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Review

Antioxidant and Anti-Inflammatory Phytochemicals for the Treatment of Inflammatory Bowel Disease: A Systematic Review

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Abstract: Inflammatory bowel disease (IBD) remains a burden for patients with increasing prevalence in industrialized countries. Phytochemicals are non-nutrient plant derived bioactive substances with antioxidant and anti-inflammatory effects that may prove beneficial to IBD patients. This review aims to overview current evidence on the application and impact of isolated phytochemicals or phytochemicals contained in plant extracts and essential oils on patients suffering from IBD. A systematic literature search was conducted for studies relating to the use of phytochemicals for the treatment of IBD. Ultimately, 37 human clinical trials and 3 systematic reviews providing human IBD patient data relevant to phytochemicals as therapeutic agents were included. Phytochemicals in the form of curcumin, *Plantago ovata* seeds, polyphenon E, silymarin, resveratrol supplements or an herbal preparation of myrrh, chamomile and coffee charcoal have evidence from human clinical trials supporting their safety and beneficial effects. Cannabinoids improve quality of life but not IBD outcomes. The addition of probiotics like *B. longum* to fructo-oligosaccharides promote healthy composition of the gut microbiome. Phytochemicals like mastiha, anthocyanins, berberine, tormentil, T2, ecabet sodium and Pycnogenol need more well-designed trials. Systematic research on phytochemicals can lead to the discovery of useful therapeutics. These secondary metabolites can be incorporated in current IBD treatment strategies to limit side effects, promote mucosal healing and provide higher quality of life to patients.

Keywords: phytochemical; inflammatory bowel disease; clinical study; prevention; treatment; antioxidant; anti-inflammatory

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1. Introduction

Inflammatory bowel disease (IBD) mainly comprises Crohn's disease (CD) and ulcerative colitis (UC) and is a group of chronic relapsing disorders characterized by inflammation of the gastrointestinal tract with variable phenotypic expression. Multiple factors have been implicated in the etiology of IBD, including environmental, genetic, microbiological and immunological interactions. However, the exact reasons remain unclear, although substantial progress in elucidating the complexity of IBD manifestation has been made in the past decades [1]. There is clinical overlap of symptoms of CD and UC, including bloody or watery diarrhea, recurrent abdominal pain, tenesmus as well as non-specific systemic symptoms such as fatigue, fever and weight loss [2]. CD can affect various parts of the intestine, i.e., both small and large intestine, while UC is known to affect only the colon.

IBD usually follows a lifelong pattern of remissions and flare-ups that impacts the quality of life of patients. The inflammation of the gastrointestinal tract during flare-ups is mediated by neutrophils that release cytokines, enzymes and reactive oxygen species (ROS) leading to damage and even ulceration of the mucosa [3]. Gut microbiota and its dysregulation are one of the environmental factors that also play a key role in the immune-mediated disease process of IBD. Thus, various medical therapies target these pathophysiologic pathways [3,4].

Phytochemicals are non-nutrient plant derived bioactive substances. As a group of heterogeneous compounds, these secondary metabolites are involved in various organic functions of plants other than growth or nutrition, such as protection from bacteria, fungi or insects [5,6]. More than 10,000 phytochemicals have been identified up to now, a number estimated to amount to less than 10% of potentially bioactive substances contained in plant matter [7,8]. The dietary consumption of fruits and vegetables containing phytochemicals has demonstrated anti-inflammatory and antioxidant effects while lowering cancer and cardiovascular risks [9]. Because various phytochemicals have been regarded as plant-derived toxins, their antimicrobial effect has also been investigated [10]. The scientific interest in these natural products is therefore high, and several in vitro or animal model studies focus on specific phytochemicals [11]. Some studies have demonstrated that the effects achievable by these compounds may be apparent at higher doses. The extraction and synthesis of these phytochemicals, however, can be laborious [12]. Indeed, preclinical studies are essential to isolate and focus on both medically applicable and easy to extract or manufacture substances [7]. Analyzing the constituents of plant extracts or essential oils with proven benefits can lead to the discovery of the effective phytochemical substances contained in them [13,14].

This analysis comprises a field of research that is vast and encompasses different fields such as biology, plant chemistry and medicine. There is in vitro and in vivo ongoing research to identify novel antioxidant and anti-inflammatory phytochemicals in animals or humans. Clinical relevance of phytochemicals and modes of delivery are also investigated.

The objective of this review is to provide a high-level overview of current knowledge on the applied use of phytochemicals on patients suffering from IBD. We aim to review and assess the impact of various phytochemicals and plant extracts on patient outcomes by systematically reviewing clinical trial data. Focusing on phytochemicals or plant extracts under clinical trials with potential beneficial results can guide researchers to plan new ones.

2. Materials and Methods

2.1. Study Protocol

This systematic review is reported according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines (Figure 1) [15].

2.2. Search Strategy

A systematic search of the literature was conducted to identify any studies related to the use of phytochemicals for the treatment of IBD. Articles including clinical data of the phytochemicals' application on humans affected by IBD were screened. Description of the potential molecular antioxidant or anti-inflammatory pathways targeted by the phytochemicals was evaluated. The influence of phytochemicals on the symptoms, clinical scores, prevention of relapse, maintenance of remission, quality of life and avoidance of complications was also examined.

We searched two major databases (PubMed/Medline and Scopus) until January 2024. Searches were conducted using the keywords "inflammatory bowel disease", "phytochemical", "antioxidant" and "anti-inflammatory". Specifically, various combinations of the following search terms and phytochemical compounds or category headings were used in the database "Advanced Search" feature of PubMed/Medline and in Scopus: "inflammatory bowel disease", "phytochemicals", "antioxidant" or "anti-inflammatory" along with "curcumin", "alkaloids", "organosulfur", "phenolics", "terpenes", "carotenoids" or

"coumarins". Filters were applied so that only randomized controlled trials (RCTs), systematic reviews and clinical trials written in English were included. After deduplication, titles and abstracts were screened for relevance to our topic during the initial search. Following retrieval of screened articles, full-text evaluation was done to reject or accept each study for inclusion. References from included studies were also screened to ensure a thorough literature review.

