Universidade de Lisboa

Faculdade de Farmácia

Plants and Plant Products in Treatment of Ulcerative Colitis

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Monografia orientada pela Professora Doutora Rita Maria Olivença Trindade dos Santos Serrano, Categoria Professora Auxiliar

Mestrado Integrado em Ciências Farmacêuticas

2022

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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2022

This thesis should be cited as:

Kuriqi, I. (**2022**). *Plants and Plant Products in Treatment of Ulcerative Colitis*. MSc. Thesis, Faculdade de Farmácia, Universidade de Lisboa, Portugal.

Resumo

A doença inflamatória intestinal (DII) é uma das doenças graves que influenciam a saúde e a qualidade de vida de milhões de pessoas em todo o mundo. É dividida em duas principais doenças Crónicas: colite ulcerosa (CU) e doença de Crohn (DC).

A etiologia da DII ainda não é conhecida. No entanto, diferentes estudos mostraram que esta é afetada por fatores imunológicos, genéticos e ambientais. Tanto a CU como a DC são caracterizadas por inflamação crónica do trato gastrointestinal. Na CU, a inflamação começa distalmente no reto e estende-se proximalmente ao cólon; a DC pode afetar todo o trato gastrointestinal, da boca ao ânus.

Com foco na CU, o Canadá tem a maior incidência e prevalência, seguido pelos EUA, países escandinavos, Finlândia, Reino Unido e Austrália.

A terapia convencional da CU consiste em aminossalicilatos, corticosteroides e imunomoduladores. Devido aos seus imensos efeitos adversos e elevado custo, essas opções terapêuticas não são suficientemente bem-sucedidas e levam ao insucesso do tratamento após algum tempo. Acredita-se que os produtos à base de plantas e plantas medicinais sejam uma importante alternativa para o tratamento desta condição.

Este estudo tem como objetivo rever a literatura sobre plantas e produtos vegetais que podem desempenhar um papel no tratamento da colite ulcerosa. Inclui os últimos 20 anos, concentrando-se mais na literatura de 2010 a 2021. Foram publicados muitos estudos experimentais in *vivo/vitro* e ensaios clínicos de plantas de produtos vegetais. Apesar de alguns dos mecanismos de ação das plantas estudadas serem conhecidos. Ainda assim, plantas e produtos vegetais têm resultados significativos em casos de colite experimental ou de ensaios clínicos, cujo mecanismo de ação permanece desconhecido ou merece maiores especificações.

O resultado desta revisão de literatura está organizado em três divisões principais: plantas e produtos vegetais que melhoram a colite experimental, algumas formulações à base de plantas e plantas e produtos vegetais em ensaios clínicos. Existem vários resultados e benefícios obtidos em cada uma dessas categorias. É de salientar a formulação à base de plantas KM1608, derivada de *Zingiber officinale*, *Terminalia chebula* e *Aucklandia lappa*. Esta formulação à base de plantas na dose de 600 mg/kg

resultou em melhores parâmetros para muitos índices usados para avaliar a colite experimental induzida por TNBS em comparação com 5-ASA e prednisolona. Portanto, estudos futuros devem concentrar-se mais na terapia de múltiplos alvos, uma vez que apenas uma terapia alvo nestas doenças complexas não obteve sucesso.

É necessário mais investimento na investigação neste campo para obter resultados satisfatórios para construir uma *guideline* de tratamento mais segura e bem sucedida para a colite ulcerosa.

Palavras-chave: colite experimental, formulações fitoterápicas, plantas medicinais, produtos vegetais, Colite ulcerosa.

Abstract

Inflammatory bowel disease (IBD) is one of the serious diseases influencing millions of people`s health and quality of life worldwide. It is divided into two main chronic diseases: ulcerative colitis (UC) and Crohn's disease (CD).

The etiology of IBD is not known yet. However, different studies have shown that it's affected by immunological, genetic, and environmental factors. Both UC and CD are characterized by chronic inflammation of the gastrointestinal tract. In UC, inflammation starts distally in the rectum and extends proximally to the colon; the CD can affect the entire gastrointestinal tract from the mouth to the anus.

Focusing on UC, Canada has the highest incidence and prevalence, followed by the USA, Scandinavian countries, Finland, the UK, and Australia.

Conventional therapy of UC consists of aminosalicylates, corticosteroids, and immunomodulators. Due to their immense adverse effects and high cost, these therapeutical options are not successful enough and lead to a failure in treatment after some time. Medicinal plants and plants product is believed to be an important alternative to treat this condition.

This study aims to review the literature on plants and plant products that can play a role in treating ulcerative colitis. It includes the last 20 years, concentrating more on literature from 2010 to 2021. Many published experimental studies in vivo/vitro and clinical trials of plants and plant products have been recorded. Despite some of the mechanisms of action of the plants studied are known. Still, plants and plant products have significant outcomes in experimental colitis or clinical trial cases, whose mechanism of action remains unknown or deserves further specifications.

The finding of this literature review is organized into three main divisions: plants and plant products that ameliorate experimental colitis, some herbal formulations, and plants and plants products in clinical trials. There are various outcomes and benefits obtained in each of these categories. To be distinguished is KM1608 herbal formulation, derived from *Zingiber officinale*, *Terminalia chebula*, and *Aucklandia lappa*. This herbal formulation at a 600 mg/kg dose resulted in better parameters for many indices used to evaluate TNBS-induced experimental colitis compared with 5-ASA and prednisolone.

Hence future studies should focus more on multiple target therapy since just one target therapy in these complex diseases has failed to succeed.

Further investment in more research in this field is needed to obtain satisfactory results to build a safer and more successful treatment guideline for ulcerative colitis.

Keywords: Experimental colitis, Herbal formulations, medical plants, Plant products, Ulcerative colitis.

Acknowledgments

Thank you to the faculty of pharmacy at the University of Lisbon and all professors during this academic journey. Thank you for all the knowledge and professionalism transmitted.

Thank you to professor doctor Rita Maria Olivença Trindade dos Santos Serrano for her help and immense support throughout the elaboration of this monography.

Thank you to all the friends who helped me adapt quickly to FFUL though having a language barrier initially. Special thanks to my colleague Sofia Teixeira for her kindness, our continued friendly relationship, and inspirative conversations.

Thank you to all the members of pharmacy "Abreu Cardoso" and the hospital pharmacy in "Garcia da Orta" for welcoming me into their friendly working environment and kindly sharing their lifelong experience and professionalism with me during my internship.

Thank you to my fantastic parents and sister Areda for their unconditional love, care, and support. Thank you for being present in my life daily and being a strong source of motivation. Forever grateful to you.

Thank you to my wonderful boys, husband Alban, and son Orhan. For showing a great team in our everyday lives and appreciating time for knowledge and progress. To my sweet and curious Orhan, thank you for converting to your interests in science the busyness of mommy with the books. Thank you to our littlest growing still inside for making it on time to be part of this university "journey." Together not just Portugal but every corner of this world is home.

Nomenclature

Acronyms and Abbreviations

5-ASA	Aminosalicylic acids
AFC	Aerial parts of Fumaria capreolata L.
ANA-1 cells	Mouse macrophage cells
AP	Activator protein-1
Bcl-2	B-cell lymphoma 2
BMDCs	Bone marrow-derived dendritic cells
C57BL/6 mice	Laboratory mouse inbred strain
Caco-2 cells	Cell line derived from a colon carcinoma
CaCo2 cells	Immortalized cell line of human colorectal adenocarcinoma cells;
CD	Crohn`s disease
CMC	Carboxymethyl cellulose
CMT93 cell line	A cell line from an induced carcinoma of mouse rectum;
C-MYC	Oncoprotein
COX-2	Ciclo-oxigenase-2
Cyclin D1	A protein required for progression through the G1 phase of the cell cycle
DAI	Disease activity index
DCs	Dendritic cells
DNBS	Dinitrobenzene sulphonic acid
DSS	Dextran sodium sulfate
EGb 761	Ginkgo biloba extract
GBF	Germinated barley foodstuff prebiotic
GCE	Garcinia cambogia extract
GDNPs	Ginger-derived nanoparticles
GELNs	Grape exosome-like nanoparticles
GG	Guggulsterone
GL-p	Glycyrrhizin natural preparation
GSH	Glutathione
GSPE	Grape seeds proanthocyanidins extract
GTE	Green tea extract
HO-I	Hypoiodous acid
HT-29 cell line	Human colon adenocarcinoma cell line
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
ICAM-I	Intercellular Adhesion Molecule 1
IECs	Intestinal epithelial cells
IKK	Inhibitor of nuclear factor-κB (IκB) kinase

