress Chaperones 16 (2011) 653–662, https://doi.org/10.1007/s12192-011-0280-8.
[210] H. Oz, T. Chen, J.S.W. Villiers, Green tea polyphenols and sulfasalazine have parallel anti-inflammatory properties in colitis models, Front. Immunol. 4 (2013) 1–10, https://doi.org/10.3389/fimmu.2013.00132.
[211] A. Gerges Geagea, M. Rizzo, A. Eid, I. Hajj Hussein, Z. Zgheib, M.N. Zeenny, R. Jurjus, M.L. Uzzo, G.F. Spatola, G. Bonaventura, A. Leone, L. Massaad-Massade, A. Jurjus, Tea catechins induce crosstalk between signaling pathways and stabilize mast cells in ulcerative colitis, J. Biol. Regul. Homeost. Agents 31 (2017) 865–877.
[212] S. Shapira, A. Leshno, D. Katz, N. Maharshak, G. Hevroni, M. Jean-David, S. Kraus, L. Galazan, I. Aroch, D. Kazanov, A. Hallack, S. Becker, M. Umanski, M. Moshkowitz, I. Dotan, N. Arber, Of mice and men: a novel dietary supplement for the treatment of ulcerative colitis, Ther. Adv. Gastroenterol. 11 (2018) 1–10, https://doi.org/10.1177/1756283X17741864.
[213] M. Brückner, S. Westphal, W. Domschke, T. Kucharzik, A. Lügering, Green tea polyphenol epigallocatechin-3-gallate shows therapeutic antioxidative effects in a murine model of colitis, J. Crohn's Colitis 6 (2012) 226–235, https://doi.org/10.1016/j.crohns.2011.08.012.
[214] Z. Bitzer, R. Elias, M. Vijay-Kumar, J. Lambert, (−)-Epigallocatechin-3-gallate decreases colonic inflammation and permeability in a mouse model of colitis, but reduces macronutrient digestion and exacerbates weight loss, Mol. Nutr. Food Res. 60 (2016) 2267–2274, https://doi.org/10.1002/mnfr.201501042.
[215] H. Asakura, T. Kitahora, Antioxidants and polyphenols in inflammatory bowel disease: Ulcerative colitis and Crohn disease, in: R.R. Watson, V.R. Preedy, S.B.T.-P.P. and T of H.D. (Second E. Zibadi) (Eds.), Polyphenols Prev. Treat. Hum. Dis, Second, Academic Press, 2018, pp. 279–292, , https://doi.org/10.1016/B978-0-12-813008-7.00023-0.
[216] H. Piberger, A. Oehme, C. Hofmann, A. Dreiseitel, P.G. Sand, F. Obermeier, J. Schoelmerich, P. Schreier, G. Krammer, G. Rogler, Bilberries and their anthocyanins ameliorate experimental colitis, Mol. Nutr. Food Res. 55 (2011) 1724–1729, https://doi.org/10.1002/mnfr.201100380.
[217] D.C. Montrose, N.A. Horelik, J.P. Madigan, G.D. Stoner, L.S. Wang, R.S. Bruno, H.J. Park, C. Giardina, D.W. Rosenberg, Anti-inflammatory effects of freeze-dried black raspberry powder in ulcerative colitis, Carcinogenesis 32 (2011) 343–350, https://doi.org/10.1093/carcin/bgq248.
[218] P. Marchi, A.P.R. Paiotti, R.A. Neto, C.T.F. Oshima, D.A. Ribeiro, Concentrated grape juice (G8000???) reduces immunoexpression of iNOS, TNF-alpha, COX-2 and DNA damage on 2,4,6-trinitrobenzene sulfonic acid-induced-colitis, Environ. Toxicol. Pharmacol. 37 (2014) 819–827, https://doi.org/10.1016/j.etap.2014.02.006.