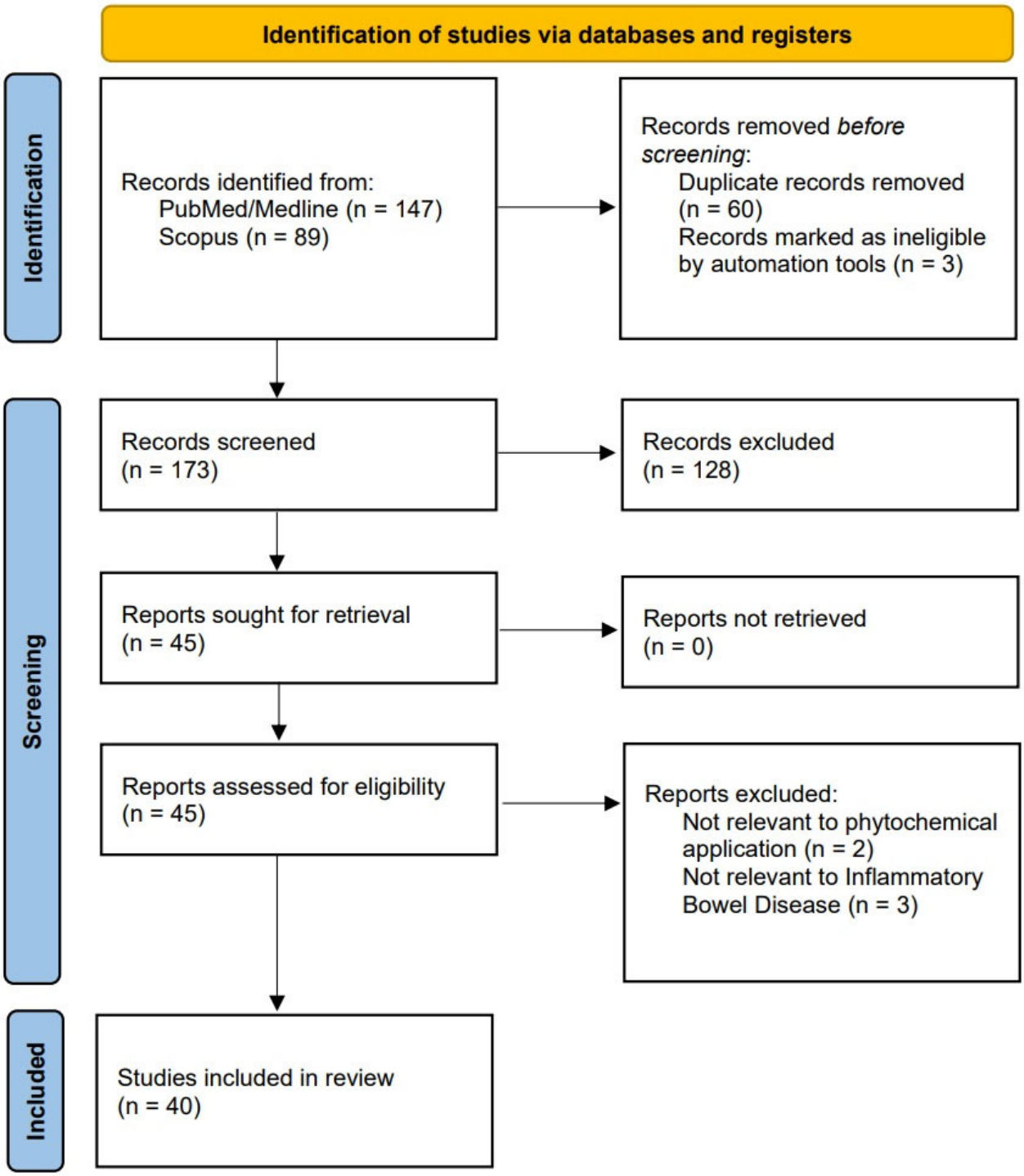


Figure 1. PRISMA flow diagram for the records identified after searching the databases.

2.3. Eligibility Criteria

Selection criteria included original clinical studies of prospective or retrospective design, i.e., RCTs and systematic reviews with data on the impact of phytochemicals in patients with IBD. Articles related to the use of either isolated specific phytochemicals or whole plant extracts were also included.

We excluded studies pertaining to the use of phytochemicals for diseases irrelevant to IBD. Similarly, we excluded animal, cell culture, ex vivo or in vitro studies. Unavailable full-text articles and articles not written in English were also excluded. Obsolete older systematic reviews superseded by newer reviews were excluded.

2.4. Study Screening

Two authors (G.P. and N.V.) independently screened the titles and abstracts of the articles for inclusion. A senior author (E.B.) verified the accuracy of the collection process and resolved any disagreements. Full-text articles were read by two authors (G.P. and N.V.) and after the removal of duplicated and excluded articles, a final review was carried out by the three authors (G.P., N.V. and E.B.) independently and disputes were resolved by consensus.

2.5. Limitations and Strengths of the Study

The present review presents data from a multitude of clinical trials utilizing isolated phytochemicals or phytochemicals contained in plant extracts or essential oils to improve IBD patient outcomes. Careful consideration should be given to the fact that there is high heterogeneity among studies because of the multitude of phytochemicals, their preparations, the dosage and the modes of administration. Therefore, the risk of bias is high due to the high heterogeneity and the inherent selection and publication bias of the included studies [16]. This applies to the 8 pilot studies that could also be at risk of generalizability bias. However, the risk of bias was assessed as low for the 27 RCTs and fair for the 2 cohort studies included in this review, using various tools like Review Manager (RevMan) 5.3 and the Newcastle–Ottawa Scale (Figures 2–4) [17,18]. Limitations also arise due to the high variability in the patients' condition and disease activity, in clinical scores and questionnaires used for assessment. However, some included studies present significant and clinically relevant results, mostly using phytochemicals as nutraceuticals and adjunctive to the mainstays of therapy. The body of evidence presented in this systematic review should help the reader to understand current progress on which phytochemicals and what formulations have been used in a clinical setting and whether they were effective in improving IBD outcomes.

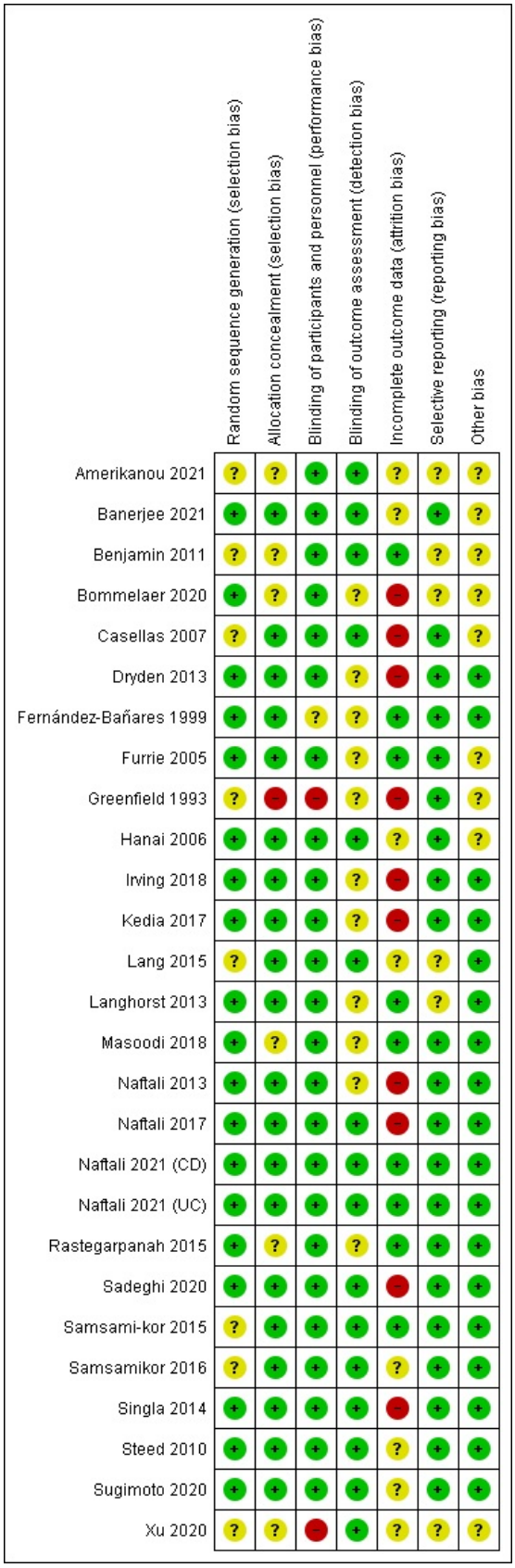


Figure 2. Risk of bias summary plot of included randomized controlled trials after assessment using Cochrane tool and RevMan 5.3. + (green), indicates low risk of bias; ? (yellow), unclear risk of bias; − (red), high risk of bias [19–45].

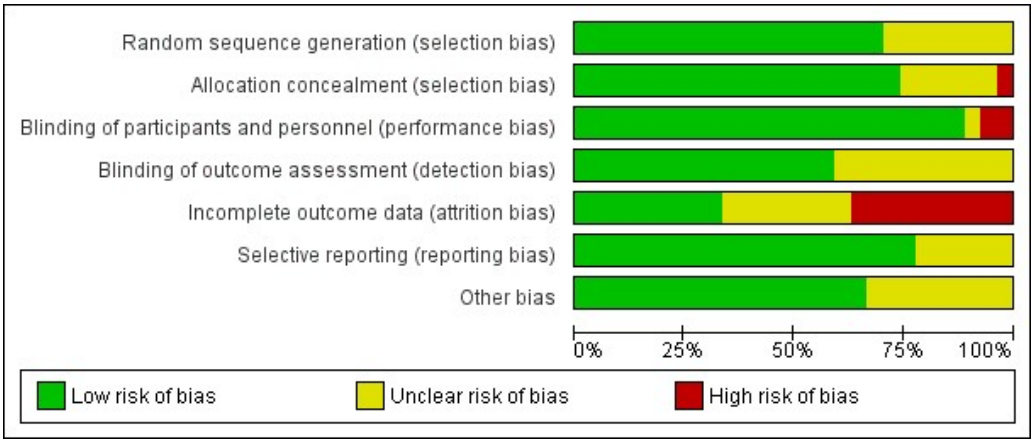


Figure 3. Risk of bias graph of included randomized controlled trials. Generated by RevMan 5.3.

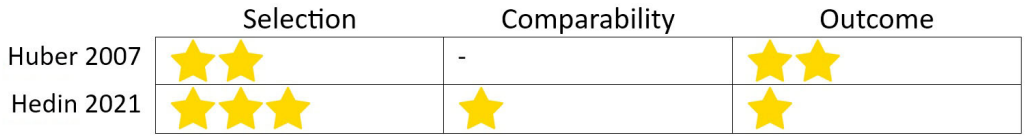


Figure 4. Risk of bias of included non-randomized cohort studies using the Newcastle–Ottawa quality assessment scale. A higher number of stars means a lower risk of bias assessment. Maximum number of stars: 4 for selection, 2 for comparability and 3 for outcome [46,47].