IKK	IkappaB kinase
IL	Interleukin
IN	Indigo naturalis capsules
iNOS	Inducible nitric oxide synthase
IRBSV25/B cell	Syringa vulgaris cell line
IκBα	Inhibitor of nuclear factor kappa B
LDH	Lactate dehydrogenase
LN	Lipid nanosphere
LNs	Lipid nanospheres
LPO	Lipid Peroxidation
LPS	Lipopolysaccharide
MAP	Modified apple polysaccharides solution
MCA-38	Cell Line derived from C57BL6 murine colon adenocarcinoma cells
MCP-1	Monocyte chemotactic protein-1
MDA	Lipid peroxidation
MMP-9	Matrix metallopeptidase
MMX	Multi-Matrix System
MPO	Neutrophil infiltration
MUC-2	Human mucin-2
NF-κB	Nuclear factor-kappa light chain enhancer of activated B cells
NF-κB	Nuclear factor-kB activation
NO	Nitric oxide
NO3/NO2 levels	Nitrate and nitrite levels
NS	Saline-treated colitic group
O2-	Superoxide
PBS	Phosphate-buffered saline
Pcur	Polycurcumin
PEG	Polyethylene glycol
PGE2	Prostaglandin E2
PLS	Noni- polysaccharides
P-selectin	Granular membrane protein and a cellular adhesion molecule
p-STAT3	Phosphorylated signal transducer and activator of transcription
PVH	Prunella vulgaris honey
RAW 264.7 cells	Monocyte/macrophage cell line;
ROS	Reactive oxygen species
SASP	Sulphasalazine
SCFA	Short-chain fatty acids
SciMAT	Science mapping analysis tool
SIRT1	Silent mating type information regulation-1
STAT3	Signal transducer and activator of transcription 3
TAC	Serum total anti-oxidant capacity
TMP	Tetramethylpyrazine
TNBS	2,4,6-trinitrobenzene sulfonic acid
TNF-α	Tumor necrosis factor
UC	Ulcerative colitis

VB	Verbascoside extract
ZO-1	Zonula occludens-1 protein

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1. Introduction

Inflammatory bowel disease (IBD) is one of the serious diseases influencing millions of people`s health and quality of life worldwide. It is divided into two main chronic diseases: ulcerative colitis (UC) and Crohn's disease (CD).

The etiology of IBD is not known yet. However, different studies have shown that it's affected by immunological, genetic, and environmental factors. Both UC and CD are characterized by chronic inflammation of the gastrointestinal tract. In UC, inflammation starts distally in the rectum. It extends proximally to the colon, where CD can affect the entire gastrointestinal tract from the mouth to the anus [1-4].

The map in Figure 1, concentrating on UC, presents the worldwide incidence of UC. Globally, Canada has the highest incidence and prevalence of IBD. Similarly, data show that USA, Scandinavian countries, Finland, the UK, and Australia are among the countries with the highest incidence of UC [5]. Noticeable is the global rise of IBD in newly industrialized countries like South America, Asia, and Africa [6].

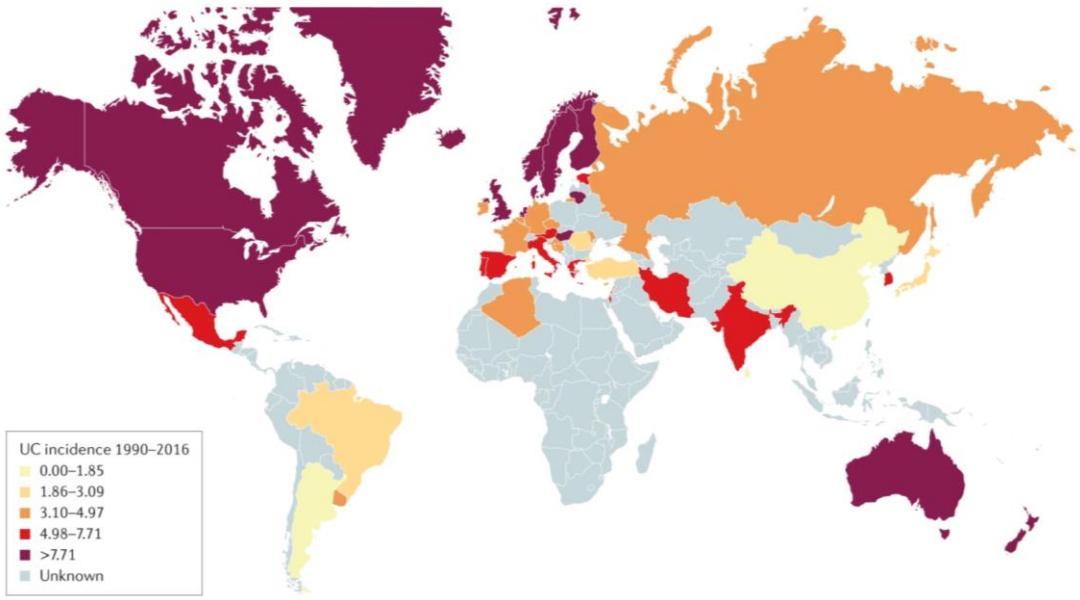


Fig. 1. Global-scale presentation of the UC occurrence per 10^5 habitants from 1990 to 2016, adapted from Kobayashi, et al. [7].

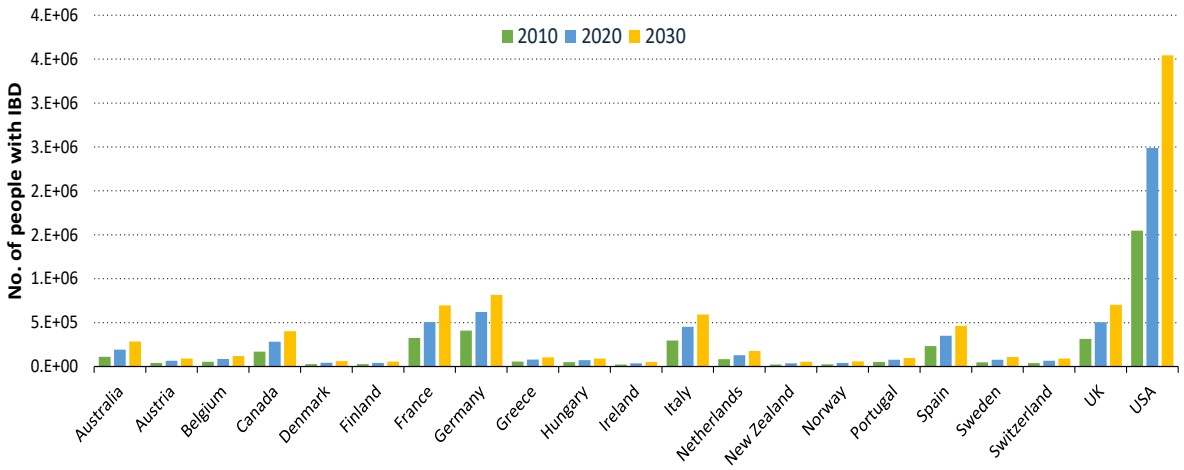


Fig. 2. Different time-scale prevalence of IBD in some of the most affected countries, adapted from Kaplan and Windsor [8].

According to Kaplan and Windsor [8], the population of individuals with IBD in chosen regions in the Western world with currently high IBD prevalence presuming a growth in prevalence from 0.5% in 2010 to 0.75% in 2020 and 1% in 2030 (Fig. 2). According to this assumption, the number of people living with IBD in the Western world in the next ten years might exceed 10 million.

1.1 Diagnosis

The classic manifestations of UC include rectal urgency, abdominal pain, cramping, vomiting, fever, bloody stool, diarrhea, fatigue, and weight loss, a marker of the severity of the disease (Fig. 3)[9-12].