[219] J.A. Uranga, V. López-Miranda, F. Lombó, R. Abalo, Food, nutrients and nutraceuticals affecting the course of inflammatory bowel disease, Pharmacol. Reports. 68 (2016) 816–826, https://doi.org/10.1016/j.pharep.2016.05.002.
[220] N. Yang, K. Sampathkumar, S.C.J. Loo, Recent advances in complementary and replacement therapy with nutraceuticals in combating gastrointestinal illnesses, Clin. Nutr. 36 (2017) 968–979, https://doi.org/10.1016/j.clnu.2016.08.020.
[221] K. Mbodji, C. Charpentier, C. Guérin, C. Querec, C. Bole-Feysot, M. Aziz, G. Savoye, P. Déchelotte, R. Marion-Letellier, Adjunct therapy of n-3 fatty acids to 5-ASA ameliorates inflammatory score and decreases NF-κB in rats with TNBS-induced colitis, J. Nutr. Biochem. 24 (2013) 700–705, https://doi.org/10.1016/j.jnutbio.2012.03.022.
[222] J.-H. Kim, S.-S. Hong, M. Lee, E.-H. Lee, I. Rhee, S.-Y. Chang, S.-J. Lim, Krill oil-incorporated liposomes as an effective nanovehicle to ameliorate the inflammatory responses of DSS-induced colitis, Int. J. Nanomedicine 14 (2019) 8305–8320, https://doi.org/10.2147/IJN.S220053.
[223] M. Balaha, S. Kandeel, W. Elwan, Garlic oil inhibits dextran sodium sulfate-induced ulcerative colitis in rats, Life Sci. 146 (2016), https://doi.org/10.1016/j.lfs.2016.01.012.
[224] L. Sang, B. Chang, J. Zhu, F. Yang, Y. Li, X. Jiang, X. Sun, C. Lu, D. Wang, Dextran sulfate sodium-induced acute experimental colitis in C57BL/6 mice is mitigated by selenium, Int. Immunopharmacol. 39 (2016) 359–368, https://doi.org/10.1016/j.intimp.2016.07.034.
[225] J. Skupsky, S. Sabui, M. Hwang, M. Nakasaki, M.D. Cahalan, H.M. Said, Biotin supplementation ameliorates murine colitis by preventing NF-κB activation, Cell. Mol. Gastroenterol. Hepatol. (2019) 1–11, https://doi.org/10.1016/j.jcmgh.2019.11.011.
[226] L.A.A.P. Derikx, L.A. Dieleman, F. Hoentjen, Probiotics and prebiotics in ulcerative colitis, Best Pract. Res. Clin. Gastroenterol. 30 (2016) 55–71, https://doi.org/10.1016/j.bpg.2016.02.005.
[227] A. Rodríguez-Nogales, F. Algieri, J. Garrido-Mesa, T. Vezza, M.P. Utrilla, N. Chueca, F. García, M.E. Rodríguez-Cabezas, J. Gálvez, Intestinal anti-inflammatory effect of the probiotic Saccharomyces boulardii in DSS-induced colitis in mice: impact on microRNAs expression and gut microbiota composition, J. Nutr. Biochem. 61 (2018) 129–139, https://doi.org/10.1016/j.jnutbio.2018.08.005.
[228] A. Rodríguez-Nogales, F. Algieri, J. Garrido-Mesa, T. Vezza, M.P. Utrilla, N. Chueca, F. Garcia, M. Olivares, M.E. Rodríguez-Cabezas, J. Gálvez, Differential intestinal anti-inflammatory effects of Lactobacillus fermentum and Lactobacillus salivarius in DSS mouse colitis: impact on microRNAs expression and microbiota composition, Mol. Nutr. Food Res. (2017), https://doi.org/10.1002/mnfr.201700144.
[229] A. Rodríguez-Nogales, F. Algieri, J. Garrido-Mesa, T. Vezza, M.P. Utrilla, N. Chueca, J.A. Fernández-Caballero, F. García, M.E. Rodríguez-Cabezas, J. Gálvez, The administration of Escherichia coli Nissle 1917 ameliorates development of DSS-induced colitis in mice, Front. Pharmacol. (2018), https://doi.org/10.3389/fphar.2018.00468.