3. Results

3.1. Study Selection

The search of PubMed yielded 147 results and Scopus yielded 89 results. After discarding duplicates, 173 articles remained and were screened by reading the abstracts and identifying that they provided human IBD patient clinical trial data regarding a phytochemical compound used as a therapeutic agent. There were 45 selected papers for full-text appraisal. Two studies not related to phytochemicals and one study not related to IBD were excluded. Moreover, two studies investigating pharmacokinetics, safety and tolerability of phytochemicals in healthy subjects were also excluded since they were not related to IBD patients. Finally, 40 full-text studies were included that met the predetermined inclusion and exclusion criteria.

3.2. Study Characteristics

Publication details are presented in Table 1 and Figure 5. Included studies were published between 1993 and 2021, and their designs consisted of 27 RCTs, 3 systematic reviews, 8 prospective pilot clinical studies and 2 controlled cohort studies. Only 9 out of the 27 RCTs were derived from multicenter studies. The majority of the studies were conducted in European countries.

Table 1. Publication details of included studies.

	Author	Type of Study	Study Period	Year of Publication	Country	Reference
1	Amerikanou et al.	Multicenter RCT and RCT	n/a	2021	Greece, Italy, Serbia	[19]
2	Banerjee et al.	RCT	January 2016–March 2017	2021	India	[20]
3	Benjamin et al.	Multicenter RCT	September 2006–April 2009 Duration 4 weeks	2011	UK	[21]
4	Bommelaer et al.	Multicenter RCT	October 2014–January 2018	2020	France	[22]
5	Casellas et al.	RCT	n/a Duration of 4 weeks	2007	Spain	[23]

Table 1. *Cont.*

	Author	Type of Study	Study Period	Year of Publication	Country	Reference
6	Dryden et al.	RCT	n/a Duration of 56 days	2013	USA	[24]
7	Fernández-Bañares et al.	Multicenter randomized controlled trial (RCT)	January 1993–May 1996	1999	Spain	[25]
8	Furrie et al.	RCT	n/a Duration of 4 weeks	2005	UK	[26]
9	Greenfield et al.	RCT	n/a Duration of 9 months	1993	UK	[27]
10	Hanai et al.	Multicenter RCT	April 2004–July 2005	2006	Japan	[28]
11	Irving et al.	RCT	n/a Duration of 12 weeks	2018	UK	[29]
12	Kedia et al.	RCT	January 2003–March 2005 Duration of 2 months	2017	India	[30]
13	Lang et al.	Multicenter RCT	July 2011–June 2014	2015	Israel	[31]
14	Langhorst et al.	Multicenter RCT	June 2008–July 2010 Duration of 12 months	2013	Germany	[32]
15	Masoodi et al.	RCT	July 2017–September 2017	2018	Iran	[33]
16	Naftali et al.	RCT (non-blinded)	September 2010–September 2011 Duration of 8 weeks	2013	Israel	[34]
17	Naftali et al.	RCT	2011–2012	2017	Israel	[35]
18	Naftali et al. (CD)	RCT	2013–2018	2021	Israel	[36]
19	Naftali et al. (UC)	RCT	n/a Duration of 10 weeks	2021	Israel	[37]
20	Rastegarpanah et al.	Multicenter RCT	September 2009–October 2010 Duration of 6 months	2015	Iran	[38]
21	Sadeghi et al.	RCT	January–September 2018	2020	Iran	[39]
22	Samsami-kor et al.	RCT	n/a Duration of 6 weeks	2015	Iran	[40]
23	Samsamikor et al.	RCT	n/a Duration of 6 weeks	2016	Iran	[41]
24	Singla et al.	RCT	August 2008–July 2009	2014	India	[42]
25	Steed et al.	RCT	January 2006–December 2008 Duration of 6 months	2010	UK	[43]
26	Sugimoto et al.	Multicenter RCT	April 2015–December 2017	2020	Japan	[44]
27	Xu et al.	RCT	August 2016–October 2017	2020	China	[45]
28	Huber et al.	Controlled cohort study	n/a Duration of 3 weeks	2007	Germany	[46]
29	Hedin et al.	Pilot cohort study	Duration of 3 weeks	2021	UK	[47]
30	Biedermann et al.	Prospective trial (not blinded or controlled)	March 2010–April 2011	2013	Switzerland	[48]
31	Suskind et al.	Prospective pilot clinical trial	n/a	2013	USA	[49]
32	Holt et al.	Open pilot clinical trial	n/a Duration of 2 months	2005	USA	[50]
33	Koláček et al.	Prospective pilot study	n/a Duration of 14 days	2013	Slovakia	[51]
34	Li et al.	Prospective trial (not blinded or controlled)	n/a Duration of 3 months	2014	China	[52]
35	Kono et al.	Open-label clinical trial	n/a Duration of 2 weeks	2001	Japan	[53]
36	Lindsay et al.	Prospective clinical trial	n/a Duration of 4 weeks	2006	UK	[54]

Table 1. *Cont.*

	Author	Type of Study	Study Period	Year of Publication	Country	Reference
37	Valcheva et al.	Pilot randomized trial	n/a Duration of 9 weeks	2018	Canada	[55]
38	Doeve et al.	Systematic Review and Meta-analysis	Not applicable	2021	Netherlands (Various)	[56]
39	Goulart et al.	Systematic Review	Not applicable	2021	Brazil (Various)	[57]
40	Liu et al.	Systematic Review and Meta-analysis	Not applicable	2021	China (Various)	[58]

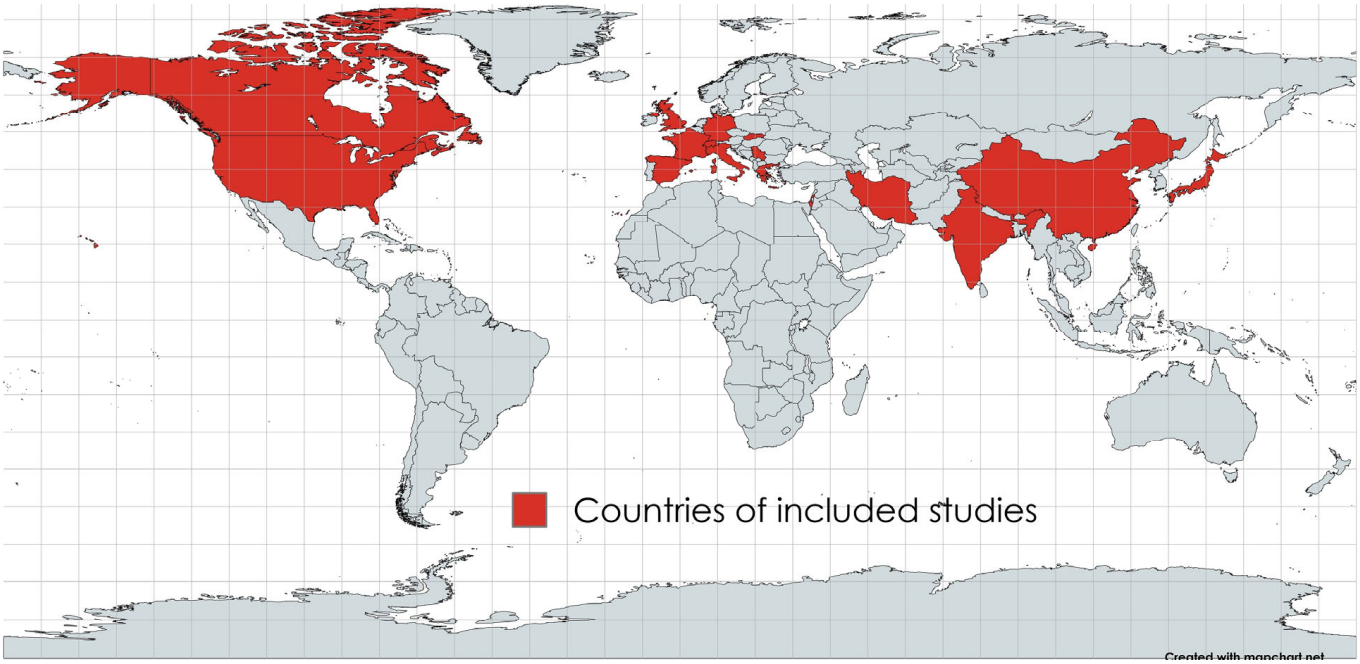


Figure 5. Countries of origin of included clinical trials (map created with MapChart.net).