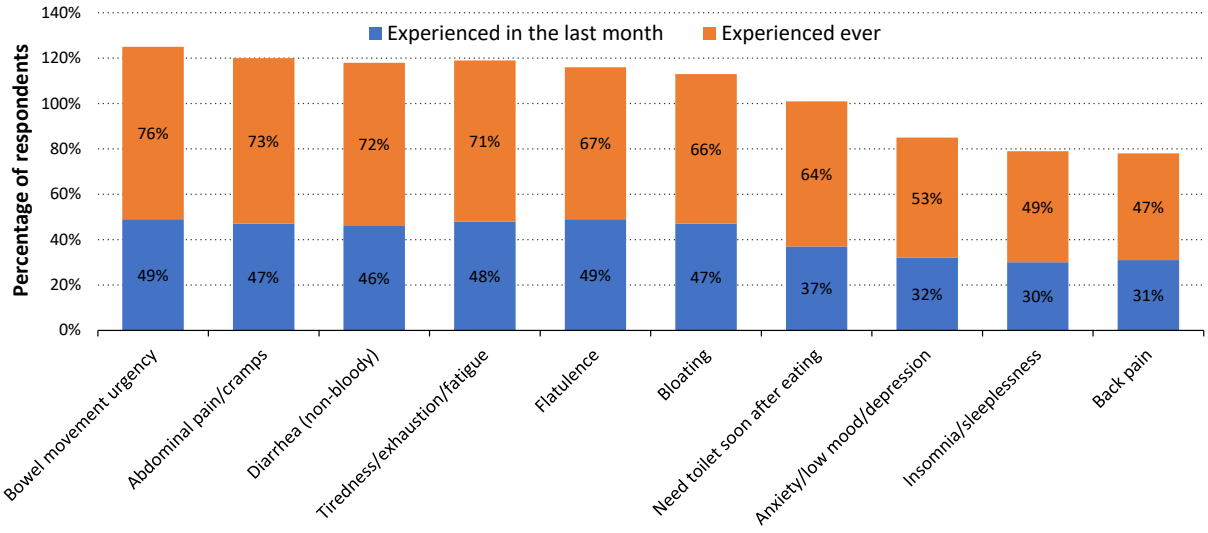


Fig. 3. Presentation of the ulcerative colitis patients worldwide who reported the most common symptoms during 2019, adapted from Rubin, et al. [13].

The genesis of UC is poorly understood, but lack of equilibrium in proinflammatory cytokines such as tumor necrosis factor α (TNF-α), interferon-γ (IFN-γ), interleukin (IL)-1, IL-6, and IL-12 and anti-inflammatory cytokines including IL-4, IL-10, and IL-11, are believed to perform a crucial role in mediating and modulating inflammation [9,14].

There are no particular criteria for the diagnosis of UC. A combination of medical history, clinical evaluation, and typical endoscopic and histological findings is where UC diagnostic is based [15]. It is fundamental to exclude the possibility of infectious etiology, as symptoms of infectious colitis, like bacterial, viral, and amebic causes, overlap with those examined in UC.

However, various biomarkers, such as fecal calprotectin, fecal lactoferrin, and bowel ultrasonography, are progressively used for non-invasive diagnosis and monitoring. Apart from this, it is thought that artificial intelligence holds the potency to increase diagnostic precision in the future. The severity of manifestations a patient face determines the patient's disease activity. Suitable categorization of disease extent and severity determines treatment potency [1,11,15,16].

1.2 Histology

UC histological diagnosis can be determined by combining four main characteristics: 1) mucosal architecture, 2) lamina propria cellularity, 3) neutrophil granulocyte infiltration, and 4) epithelial abnormality.

Change in mucosal architecture refers to crypt architectural abnormalities, decreased crypt density, and alterations in surface topography. Lamina propria cellularity implicates an increase or change in diffusion of cell types present in colorectal mucosa in standard circumstances [17]. Neutrophil granulocyte infiltration refers to neutrophils in lamina propria or the epithelium, which causes cryptitis and crypt abscesses. Neutrophil granulocyte infiltration and epithelial damage specify the disease activity. Epithelial abnormalities involve surface epithelial damage, reduced number of globet cells, and metaplastic changes [1,3,18].

1.3 Treatment targets

The primary treatment for mild to moderately active UC is oral 5-ASA (i.e., 5-aminosalicylic acid). Most patients with mild to moderate UC will respond to 2-3 gr of 5 -ASA [3]. Higher doses can be used in patients who do not respond initially to 2-3 gr of 5-ASA or have severe symptoms. UC patients should be offered a combination of 5-ASA oral and enema [3]. Topical therapy should be added to patients with a partial response to 5-ASA.

In mild to moderate UC, in patients who lack response or are intolerant to oral or/and rectal 5-ASA, corticosteroids, namely prednisolone, are recommended. Apart from conventional corticosteroids (prednisolone), an alternative to mild to moderate UC can also be topically acting oral budesonide MMX and beclomethasone disproportionate [19]. Budesonide MMX has lower systemic side effects when compared to conventional corticosteroids. Budesonide MMX is unrelated to adrenal suppression or a remarkable reduction in bone mineral density. Oral beclomethasone disproportionate at a dose of 5 mg/day has been revealed to be similar to 2.4 g of 5-ASA and has strengthened the effect of 5-ASA when combined with it compared with its effect 5-ASA monotherapy [3].

In moderate to severe UC, oral corticosteroids like prednisolone 40 mg/day gradually lessening over 6–8 weeks are recommended.

Patients who do not manifest any improvement after being treated for two weeks with prednisolone 40 mg/day treatment escalation to thiopurines should be considered.

Thiopurines such as azathioprine, mercaptopurine, cyclosporine, tacrolimus, and methotrexate are better tolerated than long-term corticosteroid therapy.

When thiopurine alternatives are no longer resultative, anti-TNF-α (infliximab, adalimumab, and certolizumab) are recommended.

In cases of bacterial infection during the pathogenesis of UC, adjunctive treatments, antibiotics such as metronidazole, ciprofloxacin, and clarithromycin are used [3,20,21].

1.4 Failure in treatment

UC patients treated initially with 5-ASA can manifest nephrotoxicity; due to this, it is crucial to obtain baseline renal function repeated after 2-3 months and then annually, as the renal disease can be a primary complication of IBD [3].

Patients encounter difficulty administering and retaining enemas when treated with an oral and enema combination of 5-ASA. This difficulty leads to failure in treatment and needs a system to educate and support patients.

In mild to moderate or moderate to severe UC patients under oral corticosteroids therapy can encounter side effects like acne, edema, sleep and mood changes, hypertension, cataracts, glaucoma, glucose intolerance, and dyspepsia [20]. These side effects lead to a failure in treatment with oral corticosteroids.

Related to treatment with thiopurines, though they are better tolerated compared to long-term corticosteroids therapy, there are numerous side effects such as bone marrow suppression with leucopenia and neutropenia, severe hepatic injuries, tremor, hirsutism, hypertension, and gastrointestinal side effects, which lead to interruption of these medications though the failure of this treatment also [20].

The use of anti-TNF-α (infliximab, adalimumab, and certolizumab) biological agents due to their side effects, such as anaphylaxis, chest pain, dyspnea, and headache, has been restricted. Their high cost makes it difficult to use as a treatment [3,20,21].

2. Knowledge Gaps and Motivation

As seen in point 1.4, actual treatment options for ulcerative colitis have many side effects that lead to a failure in treatment and progression. However, there is an urgent need to develop new treatments, natural ones derived from plants, with fewer side effects.

The mechanism of action of some plants is known, but for some plants and plant products that hold significant outcomes in ameliorating UC, their mechanism of action needs to be clarified. Since a plant can hold various active compounds, it is essential to determine which exact compound of an “x” plant is responsible for that mechanism of action.

More research in vitro and in vivo is needed in this area. Since UC is a complex disease, it is crucial not to focus on one target agent therapy but to invest more in multiple target therapy since synergistic combination has shown more effective results.

It is important to gradually step and implement the results obtained from successful herbal formulations studied in experimental colitis into accurate clinical trials. The number of patients participating in clinical trials plays an important role in achieving convincible outcomes on a larger scale.