[230] V. Lorén, J. Manyé, M.C. Fuentes, E. Cabré, I. Ojanguren, J. Espadaler, Comparative effect of the I3.1 probiotic formula in two animal models of colitis, Probiotics Antimicrob. Proteins. 9 (2017) 71–80, https://doi.org/10.1007/s12602-016-9239-5.
[231] A.A. Abdin, E.M. Saeid, An experimental study on ulcerative colitis as a potential target for probiotic therapy by Lactobacillus acidophilus with or without "olsalazine,", J. Crohn's Colitis 2 (2008) 296–303, https://doi.org/10.1016/j.crohns.2008.04.002.
[232] S. Komaki, A. Haque, H. Miyazaki, T. Matsumoto, S. Nakamura, Unexpected effect of probiotics by Lactococcus lactis subsp. lactis against colitis induced by dextran sulfate sodium in mice, J. Infect. Chemother. 26 (2020) 549–553, https://doi.org/10.1016/j.jiac.2020.01.006.
[233] R. Liu, Y. Li, B. Zhang, The effects of konjac oligosaccharide on TNBS-induced colitis in rats, Int. Immunopharmacol. 40 (2016) 385–391, https://doi.org/10.1016/j.intimp.2016.08.040.
[234] S. K-da, S. Peerakietkhajorn, B. Siringoringo, P. Muangnil, S. Wichienchot, P. Khuituan, Oligosaccharides from Gracilaria fisheri ameliorate gastrointestinal dysmotility and gut dysbiosis in colitis mice, J. Funct. Foods 71 (2020) 104021, https://doi.org/10.1016/j.jff.2020.104021.
[235] B. Ocón, A. Anzola, M. Ortega-González, A. Zarzuelo, M.D. Suárez, F. Sánchez De Medina, O. Martínez-Augustin, Active hexose-correlated compound and Bifidobacterium longum BB536 exert symbiotic effects in experimental colitis, Eur. J. Nutr. 52 (2013) 457–466, https://doi.org/10.1007/s00394-012-0347-z.
[236] T.P. Ivanovska, K. Mladenovska, Z. Zhivikj, M.J. Pavlova, I. Gjurovski, T. Ristoski, L. Petrushevska-Tozi, Synbiotic loaded chitosan-Ca-alginate microparticles reduces inflammation in the TNBS model of rat colitis, Int. J. Pharm. 527 (2017) 126–134, https://doi.org/10.1016/j.ijpharm.2017.05.049.
[237] A. Murakami, Dose-dependent functionality and toxicity of green tea polyphenols in experimental rodents, Arch. Biochem. Biophys. 557 (2014) 3–10, https://doi.org/10.1016/j.abb.2014.04.018.
[238] Y. Yang, J. He, Y. Suo, Z. Zheng, J. Wang, L. Lv, C. Huo, Z. Wang, J. Li, W. Sun, Y. Zhang, Tauroursodeoxycholate improves 2,4,6-trinitrobenzenesulfonic acid-induced experimental acute ulcerative colitis in mice, Int. Immunopharmacol. 36 (2016) 271–276, https://doi.org/10.1016/J.INTIMP.2016.04.037.
[239] L.H. Maurer, C.B.B. Cazarin, A. Quatrin, S.M. Nichelle, N.M. Minuzzi, C.F. Teixeira, I.B. Manica da Cruz, M.R. Maróstica Júnior, T. Emanuelli, Dietary

fiber and fiber-bound polyphenols of grape peel powder promote GSH recycling and prevent apoptosis in the colon of rats with TNBS-induced colitis, J. Funct. Foods (2019), https://doi.org/10.1016/j.jff.2019.103644 In Press.