3.3. Phytochemical Preparations and IBD Clinical Status

Some compounds such as curcumin, fructo-oligosaccharides (FOS), cannabinoids and resveratrol were the most popular targets in the included studies (Table 2). The smallest clinical trial included 7 patients and the largest included 105 patients. More than one article has focused on supplements containing them and their effects on IBD patient outcomes. Less researched substances are berberine, mastiha, bilberry extract, polyphenon E, *Pinus pinaster* extract (Pycnogenol®), silymarin, tormentil extract from *Tormentilla erecta* L., T2/triptolide extract of *Tripterygium wilfordii*, ecabet sodium salt from pine resin, evening primrose oil, *Plantago ovata* seeds or herbal preparations of myrrh, chamomile extract and coffee charcoal. All these preparations have been tested in clinical trials following IBD, UC or CD patients, randomized, controlled or not, but in a relatively smaller capacity. We have labeled the studies utilizing an isolated phytochemical as a standardized medicinal compound in Table 2. These are curcumin, resveratrol, silymarin, polyphenon E, ecabet sodium and FOS with or without *B. longum* as a synbiotic.

Table 2. Details of phytochemical/extract preparations and IBD clinical status.

	Author	Phytochemical or Extract	Preparation and Administration	Recruited Patients	Disease	Reference
1	Amerikanou et al.	Mastiha	MAST4HEALTH: Mastiha 0.35 g in capsules per os—2.1 g/day divided in 3 doses per os MASTIHA-IBD-GR: Mastiha tablets—2.8 g mastiha daily per os	MAST4HEALTH: 67 MASTIHA IBD-GR: 35	Crohn's disease (CD) or UC—remission or mild-to-moderate relapse	[19]
2	Banerjee et al.	Curcumin (IC)	Bioenhanced Curcumin (BEC) 50 mg capsules −100 mg oral BEC daily divided in 2 doses per os	69	UC—Active mild-to-moderate	[20]
3	Benjamin et al.	Oligofructose and Inulin (IC)	FOS 15 g/d as 7.5 mg sachets of Synergy1® given twice daily per os	103	CD—active	[21]
4	Bommelaer et al.	Curcumin (IC)	Curcumin capsules per os—3000 mg/day divided in 3 doses	62	CD—recent surgical resection, under thiopurines	[22]
5	Casellas et al.	Oligofructose and Inulin (IC)	Synergy1® 12 g divided in 3 doses daily per os	19	UC—mild to moderate	[23]
6	Dryden et al.	(-)-epigallocatechin-3-gallate (Polyphenon E) (IC)	Polyphenon E 200 mg capsules—200–400 mg/day divided in 2 doses per os	19	UC—Active mild-to-moderate	[24]
7	Fernández-Bañares et al.	*Plantago ovata* seeds (fiber)	Dried prepared seeds of *Plantago ovata* plant in 10 g sachets given twice daily per os	105	Ulcerative colitis (UC) in remission	[25]
8	Furrie et al.	Symbiotic of *Bifidobacterium longum* plus FOS (IC)	*B. longum* in gelatin capsule and sachet containing 6 g of Synergy1®, given twice daily per os	18	UC	[26]
9	Greenfield et al.	Super Evening primrose essential oil (vs olive oil and fish oil)	250 mg capsules—2 capsules daily for one month followed by 6 capsules daily for 5 months per os	43	"Clinically stable" UC	[27]
10	Hanai et al.	Curcumin (IC)	Per os yellow medications—2 g curcumin divided in 2 doses daily per os	89	UC—"in quiescent state"	[28]
11	Irving et al.	CBD-rich botanical extract	50 mg capsules—100–500 mg/day divided in 2 doses per os	60	UC—mild to moderate, refractory to 5-aminosalicylic acid	[29]
12	Kedia et al.	Curcumin (IC)	Curcumin capsules per os—450 mg/day divided in 3 doses	62	UC—mild to moderate	[30]
13	Lang et al.	Curcumin (IC)	Cur-Cure™, a 95% pure curcumin preparation in 500 mg capsules—3 g of curcumin divided in 2 doses daily per os	50	UC—Active mild-to-moderate	[31]
14	Langhorst et al.	Herbal preparation of myrrh, chamomile extract and coffee charcoal	Oral preparation of 100 mg myrrh, 70 mg chamomile extract and 50 mg coffee charcoal—12 tablets divided in 3 doses per os	97	UC—inactive	[32]
15	Masoodi et al.	Curcuminoids Nanomicelles (IC)	Curcuminoids Nanomicelles 80 mg capsules—240 mg/day divided in 3 doses per os	56	UC—Active mild-to-moderate	[33]
16	Naftali et al.	Cannabis	Cigarettes containing 11.5 mg of tetrahydrocannabinol (THC)—twice daily	21	CD—active disease	[34]
17	Naftali et al.	Cannabidiol (CBD)	5 to 800 mg/day CBD in olive oil	21	CD	[35]
18	Naftali et al. (CD)	*Cannabis indica* 'Avidekel' oil	Cannabis oil containing CBD/THC 160/40 mg/mL—1–20 drops sublingual twice daily	56	CD	[36]

Table 2. *Cont.*

	Author	Phytochemical or Extract	Preparation and Administration	Recruited Patients	Disease	Reference
19	Naftali et al. (UC)	Cigarettes (*Cannabis sativa* var. Indica "Erez")	Cigarettes containing 16% THC (80 mg THC), 0.5% CBG, 0.1% CBD	32	UC—mild to moderate	[37]
20	Rastegarpanah et al.	Silymarin (IC)	Silymarin 140 mg tablets per os once daily	80	UC—in remission	[38]
21	Sadeghi et al.	Curcumin (IC)	Curcumin capsules per os—1500 mg/day divided in 3 doses	70	UC—Active mild-to-moderate	[39]
22	Samsami-kor et al.	Resveratrol (IC)	Resveratrol supplements—500 mg trans-resveratrol capsules once daily per os	50	UC—Active mild-to-moderate	[40]
23	Samsamikor et al.	Resveratrol (IC)	Resveratrol supplements—500 mg trans-resveratrol capsules once daily per os	56	UC—Active mild-to-moderate	[41]
24	Singla et al.	Curcumin	NCB-02 (curcumin): standardized extract of *Curcuma longa*, given once daily as an enema containing 140 mg of NCB-02 dissolved in 20 mL of water	45	UC—Active mild-to-moderate	[42]
25	Steed et al.	Symbiotic of *Bifidobacterium longum* plus FOS (IC)	*B. longum* in gelatin capsule and sachet containing 6 g of Synergy1®, given twice daily per os	35	CD—active	[43]
26	Sugimoto et al.	Curcumin (IC)	Theracurmin®: high bioavailability synthesized curcumin derivative 180 mg capsules—360 mg/day divided in 2 doses per os	30	CD	[44]
27	Xu et al.	Berberine (IC)	>98% pure berberine hydrochloride in 100 mg tablets—300 mg three times daily per os	18	UC—in remission on mesalamine	[45]
28	Huber et al.	Tormentil (Extract from the rhizome of *Tormentilla erecta* L.)	200 mg tormentil capsules–Escalating doses of 1200, 1800, 2400 and 3000 mg/day divided in 3 doses per os	16	UC—active disease	[46]
29	Hedin et al.	Oligofructose and Inulin (IC)	Fructo-oligosaccharides (FOS) 15 g/d as sachets of Synergy1® daily per os	33	CD—in remission	[47]
30	Biedermann et al.	Bilberry (*Vaccinium myrtillus*)	Standardized procedure used dried, sieved bilberries and concentrated bilberry juice in 40 g aluminum trays, 160 g divided in 4 doses daily per os	24	UC—current mild-to-moderate activity	[48]
31	Suskind et al.	Curcumin (IC)	Curcumin 500 mg capsules—1 g/day to 4 g/day divided in 2 doses per os	11	CD or UC—in remission or mild disease	[49]
32	Holt et al.	Curcumin (IC)	Curcumin 550 mg capsules—1100 mg/day to 1650 mg/day divided in 2 or 3 doses per os	10	CD or UC	[50]
33	Koláček et al.	Pycnogenol® (Polyphenols—Procyanidins)	French maritime pine (*Pinus pinaster*) bark extract Pycnogenol®—2 mg/kg/day in 1 dose capsules per os	30	CD—in remission	[51]
34	Li et al.	T2 (Extract of *Tripterygium wilfordii Hook F*)	Triptolide tablets—60 mg/day tablets per os	20	CD—active disease	[52]
35	Kono et al.	Ecabet sodium (salt derived from pine resin) (IC)	Ecabet sodium 1 g + 20 or 50 mL of tepid water—Two enemas daily	7	UC—mild-to-moderate active proctosigmoiditis	[53]
36	Lindsay et al.	Oligofructose (70%) and Inulin (30%) (IC)	FOS 15 g/d as sachets of Prebio 1® daily per os	10	CD—moderately active or ileocolonic disease	[54]