3. Objectives

This literature review analyzes plants and plant products in experimental colitis, herbal formulations, and clinical trials. Experimental studies in vivo and in vitro in induced colitis in mice models and clinical trials are evaluated to assess the potential of these plants and plant products. Various plant products and herbal formulations with a perspective on the future treatment of UC are outlined. The adverse effects in clinical trials are pointed out. Different plant products entrapped in nanoparticles with encouraging results in treating IBD-related symptoms are reported. The benefits of plant products and herbal formulations in experimental

colitis and clinical trials are compared to determine how essential multiple target therapy is in treating UC due to grouped plant characteristics' capacity to act synergistically.

4. Materials and Methods

4.1 Literature search approach

The systematic literature collection was conducted following the PRISMA guideline [22]. The literature screening consists of two main tasks: publications collection and content analysis. Figure 4 presents the main steps and protocols in conducting the systematic review in this study. The first step involves consolidating literature search and collection, including different types of publications. The Web of Science (WoS), Scopus, PubMed, and Google Scholar were selected as leading search platforms. Language restriction was performed, and English language articles, books, chapters, proceedings, Ph.D. thesis, and guidelines were included. Data were collected for the years 2001-2021.

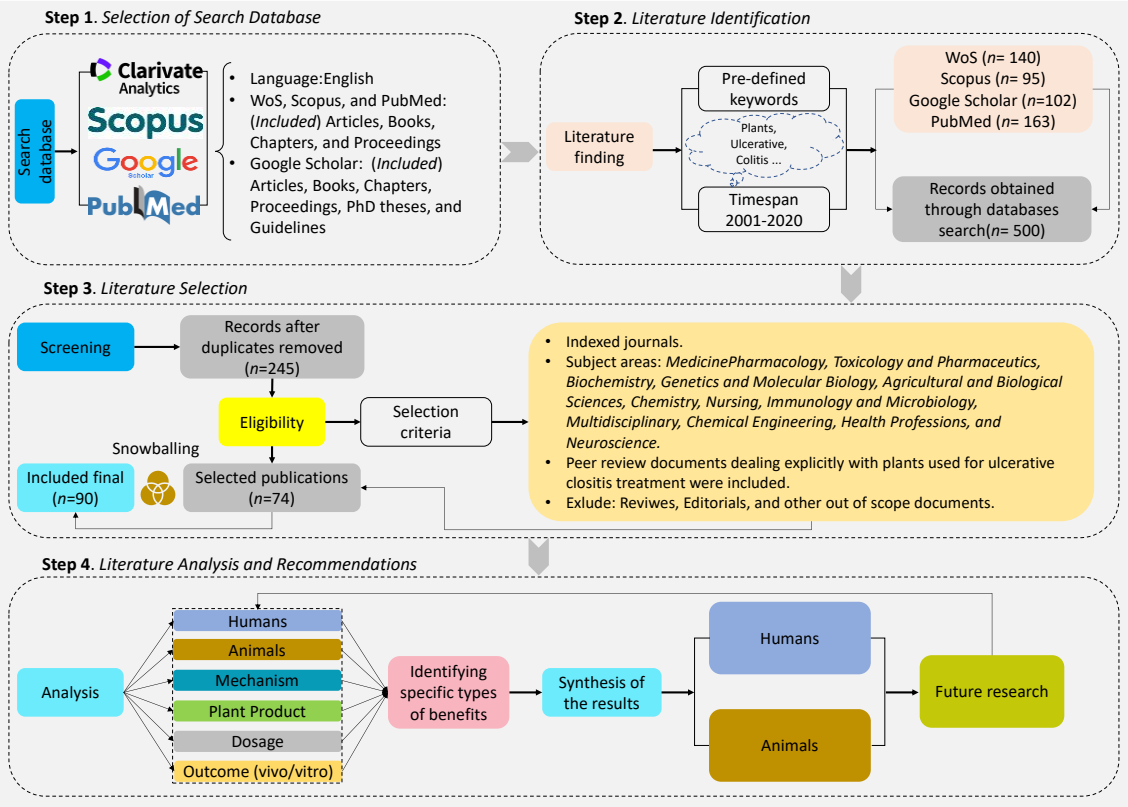


Fig. 4. Flow diagram showing different literature selection and analysis steps following the PRISMA approach.

The search string ‘’TITLE-ABS-KEY’’ was adjusted according to each platform search protocol, using the following search terms:

"Ulcerative colitis," "inflammatory bowel disease," "plants," "plants products," "herbal formulations," "experimental colitis," and "extracts," which were screened for *in vitro, in vivo,* and clinical evidence that evaluated some plants' therapeutic and preventive effects and their product in IBD ulcerative colitis.

The literature search yielded 500 records (i.e., 140 from WoS, 95 from Scopus, 102 from Google Scholar, and 163 from PubMed). After the screening process, the number of records dropped to 245 due to duplicates. After considering the selection criteria (Step 3. Fig. 4.), the total number of records was 90.

4.2 Limitations

Finding the right studies related to a specific topic is difficult because it requires screening dozens of documents scattered among multiple journals and/or databases. Furthermore, large databases' literature search may comprise some statistical bias since it is based solely on database content [22,23]. In addition, many articles used nuanced titles that may contain one or two search terms used in literature sampling. The literature search, at first, based on the pre-defined terms, yielded hundreds of documents belonging to cross-sectional subjects, making the relevant literature identification challenging. Therefore, each route to the full text of the accessible documents was slightly different. Also, only literature in the English language was analyzed; it is acknowledged that some valuable information from literature in other languages might have been missed.

The analyzed literature consisted of peer-review/non-peer-review documents that were available online. Grey literature, such as case reports, was not considered because of limited access and time limitations. The analysis was focused mainly on identifying plants with the most prominent effects. Therefore, in future research, an in-depth analysis is needed to determine the degree of effect for each type of plant.

5. Results

5.1 Bibliometric findings

The number of peer-reviewed publications is an important indicator that evaluates the evolution trend of scientific research. As displayed in Figure 5, the number of publications related to UC topics per year has increased since 2001.

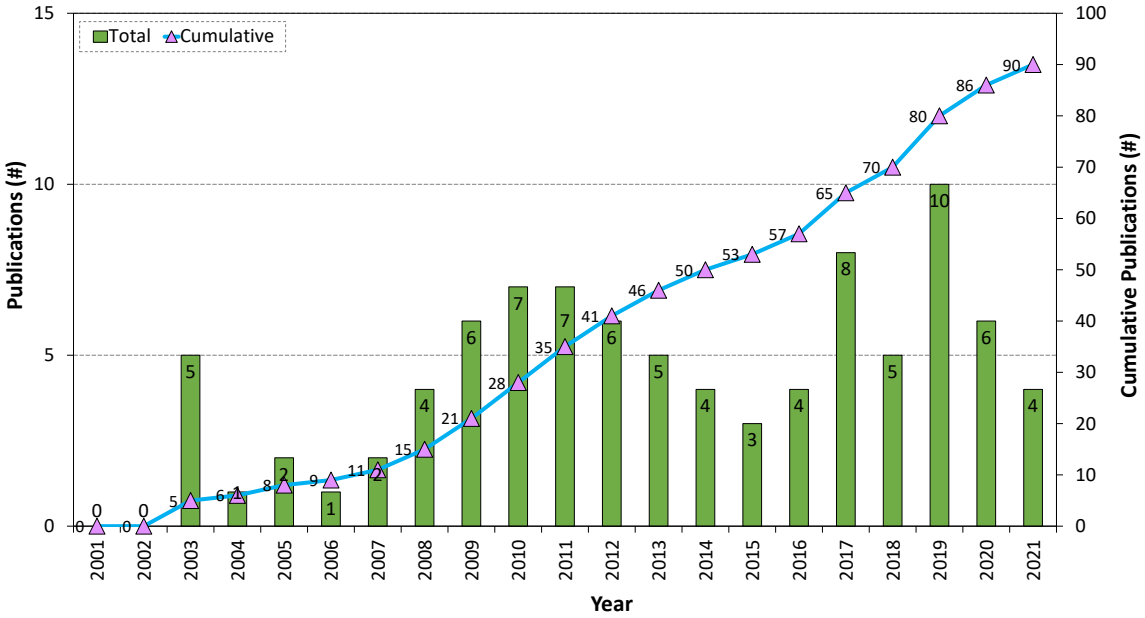


Fig. 5. Annual distribution of publications considered in the analysis.