[240] W. He, M. Liu, Y. Li, H. Yu, D. Wang, Q. Chen, Y. Chen, Y. Zhang, T. Wang, Flavonoids from Citrus aurantium ameliorate TNBS-induced ulcerative colitis through protecting colonic mucus layer integrity, Eur. J. Pharmacol. 857 (2019) 172456, , https://doi.org/10.1016/j.ejphar.2019.172456.
[241] Y. Yang, J. He, Y. Suo, L. Lv, J. Wang, C. Huo, Z. Zheng, Z. Wang, J. Li, W. Sun, Y. Zhang, Anti-inflammatory effect of taurocholate on TNBS-induced ulcerative colitis in mice, Biomed. Pharmacother. 81 (2016) 424–430, https://doi.org/10.1016/j.biopha.2016.04.037.
[242] Q. LV, K. WANG, S.-M. QIAO, Y. DAI, Z.-F. WEI, Norisoboldine, a natural aryl hydrocarbon receptor agonist, alleviates TNBS-induced colitis in mice, by inhibiting the activation of NLRP3 inflammasome, Chin. J. Nat. Med. 16 (2018) 161–174, https://doi.org/10.1016/S1875-5364(18)30044-X.
[243] H. Zatorski, M. Sałaga, M. Zielińska, A. Piechota-Polanczyk, K. Owczarek, R. Kordek, U. Lewandowska, C. Chen, J. Fichna, Experimental colitis in mice is attenuated by topical administration of chlorogenic acid, Naunyn Schmiedeberg's Arch. Pharmacol. 388 (2015) 643–651, https://doi.org/10.1007/s00210-015-1110-9.
[244] S. Zong, Y. Pu, S. Li, B. Xu, Y. Zhang, T. Zhang, Beneficial anti-inflammatory effect of paeonol self-microemulsion-loaded colon-specific capsules on experimental ulcerative colitis rats, Artif. CELLS, NANOMEDICINE, Biotechnol 46 (2018) S324–S335, https://doi.org/10.1080/21691401.2017.1423497.
[245] S. Valcheva-kuzmanova, A. Kuzmanov, V. Kuzmanova, M. Tzaneva, Aronia melanocarpa fruit juice ameliorates the symptoms of inflammatory bowel disease in TNBS-induced colitis in rats, Food Chem. Toxicol. 113 (2018) 33–39, https://doi.org/10.1016/j.fct.2018.01.011.
[246] C. Baú, B. Cazarin, J. Kelly, T. Cristina, Â. Giovana, L. Maria, M. Meletti, J. Augusto, R. Paschoal, F. Guillermo, R. Reyes, F. Augusto, L. Rodrigues, D. Meirelles, R. De Lima, M. Roberto, M. Júnior, Intake of Passiflora edulis leaf extract improves antioxidant and anti-inflammatory status in rats with 2 , 4 , 6-trinitrobenzenesulphonic acid induced colitis, J. Funct. Foods 17 (2015) 575–586, https://doi.org/10.1016/j.jff.2015.05.034.
[247] A.E. González-Ramírez, M.E. González-Trujano, S.A. Orozco-Suárez, N. Alvarado-Vásquez, F.J. López-Muñoz, Nerol alleviates pathologic markers in the oxazolone-induced colitis model, Eur. J. Pharmacol. 776 (2016) 81–89, https://doi.org/10.1016/j.ejphar.2016.02.036.
[248] X. Long, Y. Pan, X. Zhao, Prophylactic effect of Kudingcha polyphenols on oxazolone induced colitis through its antioxidant capacities, Food Sci. Hum. Wellness. 7 (2018) 209–214, https://doi.org/10.1016/j.fshw.2018.06.002.
[249] Y. Yoshioka, H. Akiyama, M. Nakano, T. Shoji, T. Kanda, Y. Ohtake, T. Takita, R. Matsuda, T. Maitani, Orally administered apple procyanidins protect against experimental inflammatory bowel disease in mice, Int. Immunopharmacol. 8 (2008) 1802–1807, https://doi.org/10.1016/j.intimp.2008.08.021.