Table 2. *Cont.*

	Author	Phytochemical or Extract	Preparation and Administration	Recruited Patients	Disease	Reference
37	Valcheva et al.	Oligofructose and Inulin (IC)	FOS 7.5–15 g/d as 7.5 mg sachets of Synergy1® given once or twice daily per os	31	UC—active	[55]
38	Doeve et al.	Cannabis—Cannabinoids	Systematic review—Various preparations in each included study †	146	CD or UC	[56]
39	Goulart et al.	Curcumin	Systematic review—Various preparations in each included study †	750	CD or UC	[57]
40	Liu et al.	Polyphenols	Systematic review—Various preparations in each included study †	639	CD or UC	[58]

IC: isolated compound. † Phytochemical doses of these studies are also presented individually in this table.

3.4. Phytochemical or Plant Extract Effectiveness on IBD Patients

The included studies were conducted to assess clinical applications of various phytochemical substances or plant extracts as therapeutic agents or adjuncts to therapy of CD or UC. A summary of their findings will be provided to evaluate their effectiveness and significance.

The safety and efficacy of highly fermentable dietary fiber in the form of *Plantago ovata* seeds vs. mesalazine for maintaining remission in inactive UC patients was assessed. Out of the 105 recruited patients, 102 completed the study. They were divided into three groups: those receiving *Plantago ovata* seeds, mesalazine and a group receiving both. Treatment failure rates were 40%, 35.1%, and 30%, respectively. This study suggests that *Plantago ovata* seeds as an alternative to mesalamine are safe to maintain remission in ulcerative colitis patients [25].

An RCT sought to estimate the effects of fatty acid supplementation on symptomatic relief, relapse prevention and proctitis improvement in patients with UC. A comparison of evening primrose oil vs. fish oil vs. olive oil supplements was conducted in regard to their ability to alter cell membrane composition. Out of 43 patients, 36 completed the study, and the main conclusions were that evening primrose might have minor beneficiary effects in patients with ulcerative colitis, but further studies are needed with other placebos and higher concentrations of gamma-linolenic acid [27].

In the MASTIHA-IBD-GR study, 20 UC or CD patients receiving mastiha were compared to 15 patients receiving placebo. Statistically significant lower levels of the proinflammatory microRNA-155 were found in the mastiha group without clear clinical correlation [19].

Berberine, a Chinese traditional medicine substance, derived from *Coptidis* rhizome was verified as safe when administered with mesalazine in UC patients, with low systemic absorption. However, there was a low number of participants to explore if there was any beneficial effect [45].

Anthocyanins, found in high concentrations in blueberries or black raspberries, have been studied in relation to cardiovascular disease. An open, prospective, non-blinded and non-controlled pilot trial was conducted using an anthocyanin-rich bilberry (*Vaccinium myrtillus*) preparation in patients with mild-to-moderate UC. Eleven patients completed this study. Serum inflammation markers, such as C-Reactive Protein (CRP), were not altered. However, fecal calprotectin was lower, suggesting therapeutic effect. This was further suggested by endoscopy score improvements, quality of life questionnaires and achievement of remission in 63% of the patients. Response rate to treatment was 90% [48].

Resveratrol is a polyphenolic compound found mainly in grapes, berries and peanuts. Two RCTs were conducted to investigate the administration of resveratrol on 50 and 56 patients with UC in 2015 and 2016, respectively. The trial was completed by 49 and 53 patients, respectively. Quality of life, measured by questionnaires, was improved, and

disease activity was reduced in the resveratrol group of UC patients with mild-to-moderate disease. Resveratrol increased the antioxidant capacity and reduced the oxidative stress in this group of patients [40,41].

The main polyphenolic compound of green tea, namely (-)-epigallocatechin-3-gallate (EGCG), was administered as oral Polyphenon E in 19 patients with mild-to-moderate UC. The study was completed by 16 patients, and the remission rate was 53.3% with a drop in the disease activity index after 56 days of therapy. This rate was the same for the low or high dosage groups (400 or 800 mg EGCG daily). Quality of life and endoscopic scores also improved while no serious adverse effects were noted [24].

Pycnogenol® is an extract from the French maritime pine (*Pinus pinaster*) bark that is rich in polyphenols, specifically 70 ± 5% procyanidins. The effect of Pycnogenol® on oxidative stress in pediatric CD patients in remission was studied by measuring several potentially interesting biomarkers such as enzyme diamine oxidase (DAO) and calprotectin. Fourteen CD patients and 15 healthy children completed the study. Pycnogenol® had no effect on markers of inflammation (CRP, calprotectin) or disease activity index, but it reduced oxidative stress. It also increased DAO which could be beneficial to these patients [51].

Silymarin, a phytochemical isolated from an extract of *Silybum marianum* seeds, demonstrated anti-inflammatory effects in experimental studies. It was investigated in an RCT of 80 UC patients. Only 70 patients completed the study, and 38 of them in the silymarin group showed an improvement in disease activity index and erythrocyte sedimentation rate. In the same group, 33 of the 38 patients also had increased hemoglobin levels after 6 months of treatment. In contrast, the placebo group did not have significant alterations of these parameters. Thus, silymarin supplements were recommended to maintain UC in remission [38].

Tormentil (*Tormentilla erecta*) belongs to the *Rosacea* family of plants and contains high amounts of tannins. A tormentil extract was used in a controlled trial to verify its safety, side effects and potential impact in 16 UC patients. The trial was completed by 15 patients whose disease activity was reduced. These patients were also able to lower steroid dosages. Safety and tolerability of tormentil extract was also verified [46].

An extract of *Tripterygium wilfordii Hook F.* called T2 was administered to 20 CD patients for 3 months to conduct a clinical trial. Biopsies were taken before and after the intervention, but no other clinical data was provided. Treatment with T2 seemingly ameliorated mucosal inflammation and promoted mucosal healing. Histology also showed upregulation of Foxp3+ protein expressing regulatory T-cells and interleukin(IL) 10 with lowered levels of proinflammatory Tumor Necrosis Factor alpha (TNF-a) [52].

Pine resin was applied as an herbal remedy in ancient China. Ecabet sodium has been isolated from it and used for gastritis and gastric ulcer. Seven patients with mild-to-moderate UC were recruited, with 6 of them completing a trial of ecabet sodium enemas administered twice per day for two weeks. Statistically significant improvements were reported in disease activity index and endoscopy. However, this trial had no control group or blinding, thus limiting its power [53].

A herbal combination of myrrh, chamomile flowers and coffee charcoal was compared with mesalazine. This RCT was conducted for 12 months, and the ability to maintain remission in UC patients was studied. Initially, 97 patients were recruited and 82 completed the study. Non-inferiority for the use of this herbal combination was proven in comparison to mesalazine, with a safe and tolerable profile warranting further investigation [32].

A systematic review and meta-analysis reviewed 5 RCTs and 15 non-randomized clinical trials. These RCTs have been meta-analyzed by this review [29,34–37]. The effectiveness of isolated phytochemicals or plant extracts derived from cannabis on IBD patients, delivered in various forms and modes of administration, i.e., orally, sublingually or by inhalation as pills, essential oils, teas, cigarettes or vapors, was reviewed. Significant improvement was reported in quality of life and maybe in reduction of hospital stays, while cannabinoids did not seem to induce remission or changes in inflammatory biomarkers.

More uniform trials with different and discrete doses of substances like cannabidiol or tetrahydrocannabinol and outcomes like inflammatory markers, endoscopy, disease activity index, adverse events and quality of life questionnaires are needed. Until then, caution is recommended, and cannabinoids should be reserved for patients with low quality of life or as an adjunct to established medication as suggested by the authors [56].