There were only five publications related to UC in 2003; then, until 2007, there were only eleven. In general, an increase in publications was observed from 2008 on, especially in 2019, representing the year with the highest number of publications on UC. A decline was observed from 2012-to 2015. The reason for this decline is not fully understood. Focusing on the cumulative number of publications (Fig. 5), the UC research has increased from 2001 to 2021 (until July), reaching 990 publications. The geographical distribution of publications regarding analyzed literature is shown in Figure 6. The intensity of the blue color indicates the number of published articles.

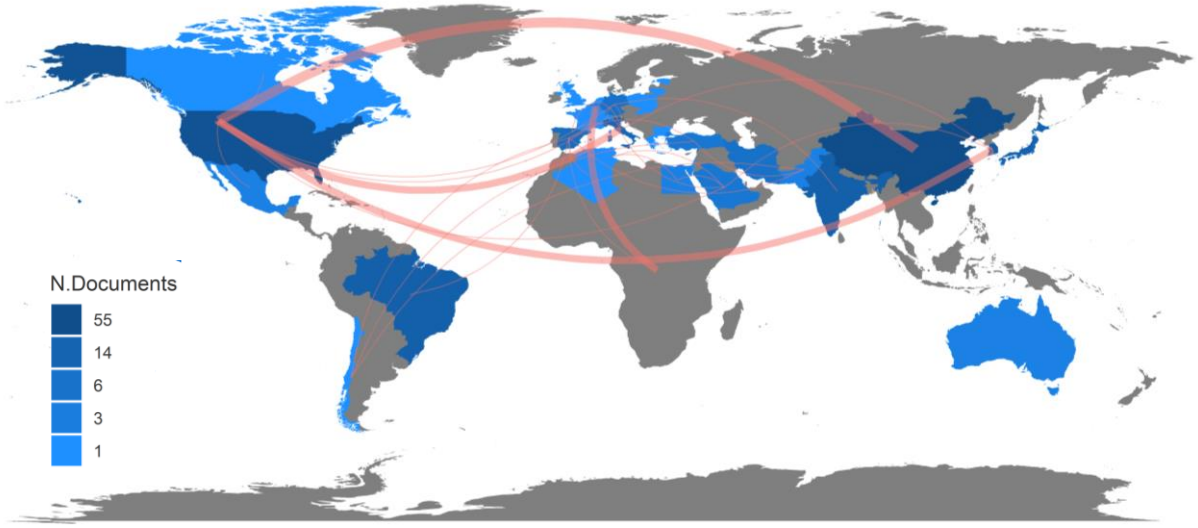


Fig. 6. The geographical distribution of publications numbers on the global scale; the red lines represent the collaboration among countries. The thicker the line, the higher the number of publications among respective countries.

The thickness of the red line indicates the strength of the collaboration based on frequency. The top three strongest collaborations were between the United States and other countries, specifically China, Italy, and South Korea. Based on a Sankey diagram, the three-field plot in Figure 7 shows the connections from the institutions to countries and the most frequent terms. The height of the rectangle nodes is proportional to the frequency of occurrence of a certain institution, country, or term within the collaboration network. The width of the lines between the nodes (gray color) is proportional to the number of connections.

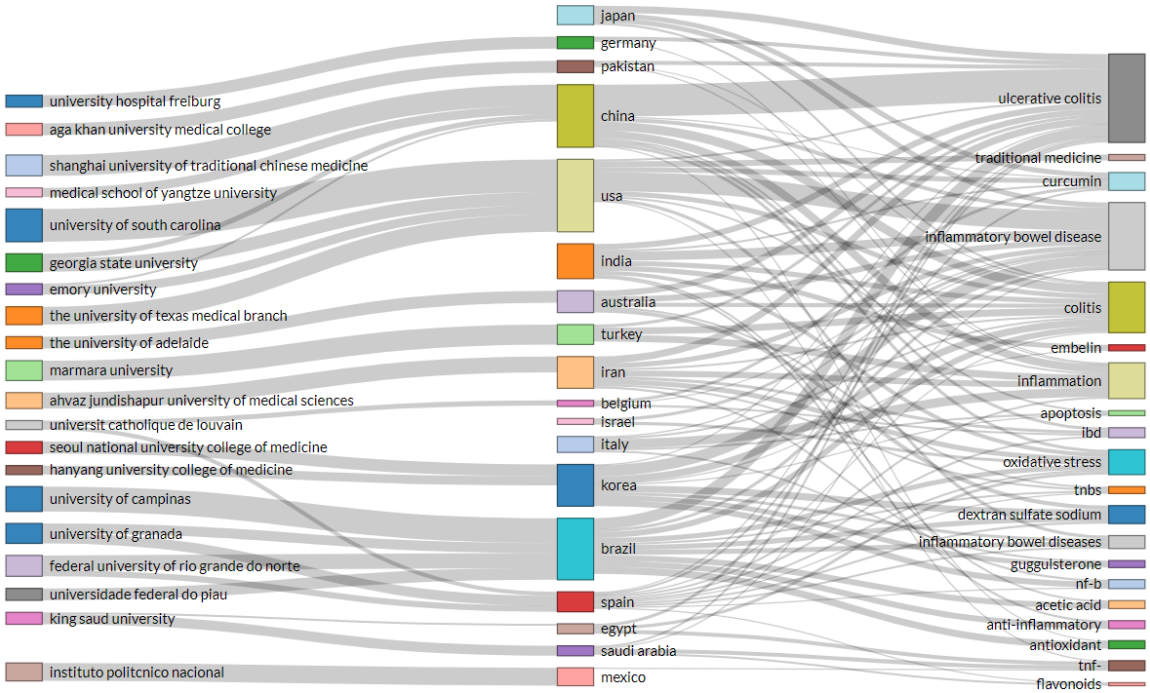


Fig. 7. Three-fields plot shows the most contributing institutions (left) regarding each country (middle) and the most frequent terms (right) in the analyzed literature.

The Figure shows that the United States had the most connections, followed by Brazil and China. The top contributing institution in the United States was the University of South Carolina, followed by the University of Texas Medical branch. In Brazil, the top contributing institution was the University of Campinas, followed by the Federal University of Rio Grande do Norte and the University of Granada. In China, the top contributing institution was the Shanghai university of traditional Chinese medicine, followed by the medical school of Yangtze University.

Concerning the most frequent terms on the right side of the three-field plot, ulcerative colitis was the most frequently used, followed by inflammatory bowel disease. The collaboration network map in Figure 8 shows that the authors are divided into six main clusters. The size of the cylinder indicates the leading Eigenvalues. Eigenvalues represent importance. So, the larger the size of the cylinder, the higher the Eigenvalue it holds.

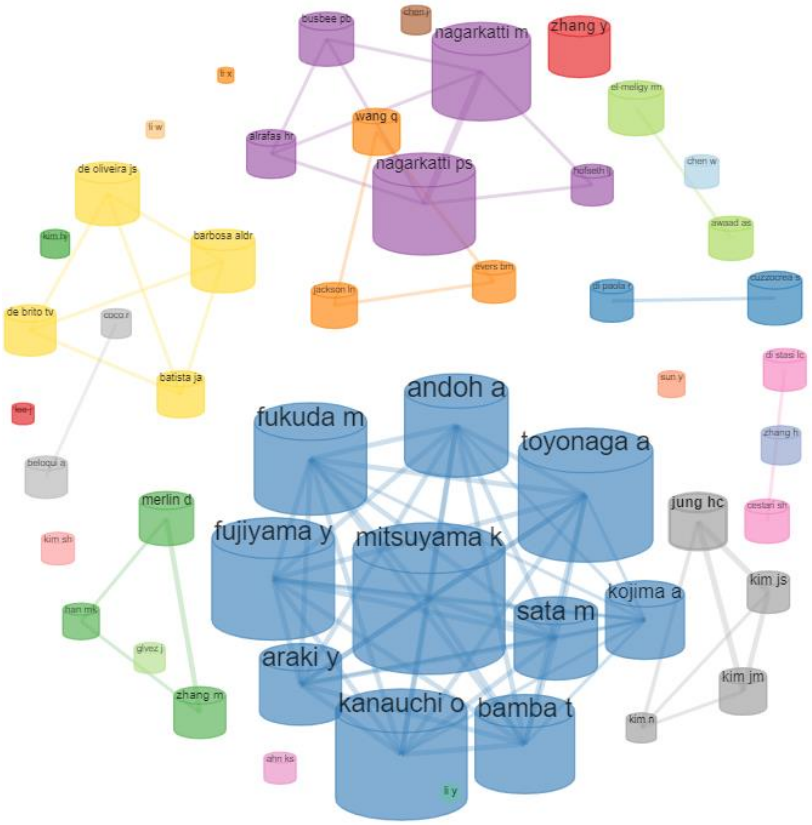


Fig. 8. Collaboration network among different scholars working in ulcerative colitis, the clustering algorithm was generated based on the leading Eigenvalues; higher Eigenvalues correspond to the larger size of the size of cylinder.