[250] C.-T. Mai, M.-M. Wu, C.-L. Wang, Z.-R. Su, Y.-Y. Cheng, X.-J. Zhang, Palmatine attenuated dextran sulfate sodium (DSS)-induced colitis via promoting mitophagy-mediated NLRP3 inflammasome inactivation, Mol. Immunol. 105 (2019) 76–85, https://doi.org/10.1016/j.molimm.2018.10.015.
[251] E. Kim, J. Bae, J. Lee, J.-H. Shin, P.R. Seok, Y. Kim, S.-H. Yoo, Purification and characterization of turanose, a sucrose isomer and its anti-inflammatory effects in dextran sulfate sodium (DSS)-induced colitis model, J. Funct. Foods 63 (2019) 103570, https://doi.org/10.1016/j.jff.2019.103570.
[252] J. Jang, S.-M. Kim, S.-M. Yee, E.-M. Kim, E.-H. Lee, H.-R. Choi, Y.-S. Lee, W.-K. Yang, H.-Y. Kim, K.-H. Kim, H.-S. Kang, S.-H. Kim, Daucosterol suppresses dextran sulfate sodium (DSS)-induced colitis in mice, Int. Immunopharmacol. 72 (2019) 124–130, https://doi.org/10.1016/j.intimp.2019.03.062.
[253] A.S. Lee, K.M. Lee, J.-A. Lee, I. Choi, Peanut shell extract inhibits the development of dextran sulfate sodium (DSS)-induced colitis, Int. Immunopharmacol. 70 (2019) 235–240, https://doi.org/10.1016/j.intimp.2019.02.040.
[254] S.K. Mishra, J.-H. Kang, D.-K. Kim, S.H. Oh, M.K. Kim, Orally administered aqueous extract of Inonotus obliquus ameliorates acute inflammation in dextran sulfate sodium (DSS)-induced colitis in mice, J. Ethnopharmacol. 143 (2012) 524–532, https://doi.org/10.1016/j.jep.2012.07.008.
[255] M. Xu, X.-Y. Duan, Q.-Y. Chen, H. Fan, Z. Hong, S.-J. Deng, Z. Nan, H. Wu, Y.-L. Dong, Y.-J. Liu, C.-Z. Zhou, Effect of compound sophorae decoction on dextran sodium sulfate (DSS)-induced colitis in mice by regulating Th17/Treg cell balance, Biomed. Pharmacother. 109 (2019) 2396–2408, https://doi.org/10.1016/j.biopha.2018.11.087.
[256] S. Chen, H. Zhao, N. Cheng, W. Cao, Rape bee pollen alleviates dextran sulfate sodium (DSS)-induced colitis by neutralizing IL-1β and regulating the gut microbiota in mice, Food Res. Int. 122 (2019) 241–251, https://doi.org/10.1016/j.foodres.2019.04.022.
[257] J. Cao, J. Cheng, S. Xi, X. Qi, S. Shen, Y. Ge, Alginate/chitosan microcapsules for in-situ delivery of the protein, interleukin-1 receptor antagonist (IL-1Ra), for the treatment of dextran sulfate sodium (DSS)-induced colitis in a mouse model, Eur. J. Pharm. Biopharm. 137 (2019) 112–121, https://doi.org/10.1016/j.ejpb.2019.02.011.
[258] P.R. Yeganeh, J. Leahy, S. Spahis, N. Patey, Y. Desjardins, D. Roy, E. Delvin, C. Garofalo, J.P. Leduc-Gaudet, D. St-Pierre, J.F. Beaulieu, A. Marette, G. Gouspillou, E. Levy, Apple peel polyphenols reduce mitochondrial dysfunction in mice with DSS-induced ulcerative colitis, J. Nutr. Biochem. 57 (2018) 56–66, https://doi.org/10.1016/j.jnutbio.2018.03.008.