Oligofructose and Inulin or FOS are phytochemicals that have been studied in IBD patients as complementary medicine. Three included clinical studies documented the results of administering FOS supplements to a total of 146 recruited CD patients [21,47,54]. Two other studies evaluated FOS given to 50 UC patients [23,55]. FOS supplement Synergy1® was given in 4 studies, and in 1 CD study, Prebio 1® supplement was used. In UC patients, the studies concluded that gut microbiota composition and fecal calprotectin levels were improved without having evident clinical significance [23,55]. Combined with mesalazine, FOS can be effective and safe. Initially, small open label studies suggested that CD activity decreased and intestinal bifidobacteria counts increased [54]. Conversely, in a later RCT, 103 CD patients experienced more functional gastrointestinal symptoms receiving FOS supplements without clinical benefit [21]. Moreover, it was proposed that FOS supplements did not provide benefit to CD patients but could protect at-risk individuals like their healthy siblings [47].

The addition of probiotics, i.e., live microbes such as *Bifidobacterium longum*, to FOS creates supplements known as synbiotics. A combination of Synergy1® with *Bifidobacterium longum* increased bifidobacteria populations while reducing IL-1a and TNF-a in intestinal tissues. This was associated with clinical benefits for UC patients, as shown in an RCT with 18 active UC patients [26]. Similarly, the administration of this synbiotic to CD patients for 6 months showed a TNF-a reduction along with microbiota composition, clinical symptoms and histology improvement [43].

The phytochemical with the most included studies regarding its application for IBD treatment is curcumin. As it is a well-known food additive with anti-inflammatory and antioxidant properties, it seems logical to explore its potential as a therapeutic agent for IBD. A pilot study of curcumin for UC and CD showed improvements in proctitis and inflammatory markers [50]. Another pilot study of curcumin use by pediatric IBD patients indicated that curcumin decreased relapse and recurrence rates with clinical and endoscopic disease activity index improvements [49]. Several RCTs that were conducted reached the same conclusions with statistical significance [20,28,31,33,39,44]. Two of them utilized novel curcumin derivatives, like Theracurmin® or bio-enhanced curcumin that exhibit higher bioavailability [20,44]. In contrast to this, another RCT demonstrated no statistically significant effect on IBD patients with lower dosages of curcumin, suggesting a dose dependent effect [30]. Some RCTs also report improvements in self-reported quality of life [33,39]. The aforementioned studies ratify curcumin's safety and lack of serious adverse events. Special mention must be made to a study investigating the use of NCB-02, a curcumin enema that displays similar results but without statistical significance [42]. A multicenter RCT reported that a higher proportion of postoperative CD patients receiving curcumin experienced endoscopic but not clinical recurrence vs. placebo, with no difference in quality of life [22]. Ultimately, two systematic reviews that reviewed the previously mentioned studies, confirm that curcumin as an adjuvant therapy for IBD is promising [57,58]. One of them conducted a meta-analysis and verified that curcumin improved UC remission, clinical and endoscopic response rates. It must be noted that statistical significance was reached only for improved UC clinical remission odds [58]. Since there is high variability among trials, better designed clinical trials are needed to establish optimal formulations and doses of curcumin for the treatment of IBD [57].

4. Discussion

4.1. Phytochemicals

4.1.1. Classification of Compounds

Phytochemicals (secondary metabolites) can be described as a class of compounds extracted from plants that display bioactive properties without being nutrients. They have numerous effects such as antioxidant, anti-inflammatory and anticancer. These effects depend on the concentration of each phytochemical in tissues, lumens or plasma. Comprising an enormous list of variable biochemical structures and characteristics, classification of these substances in groups is essential for further study. Broad categories are alkaloids, phenolics, organosulfur and terpenoids [59]. Further subdivision based on biogenesis or structure is possible. This results in the following classes of phytochemicals: (a) Polyphenols that include flavones, isoflavones, flavonols, anthocyanins, lignans, phenols, stilbenes, tannins and coumarins; (b) carotenoids such as beta-carotene, lutein, cryptoxanthin and zeaxanthin; (c) glucosinolates; (d) polysaccharides including cellulose, pectins, gums, arabinoxylans, oligosaccharide, inulin and oligofructans; (e) lectins; (f) terpenes; (g) betalains; (h) capsaicinoids with the main one being capsaicin; (i) polyacetylenes; (j) allium compounds mainly methiin, propiin and isoalliin; (k) alkaloids that include well-known substances such as caffeine, morphine, nicotine, irinotecan, berberine, oxycodone, papaverine and (l) chlorophyll [7,60].

4.1.2. Phytochemical Administration and Delivery in IBD Patients

The use of phytochemicals in the form of herbal preparations, plant extracts or supplements, if effective, is of great value. The study of an effective extract can guide the research of its constituent phytochemicals to isolate the more potent ones [13,14]. In a similar way, inclusion of specific vegetables, legumes, fruits or grains as part of dietary consumption is a useful way to deliver anti-inflammatory and antioxidant phytochemicals to patients. Bioavailability in this mode of administration can be low. However, beneficiary effects have been noted for IBD patients following specific diets such as CDED, low-FODMAP and others [61–63]. A confounding factor is that these diets also lower processed food intake, an independent variable of improved gut homeostasis. Also, synergistic boost of phytochemical action, e.g., by co-administration of probiotics and prebiotics, has been proposed for many diseases. Synbiotics, as some authors have been calling them, are under active research [64]. Additionally, UC and CD have a number of pathogenetic and clinical differences that indicate their research as separate entities regarding phytochemical use. It is understandable that substances with proven antioxidant, anti-inflammatory or antibacterial effects in vitro or in animal IBD model studies would progress through preclinical trials to reach the stage of validation by RCT.

4.2. IBD

4.2.1. Pathophysiological Pathways of Inflammation and Oxidative Stress

Genetic factors appear to play an important role in IBD pathogenesis. Multiple genes are reported to be associated with increased risk for IBD. However, aside from the genetic factors, gut microbiota imbalance, environmental factors and immunological abnormalities are implicated in the pathogenesis of IBD [3].

Gut microbiota seems to have an important role in the initiating events leading to IBD, as illustrated in the difference of gut microbiota composition between healthy study participants and IBD patients [65]. Although genetic background is considered a major part in the pathogenesis of IBD, recent studies in twins, with one healthy twin and the other an IBD patient, demonstrate the importance of environmental factors on the onset of IBD. Specifically, the differences in gut microbiota between the twins seem to explain why one twin suffers from IBD whereas the other does not [66]. The use of antibiotics leads to changes in the composition of gut microbiota and is also described as an initial part in the pathogenesis of IBD [67]. Furthermore, changes in diet may induce inflammatory responses leading to IBD onset [66].

Studies have further analyzed these gut microbiota imbalances, known as dysbiosis. *Clostridium* spp. was significantly increased in IBD patients, whereas *Roseburia* spp. and *Phascolarctobacterium* spp., though abundant in healthy individuals, remained significantly low in IBD patients [68]. *Roseburia* enhances the production of regulatory T-cells, thus expressing an anti-inflammatory effect in the intestinal tract [69]. *Phascolarctobacterium* produces propionic acid, a short-chain fatty acid with known anti-inflammatory effects [70]. The significantly lower concentration of both bacteria in the gut microbiota of IBD patients may contribute to the disease's etiology. Furthermore, *Clostridium leptum* group, a major bacterial group of gut microbiota, shows differences between healthy individuals and IBD patients in remission. *Faecalibacterium prausnitzii*, a dominating bacteria of *Clostridium leptum* group, show lower concentration in gut microbiota of IBD patients with both active disease and disease in remission [71,72]. Moreover, low concentration of *F. prausnitzii* in the ileum of surgically treated patients with IBD is a risk factor for endoscopic recurrence. As a result, *F. prausnitzii* has shown promise when administered as a probiotic. It appears to protect IBD patients from relapse due to the anti-inflammatory effects that have been reported both in vitro and in vivo [73].

Recent articles on IBD epidemiology show a significant increase of CD's prevalence in the developed world, as a result of progressive industrialization [74]. This fact underlines the crucial role that environmental factors play in IBD pathogenesis. Diet remains a major risk factor. High intake of fruits and vegetables is associated with a reduced risk of CD [75], whereas high intake of fatty and sugar-rich foods is associated with an increased risk of CD [76]. Moreover, artificial food additives seem to worsen intestinal inflammation as they interfere with the function of the gut barrier [75]. Another study shows that diets that contain high levels of animal protein induce a proinflammatory macrophage response [77]. Other environmental factors, implicated in the pathogenesis of IBD, are appendectomy, medications or other iatrogenic factors, psychological stress and smoking [78]. Although smoking worsens CD, it seems to produce a protective effect for UC, mainly due to the protective inhibitory effects that nicotine has on T-helper 2 cell function [74].