Utilizing SciMAT (science mapping analysis tool), we could analyze in Fig. 9 the importance of each theme according to two measures: centrality and density. Centrality measures a network's interaction level with other networks; meanwhile, density measures the internal strength of the keywords found within a theme or network [24].

In Figure 9, the thematic networks represented according to the two measures are divided into four quadrants. Quadrant 1 (upper-right) represents motor themes with high density and centrality. The themes found inside this quadrant have distinct attention. Quadrant 2 (upper-left) represents Niche themes, themes that have been ignored but hold potential in research. Quadrant III (lower-left) represents emerging or declining themes with low innovation and attention levels.

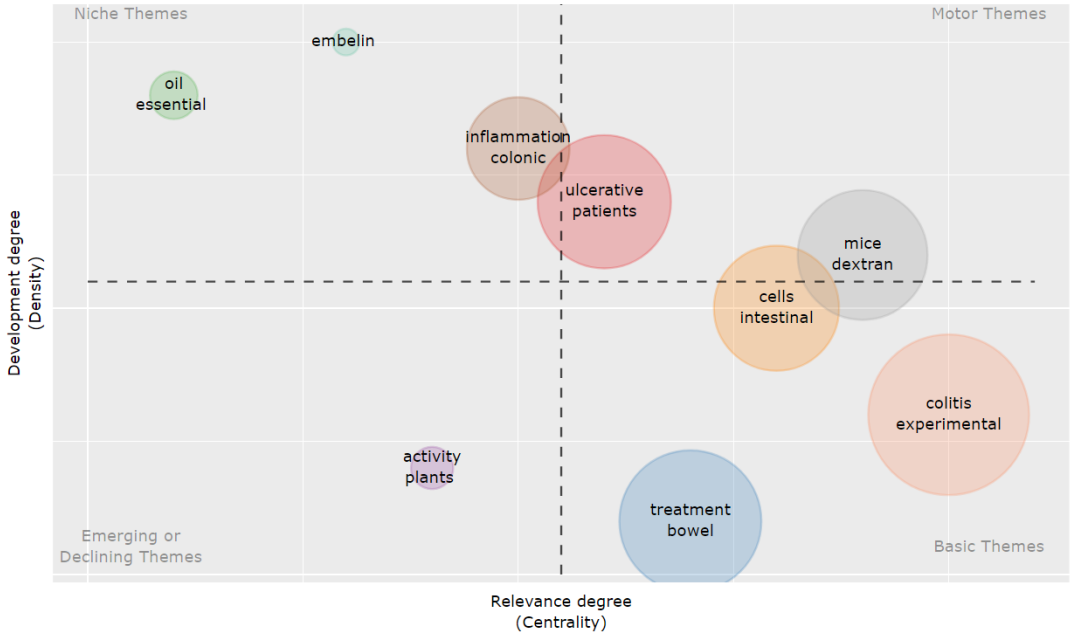


Fig. 9. Thematic evolution regarding types of research conducted on ulcerative colitis.

These research themes are old-fashioned, though not relevant to the current trend of research. Quadrant IV (lower-right) contains basic themes with a high degree of attention but is not well developed. The co-occurrence network of the most frequent terms that appeared in the analyzed literature is shown in Figure 10.

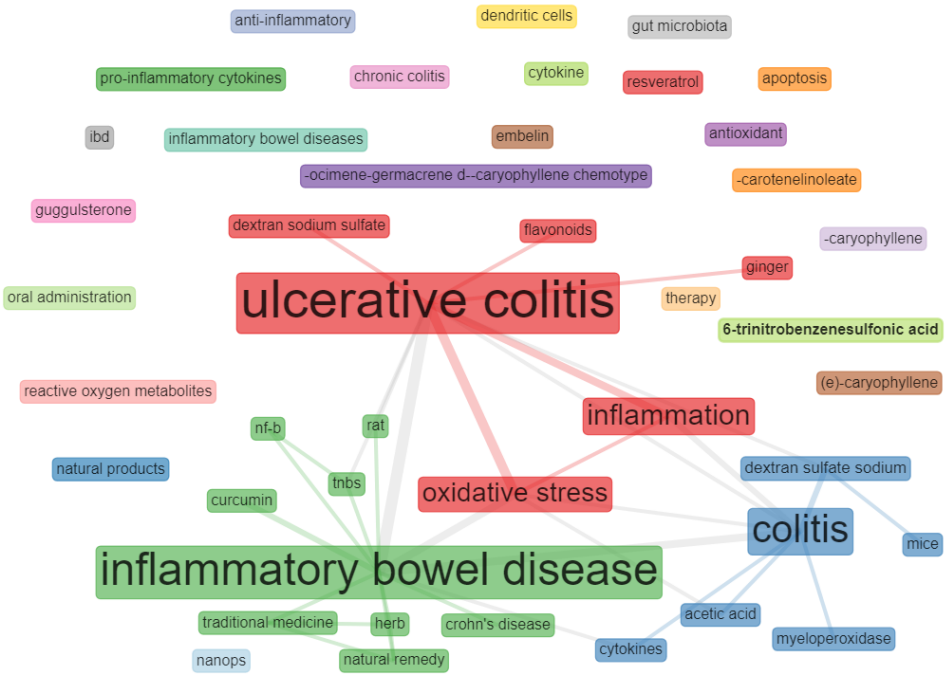


Fig. 10. Co-occurrence network among the most frequent terms occurred in the analyzed literature; the thicker the connection line among terms, the higher the frequency that respective terms have been investigated in relation to each other.

The rectangle size shows the number of articles in which the term occurs. A total of three interconnected clusters were observed, namely: ulcerative colitis (red), inflammatory bowel disease (green), and colitis (blue).

5.2 Plant and plant products that ameliorate experimental colitis

Every day more and more studies are done on plant and plant products that ameliorate experimental colitis. Table 1 summarizes some important studies from 2003 to 2020, mostly from the last ten years. According to target therapy, Table 1 is structured into two groups: plant and plant products composed of a single plant with a single target agent (plants line 1 to 19) and herbal formulations composed of four or more plants with multiple target therapy (herbal formulations line 20 & 21).

Many of the selected agents in Table 1 have their mechanism of action. However, still, there are some of them whose mechanism of action is unknown or needs further clarification. The experiments are done in different mice, inducing colitis by different methods. Each case has a control group to be compared with. Each of the experimental colitis cases is studied *in vivo* and 14 *in vitro* in a different types of cells. The most significant outcomes of these experimental cases are registered briefly in Table 1.

Table 1. Summary of the Plant and plant products that ameliorate experimental colitis.