Immunological abnormalities in IBD patients result in epithelial damage. The main factors implicated in epithelial damage are abnormal mucus production and defective reparative mechanisms. Further expansion of inflammation is driven by intestinal flora with the involvement of immune cells that infiltrate into the lamina propria. Those cells include B-cells, T-cells, macrophages, neutrophils and dendritic cells. Immune regulation, which is a major factor for a correct immune response, remains defective, which leads to uncontrollable inflammatory response [79,80]. Consequently, high levels of proinflammatory cytokines in local tissues, such as TNF-a, IL-1b, interferon gamma and cytokines of the IL-23/T-helper 17 (Th17) pathway, are produced [81,82].

Oxidative stress (OS) may lead to damage of the mucosal layer and bacterial invasion, stimulating the immune response that initiates IBD [83]. Although detailed pathways in IBD remain unclear, OS could be activated by environmental factors that include chemotherapy, radiation, smoking, drugs and alcohol [84]. High alcohol intake directly impairs the mucosal barrier, resulting in IBD [85]. High iron and copper intake, as well as fatty acids, increase the level of OS in the gastrointestinal tract [86]. Other chemical substances like acrylamide, a chemical included in snacks, may trigger OS that leads to IBD [87]. Conversely, diet-derived antioxidants can modulate inflammation and gut microbiota [88]. Phytochemicals interact with the intestine by ameliorating oxidative stress, regulating cytokines, modulating gene expression and signaling to restore intestinal permeability [89,90]. By exerting antioxidative and antimicrobial actions, they may affect the structure of gut microbiota [91–94].

4.2.2. Current Practice for IBD Treatment

IBD's severity can vary between individuals, and complications such as bowel perforation or obstruction, failure to thrive and increased cancer risk are among the notable ones. Therapy for IBD comprises medical agents/pharmacotherapy that include aminosalicylates

(mesalazine or sulfasalazine), corticosteroids (prednisone), immune system modulatory agents (azathioprine), cell therapy, exosome therapy and biologic agents/biologics (infliximab), with surgical intervention reserved for complications of IBD or as a therapeutic modality when necessary [95–99]. General measures such as lifestyle changes, dietary interventions and patient education on IBD as a disease can improve outcomes. Recent advances in biologics and new therapeutic strategies aim to achieve remission and prevent relapses. By modifying the disease course, a new concept is to promote mucosal healing as a treatment goal. This can be monitored by measuring specific biomarkers and by endoscopy. Several studies have demonstrated the benefits of these approaches with improved overall outcomes for patients [97,100].

Some patients can be non-responders to one or more of these pharmacological agents and even stop responding secondarily, after initial successful use of a specific agent. Side effects induced by the usage of the aforementioned agents can be rather severe [100]. Therefore, discovering novel modalities for the treatment of IBD remains a fervent field of research [101].

4.3. Antioxidant and Anti-Inflammatory Pathways Targeted by Phytochemicals for the Treatment of IBD

Phytochemicals and plant extracts target activated inflammatory and OS pathways in patients suffering from IBD (Figure 6). These substances seem to reverse or counterbalance the activated damaging pathways in various ways and are presented separately for each compound.

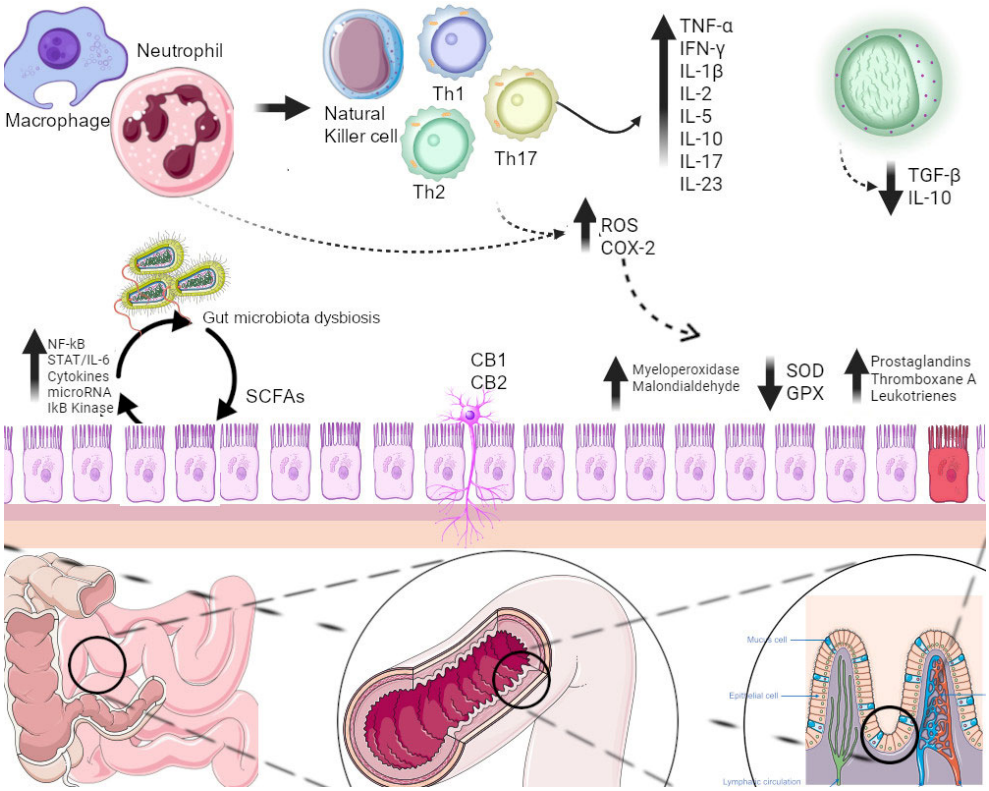


Figure 6. Various inflammatory and oxidative stress pathways activated in patients with IBD. Phytochemicals and plant extracts target these pathways. CB1-2: cannabinoid receptor 1-2, COX-2: cyclooxygenase-2, GPX: glutathione peroxidase, IFN-γ: interferon gamma, IL: interleukin, NF-kB: nuclear factor kappa B, ROS: reactive oxygen species, SCFAs: short-chain fatty acids, SOD: superoxide dismutase, STAT: signal transducer and activator of the transcription factor, TGF-b: transforming growth factor b, Th1-17: T helper 1-17 cells, TNF-a: tumor necrosis factor a.

Plantago ovata seeds are used as a form of dietary fiber, also known as *Ispaghula* seeds [25]. These are fermented and degraded by the anaerobic bacteria along the intestine to yield large amounts of short-chain fatty acids (SCFA), mostly butyrate and acetate. Diminished b-oxidation of luminal butyrate deprives the colonic microbiota of its preferred fuel and also results in energy deficiency of colonic epithelial cells. This has also been implicated in the pathogenesis of UC, as shown in rat studies [102]. Butyrate also inhibits the production of some cytokines and lowers the transcription of the nuclear factor kappa B (NF-kB) factor while improving the health of the gut microbiota [103]. Cancer protective effects of butyrate have also been described in a rat model [104]. These effects have also been researched in butyric acid supplements that can modulate the gut microbiota but were deemed mostly ineffective on IBD patients as shown in several studies [105–107]. Since butyric acid is not strictly a phytochemical, although it is a product of fermentable plant fiber, we excluded these studies [107].

Plant essential oil supplementation to lower prostaglandin E2 and thromboxane A concentrations in the gut has been investigated [27]. Increased concentrations of these inflammatory eicosanoids in biopsies of active UC patients have been documented. The arachidonic acid inflammatory pathway resulting in the production of prostaglandins, thromboxane and leukotrienes has been associated with UC [108]. Thus, gamma-linolenic acid found in evening primrose essential oil that lowers arachidonic acid release was selected to target this pathway [109].

The regulation of pathways of lipid metabolism or oxidative stress in immune-mediated diseases by microRNAs is a field of research receiving a lot of attention. In IBD, microRNAs are implicated in intestinal barrier function regulation as well as inflammatory pathways such as the NF-kB, the signal transducer and activator of the transcription (STAT)/IL-6 and Th17 signaling pathway. Phytochemicals have been shown to modulate microRNA expression [110,111]. Mastiha is a plant extract with anti-inflammatory and lipid lowering properties [112]. The results after using it as a supplement in IBD patients indicate that it appears to regulate circulating levels of microRNA-155, a critical player in the differentiation of Th17 cells and other pro-inflammatory cells responding to TNF-a and interferons [19].

Berberine has anti-inflammatory effects as described in animal studies, along with antioxidant and anti-cancer properties [113,114]. Another interesting property, also found in other bioactive phytochemicals of interest in IBD, is that it maintains high concentration inside the lumen of the gut with low systemic absorption. In contrast, another study showed that berberine did not alter gut tissue inflammation biomarkers COX-2 and NF-kB or cell proliferation marker Ki-67. As expected, plasma cytokine levels like TNF-a, IL-6 and IL-8 were also not altered by berberine administration [45].

Anthocyanins that have anti-inflammatory and antioxidant properties seem to attenuate the course of colitis in animal models [115–117]. Macrophages and neutrophils produce ROS in the inflamed bowel in IBD. The antioxidant system of the intestine is overwhelmed and thus potential antioxidants, such as anthocyanin rich compounds, have been investigated for their potential therapeutic effect.

Resveratrol, a polyphenolic flavonoid substance, has antioxidant and anti-inflammatory effects as verified by experimental models for colitis, where oxidant/antioxidant balance appears to play an important role in pathogenesis [118]. Several articles indicate that resveratrol decreases oxidative stress, increases antioxidant enzyme concentration in tissues and decreases inflammatory biomarkers in animal models of UC [119]. Other experimental studies showed that resveratrol reduces colonic tissue malondialdehyde and myeloperoxidase but increases superoxide dismutase (SOD) and glutathione peroxidase (GPX) activity while it inhibits collagen I synthesis in IGF-1-stimulated fibroblasts [120,121].

Polyphenon E—EGCG is a part of the catechin family of polyphenols contained in green tea. This family of phytochemicals has been extensively studied in regard to anti-inflammatory and antineoplastic effects due to its potent antioxidant properties. EGCG has an effect in preventing NF-kB nuclear translocation by the inactivation of IkB kinase.

This suppresses production of cytokines, inflammatory enzymes and inflammatory protein kinases while upregulating anti-inflammatory pathways [122,123].

Procyanidins and other phenols in Pycnogenol® display various biomodulating, antineoplastic and antioxidant effects such as inhibition of NF-kB and cyclooxygenase stimulation of nitric oxide (NO) synthase and antihypertensive effect by inhibition of angiotensin-converting enzyme [124–126]. It was shown that it increased SOD and GPX antioxidant enzymes while it reduced oxidative damage to proteins and lipids. It also increased DAO after 5 and 10 weeks of Pycnogenol® administration. DAO is found primarily in the mucosa of the gut and is a marker of histamine intolerance and also of disease activity. It inversely correlates with small intestine barrier permeability [51].

Silybinin is the main component of silymarin flavanolignans, the extract of a species of thistle (*Silibum marianum*). Reports from experimental murine and rat models of colitis provide evidence for immune-mediated intestinal wall healing with reduction in TNF-a, NF-kB and intereleukin-1b and also in disease activity [127–129].

Tormentil extract contains tannins, mainly agrimoniin, pedunculagin, laevigatin B and F found in the *Tormentillae rhizoma*. The mechanisms of its actions are not fully understood. However, tannins are known to promote wound healing and they have anti-inflammatory and anti-secretory results while their antibacterial properties may regulate the gut microbiota [46].

T2 is a chloroform/methanol extract of *Tripterygium wilfordii* containing triptolide. It is used in China for a variety of immune mediated disorders such as rheumatoid arthritis. Triptolide inhibition of NF-kB and TNF-a signaling pathways, suppression of IL-6/STAT3 signaling pathway and down-regulation of IL-17 has been proven in experimental animal models of colitis [130–132]. Regulatory T-cells modulate the immune response in the intestine by secretion of inhibitory cytokines such as IL-10 and transforming growth factor-b (TGF-b). Their disruption can affect CD and T2 can upregulate Foxp3+ CD4+ T-Cells [52]. It should be mentioned that the safety of *Tripterygium wilfordii Hook F.* remains a matter of significant debate and ongoing research [133].

Ecabet sodium is a pine resin derivative phytochemical. Its anti-inflammatory effects are thought to come from its affinity to adhere to gastric mucosa, epithelial cells and ulcer regions. It enhances defensive factors of the mucosa such as NO systems, prostaglandins like PGE2 and the mucin pathway whose depletion is related to UC pathogenesis [134–137].

Herbal preparations used as IBD complementary or alternative therapies are being utilized more often. An interesting example can be made out of the herbal combination of myrrh, chamomile flowers and coffee charcoal, which has been used for 50 years as a simple remedy for diarrhea. After considering the individual constituents and their known and validated effects from animal and experimental studies, it was concluded that the herbal preparation ought to target multiple pathways. Furanosesquiterpene, commiporic, commiphorinic acids and volatile oils contained in myrrh resin have demonstrated anti-inflammatory and antibacterial effects in animal studies. Inhibition of leukotriene production is hypothesized as the substrate. Chamomile tea or dry extract contain flavonoids, hydroxycoumarines and many other phytochemicals which are known for their anti-inflammatory, spasmolytic and antimicrobial properties. Finally, coffee charcoal is used for its antibacterial and absorbing properties. After confirmation of the preparation's beneficial effect, further clarification of individual phytochemical bioactive substances and development can be undertaken [32].

Cannabis consists of many phytochemicals like alkaloids, glycoproteins, terpenoids, flavanoids and cannabinoids. Among them, cannabidiol, tetrahydrocannabinol and cannabigerol are the most investigated bioactive substances for various diseases [138,139]. Cannabidiol and tetrahydrocannabinol interact with the endocannabinoid system to produce their effects. Cannabinoid receptor 1 (CB1) and 2 (CB2) are found in the brain but also in the submucosal and myenteric nerve plexus of the intestine, with the latter also appearing in immune system cells [140]. Cannabinoids also target various other receptors in a complex process that must be further clarified. Endogenous and phytochemical

cannabinoids acting as CB2 agonists or fatty acid amide hydrolase inhibitors display reduced inflammation in colitis animal models as demonstrated by recent studies [141]. CB2 also appears to be upregulated in UC patients [142].

Inulin-type fructans or FOS have been suggested to be effective in human IBD as prebiotics, ultimately enhancing the gut microbiota by stimulating the growth in protective bifidobacteria and *F. prausnitzii* populations. They are non-digestible polymers of fructose that in animal models of colitis decreased disease activity and decreased NF-kB. In addition, fermentation of such prebiotics produces SCFAs that enhance intestinal epithelial barrier integrity. Furthermore, in combination with FOS, bacteria such as *B. longum* taken from healthy subjects appear to have a clinical benefit [143,144].

Curcumin is a bioactive phytochemical compound isolated from the well-known plant turmeric (*Curcuma longa*). It has been used as a food additive or spice with antioxidant, anti-inflammatory and antineoplastic properties [145–147]. In vitro experimental studies on human colon cell lines provide evidence that curcumin inhibits carcinogenesis and inflammation through reduction of NF-kB, cytokines and cyclooxygenase-2 activation [148]. Similar findings have been found in animal model studies [149,150].

5. Conclusions

Phytochemicals present a promising scientific field for researchers from many disciplines that can lead to the discovery of useful therapeutics. IBD's prevalence is increasing, and current strategies focus on mucosal healing, limiting side effects and providing higher quality of life to patients suffering from this disease. Experimental studies and herbal extract studies on IBD can guide phytochemical research and, in parallel, elucidate the relevant anti-inflammatory, immunoregulatory, antimicrobial or antioxidant mechanisms involved. Pilot studies exploring the safety and efficacy of isolated compounds are essential and can later lead to well-designed large scale RCTs for confirmation. Phytochemicals in the form of curcumin, *Plantago ovata* seeds, EGCG, silymarin, resveratrol supplements or an herbal preparation of myrrh, chamomile and coffee charcoal have evidence from human clinical trials and RCTs supporting their safety and beneficial effects. Cannabinoids improve quality of life but not IBD outcomes. FOS do not seem to improve the status of IBD patients. However, the addition of probiotics like *B. longum*, along with FOS promotes healthy composition of the gut microbiota and appears to have a clinical benefit according to included trials. Promising results may be apparent in small trials for other phytochemicals like mastiha, anthocyanins, berberine, tormentil, T2, ecabet sodium and Pycnogenol®, but further well-designed trials are needed to support further usage in IBD patients. There are many confounding factors involved in the study of IBD, including variability in severity of disease or medications used. Use of phytochemicals and plant extracts exhibits variability in formulations, preparations and dosages. Standardized, multicenter RCTs with proper protocols for the aforementioned phytochemicals must be designed.

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