Name of plant	Plant product	Mechanism of action (potential)	Control	Colitis induced by	Study in mice (nr)	Dosage	Success in mice	Outcome (*in vivo*)	Outcome (*in vitro*)	Reference
Allium cepa L.	Quercetin-loaded microcapsules	Quercetin-Loaded Microcapsules reduced the inflammation by impeding pro-inflammatory cytokine production, maintaining the antioxidant defenses and the anti-inflammatory cytokine IL-10.	Saline; Acetic acid solution	Acetic acid	968 male Swiss mice (25 ± 5 g)	100 mg/kg	Quercetin-loaded microcapsules ameliorate experimental acetic acid-induced colitis in mice.	Quercetin-Loaded Microcapsules: ↓ neutrophil influx, oedema, histological and macroscopical damage scores in the colon; ↓ levels of IL-1β and IL-33 prevented the reduction of IL-10 and maintained the endogenous antioxidant levels.	n/a	[25,26]
Curcuma longa	Curcumin emulsion	Curcuma longa can act by regulating numerous molecular targets, multiple signaling pathways, and gene expression.	Control (30% ethanol in phosphate-buffered saline (PBS))	TNBS (2,4,6-trinitrobenzene sulfonic acid)	Female BALB/c mice (25 – 30 g)	50mg/kg of curcumin	Curcumin reduces mucosal injury in TNBS acid-induced colitis.	Curcumin (50mg/kg): Improved the appearance of diarrhea and the disruption of colonic architecture; ↓ neutrophil infiltration (MPO) and lipid peroxidation (MDA); ↓ serine protease activity; ↓ the levels of nitric oxide (NO) and O2-; Repressed the nuclear factor-kB activation.	n/a	[27]
	Polycurcumin		Normal; DSS Colitis; Cur suspension ; SSZ	DSS solution	Sprague–Dawley (SD) rats (180–220 g); Female C57BL/6 mice (8 weeks, 18–20 g)	50 mg/kg of Cur in PCur	Orally administered PCur ameliorates experimental DSS-induced colitis in mice.	PCur: Improved intestinal absorption and plasma drug concentration, compared with Cur suspension; Improved weight loss, severe diarrhea, rectal prolapse; Recovered shortened length symptom; Regulated crypt structures, lowered neutrophil invasion; ↓ MPO activity and MDA content.	Cytotoxicity study was performed in CaCo2 cells. Cur solution and Pcur did not originate any notable change in cellular viability at these concentrations of 1 to 100 mg/mL.	[28]
	Nanoparticle curcumin		Normal; Theracurmin; DSS	DSS (Dextran sodium sulfate)	BALB/c mice (6–8-week-old females)	n/a	Nanoparticle curcumin ameliorates experimental DSS-induced colitis in mice.	Nanoparticle curcumin: Ameliorated body weight loss, DAI, histological colitis score, and mucosal permeability; Inhibited NF-κB activation in colonic epithelial cells; Suppressed mucosal mRNA expression of inflammatory mediators; ↑ the butyrate-producing bacteria and fecal butyrate level; ↑ extension of CD4+ Foxp3+ regulatory T cells and CD103+ CD8α− regulatory dendritic cells in the colonic mucosa.	Nanoparticle curcumin blocked in a direct way NF-κB activation in intestinal epithelial cells, shown in vitro using HT-29 cell line.	[29,30]

Vitis vinifera (Grapes)	Resveratrol solution	Resveratrol may protect against colitis through up-regulation of SIRT1(silent mating type information regulation-1) in immune cells in the colon.	Vehicle (CMC); 100 mg/kg resveratrol dissolved in CMC.	TNBS (2,4,6-trinitrobenzene sulfonic acid)	Female BALB/c mice (aged 6–8 weeks)	100 mg/kg Resveratrol	Resveratrol modulates the gut microbiota to prevent murine colitis development by promoting anti-inflammatory T-cell subsets.	Resveratrol: ↑ colon length; ↓ inflammatory biomarkers level; ↓ tissue disruption; ↓ cellular infiltration; Improved disease parameters; ↓ the inflammatory T cell response; promoted anti-inflammatory T cell subsets; Altered gut microbiome composition and ↑ the SCFA production.	n/a	[31] [32]
	Grape seeds proanthocyanidins extract	GSPE, due to its potent antioxidant properties, is thought to reduce granulocyte infiltration and lower the production of pro-inflammatory cytokine IL-b.	Normal control; TNBS control; SASP positive control	TNBS (2,4,6-trinitrobenzene sulfonic acid)	Male Wistar rats (9–10 weeks old; 180–200 g)	Low dose (GSPE-L, 100 mg/kg), Medium dose (GSPE-M, 200 mg/kg), High dose (GSPE-H, 400 mg/kg)	Intragastrical administrated GSPE ameliorates experimental TNBS-induced colitis in rats.	GSPE: ↑ body weight; showed an intestinal anti-inflammatory effect, restored gradually histologic lesions; ↓ neutrophil infiltration by reducing MPO activity, MDA, and IL-1b production; ↑ IL-2 and IL-4 levels (in 400 mg/kg GSPE group).	n/a	[34]
	Grape exosome-like nanoparticles (GELNs)	GELNs modulate intestinal tissue renewal processes.	PBS; DSS + PBS	DSS	Male mice (18–25 g, six weeks old)	2 mg/mouse of GELNs	GELN treatment is profitable for regenerating intestinal epithelium in DSS-induced colitis in mice.	GELNs can migrate to intestinal mucus, be captured by mouse intestinal stem cells, and stimulate the proliferation of intestinal stem cells in the induced colitis model. Promoted a quick restoration of the intestinal architecture.	GELNs (40 μg/ml) directly promote Lgr5-EGFPhi intestinal stem cells' proliferation and accelerate organoid structure formation.	[35]
Embelia ribes Burm (Embelin)	Embelin suspension	Embelin impedes STAT3 activation, becoming potentially effective in suppressing tumor cell survival, proliferation, and angiogenesis.	Sodium CMC (0.3% w/v); Acetic acid-induced colitis control	Acetic acid (3% v/v)	Male Wistar rats (180–200 g)	25 and 50 mg/kg, p.o embelin	Embelin shows a protective effect against acetic acid-induced ulcerative colitis in rats.	Embelin: ↓ the clinical activity scores, gross lesion score, percent affected area, and wet colon weight; ↓ MPO, lipid peroxides, and LDH; ↑ the GSH level; At 50 mg/kg showed remarkable recovery of colonic mucosa previously damaged from induced colitis.	n/a	[36,37]
	Embelin lipid nanospheres		Sodium CMC (0.3%w/v, 1 ml / 100 g)	Acetic acid	Male Wistar rats (220–260 g)	50 mg of embelin in all the formulations	Embelin LNs ameliorate experimental acetic acid-induced colitis in mice.	LNs: ↓ MPO, LDH, and LPO levels; ↓ GSH levels; Improved oedema, necrotic destruction, inflammatory cellular infiltration, and hemorrhages.	Nanospheres stabilized with egg lecithin released a slightly higher percentage of embelin when compared with nanospheres stabilized with soya lecithin, in vitro, in the Franz diffusion cell.	[38]

Zingiber officinale (Ginger)	Ginger-derived nanoparticles	GDNPs-2 presents a new mechanism for improving IBD through its advantage of mastering production scale and potential toxicity limitations.	Water control	DSS (Dextran sodium sulfate)	Female C57BL/6 or FVB/NJ mice (6-8 wk old)	0.3 mg/mouse GDNPs	GDNPs-2 showed better results in the treatment of DSS-induced colitis than GDNPs 1	GDNPs 2: ↓ acute colitis, enhanced intestinal repair, prevented chronic colitis and colitis-associated cancer; ↑ the survival and proliferation of IECs; ↓ the pro-inflammatory cytokines (TNF-a, IL-6, and IL-1b); ↑ the anti-inflammatory cytokines.	GDNPs-2 did not alter the viability of colon-26 and RAW 264.7 cells for 24h.	[39]
Commiphora wightii	GuggulsteroneGG-52 solution (via oral gavage)	GG-52 attenuates inflammation by impeding LPS-induced IL-12p40, TNF-α gene expression, IκBα degradation, and NF-κB DNA binding activity in BMDCs but also by suppressing IKK activation in DCs in colonic tissue.	Samples without piroxicam (negative control); Piroxicam, and methylcellulose (positive control)	Piroxicam	IL-10−/− mice (6-7-week-old)	200 mg/kg dose of GG-52	GG-52 attenuated experimental piroxicam-induced colitis in mice.	GG-52: ↓ inflammatory lesions and ulceration; Attenuated histological scoring; ↓ the expression of TNF-α and IL-12p40 mRNA.	GG-52 mediates NF-κB inhibition in BMDCs (bone marrow-derived dendritic cells).	[40]
	GuggulsteroneGG-52 solution (via rectal route)	GG-52 impedes the expression of chemokines IL-8 and MCP-1 by blocking NF-kB signaling in IEC. Further investigations are needed to comprehend the mechanism of action of GG-52 due to the possible role of AP-1 in chemokine suppression.	0.5% methylcellulose solution (vehicle)	DSS (Dextran sodium sulfate)	C57BL/6NCrljBgi mice (20–25 g, 7–8 weeks)	200 mg/kg dose of GG-52	GG-52 attenuated experimental DSS-induced colitis in mice.	GG-52: ↓ clinical and macroscopic inflammatory indices; Attenuated acute colitis histologically; Had an efficacy equal to that of sulfasalazine and prednisolone.	GG-52 could exert anti-inflammatory effects by blocking IKK (IkB kinase) activity in IEC(intestinal epithelial cells).	[41]
Aster tataricus	Astin C extract	A. tataricus induced activated T-cell apoptosis via a mitochondria-mediated pathway.	Vehicle control (Lymph node cells experiment); Sham (TNBS induced colitis experiment).	TNBS (2,4,6-trinitrobenzene sulfonic acid)	Female C57BL/6 mice (6–8 weeks of age)	2 and 4 mg/kg of Astin C	Astin C can induce apoptosis in activated T cells and its potential plant product to treat colonic inflammation.	Astin C: ↓ the weight/ length ratio; At 4 mg/kg ameliorated the sign of colitis; ↓ TNF-α level; ↓ IL-4 and IL-17 levels.	In Lymph node cells isolated from C57BL/6 mice, Astin C: Suppressed proliferation and induced apoptosis in activated T cells; In the mitochondria pathway, Astin C prompts the changes of relevant molecules.	[42]

Syringa vulgaris	Verbascoside extract	VB would intercept the tissue injury cycle at the level of NF-κB activation and cytokine release. It proposed that VB functions as an intracellular radical scavenger.	Sham + vehicle group; DNBS + vehicle	DNBS (dinitrobenzene sulphonic acid)	Male Sprague–Dawley rats (300–350 g)	VB (2 or 0.2 mg/kg)	VB from S. Vulgaris IRBSV25/B cell cultures attenuate DNBS-induced colitis in rats.	VB: ↓ the extent and severity of the signs of colon injury; Attenuated the loss of body weight; ↓ TNF-α and IL-1β levels (2mg/kg had a better effect); At 2 mg/kg: ↓ the staining for ICAM-I, P-selectin, iNOS, and nitrotyrosine; ↓ the loss of IκB-α levels in the colon also NF-κB p65 nuclear levels; Suppressed DNBS-induced MMP-9expression.	n/a	[43]
Ligusticum wallichii	Tetramethylpyrazine solution	TMP could alleviate the induced Colitis inhibits the NF-κB pathway and suppresses downstream signaling via iNOS, COX-2, C-MYC, cytokine production, and decreases ROS production.	Non-colitic control (N); Saline-treated colitic group (NS); Sulphasalazine positive control	Oxazolone	Male KM mice (25–30 g, seven weeks old)	80 mg/kg TMP	TMP improved oxazoline-induced colitis.	TMP: Promoted recovery of the intestinal cytoarchitecture, reduced ulceration and oedema, and depletion of mucus in the submucosal layers; ↓ the nucleus translocation of NF-κB; ↓ the downstream signaling, as C-MYC, iNOS, and COX-2.	TMP in vitro: Inhibited NF-κB translocation and its downstream production of inflammatory factors, such as TNF-α, IL-6, IL-8, and ROS production induced by LPS in Caco-2 cells.	[44] [45]
Ginkgo biloba	Ginkgo biloba extract (EGb 761)	EGb 761 can drive CD4+ effector T cell apoptosis, providing a protective mechanism against inflammation.	Water control	DSS (Dextran sodium sulfate)	8-week-old C57BL/6 mice	3.5 g EGb 761	Ginkgo biloba extract EGb 761 ameliorates colitis in mice by driving effector T cell apoptosis	EGb 761: Ameliorated systemic stress; ↓ levels of TNF-alpha; ↓ to normal levels of iNOS, Cox-2, TNF-alpha, p53, and p53-serine 15 phosphorylation; ↓ the colonic cell numbers as CD4+/CD25-/Foxp3- T; Drives apoptosis of activated CD4+ effector T cells upstream of the colon.	EGb 761 attenuates pro-inflammatory protein iNOS in a dose-response manner in an in vitro experiment where ANA-1 cells are used.	[17]
Corydalis dubia	Capnoidine solution	The exact mechanism of action of capnoidine is unknown.	Healthy naive control mice; Vehicle-treated TNBS-treated mice	TNBS (2,4,6-trinitrobenzene sulfonic acid)	6-week-old male C57BL/6 mice	Cap 50, 50 μg/mouse	Capnoidine, prevents the start of inflammation in the TNBS-induced mouse model of colitis.	Capnoidine: Improved body weight loss, mobility, piloerection, and faecal consistency; ↓ adhesion, oedema, ulceration, and colon length; Altered inflammatory cytokines level; ↓ levels of p-IκB-α (Ser32) and pNF-κB p65 (Ser536);	n/a	[46]
Camellia sinensis	Green tea extract (GTE)	GTE attenuates inflammation by reducing the nitration of proteins, forming the pro-inflammatory cytokines, expressing the adhesion molecule ICAM-1, and enhancing the HO-I formation.	Vehicle (saline solution)	DNBS (dinitrobenzene sulphonic acid)	Male Sprague-Dawley rats (300–350 g)	50 mg/kg GTE	Green tea polyphenol extract attenuates colon injury induced by experimental colitis	GTE: Attenuated diarrhea and body weight loss; Ameliorated the disruption of the colonic architecture; ↓ MPO and TNF-α production; ↓ the appearance of nitrotyrosine immunoreactivity in the colon and reduced the up-regulation of ICAM-1.	n/a	[47]

Malus domestica (Red Fuji apples)	Modified apple polysaccharides solution (MAP)	The mechanisms may be the potential of MAP in downregulating the IL-22 level and up-regulating the expression of IL-22BP.	Pure drinking water	DSS (Dextran sodium sulfate)	90 male ICR mice five weeks old	0.5 mg/mL MAP	Modified apple polysaccharide (MAP) is thought to prevent DSS-induced colitis through modulating IL-22 and IL-22BP expression	MAP was potentially protective against intestinal toxicity caused by DSS; Ameliorated colon length shortening and body weight; ↓ IL-22 serum level; ↓ the expression of p-STAT3, Bcl-2, and cyclin D1.	MAP: Suppressed IL-22 induced activation of STAT3 in MCA-38 cells; Apple oligolactan inhibited the proliferation of MCA-38 cells in the co-culture system; MAP could up-regulate the expression of IL-22BP in DC2.4 cells;	[48,49]
Garcinia cambogia	Garcinia cambogia extract	Garcinia attenuates inflammation by reducing MPO activity, COX-2, iNOS expression, PGE2, and IL-1β colonic levels. Whereas in isolated colonocytes by reducing DNA damage.	Water control	TNBS/ethanol	Male Wistar rats (220–250 g) and female Swiss mice (23–28 g)	GCE; 0.5 or 1 g/kg p.o.	Garcinia cambogia Extract attenuated TNBS Colitis Injury in Rats	Garcinia cambogia extract (0.5 and 1 g/kg): Led to a slight weight gain, which was not statistically significant; ↓ MPO activity; At 1 g/kg: ↓ colonic IL-1β expression; Inhibited the iNOS colonic expression; Preventing the DNA damage induced by TNBS.	Garcinia cambogia extracts in isolated colonocytes of colitis showed the impact at a dose of 1 g/kg to prevent DNA damage induced by TNBS/ ethanol.	[50]
Fumaria capreolata L.	Alkaloid extract	AFC ameliorated inflammation by Inhibiting IL-6 and TNF- α in vitro and suppressing the transcription of IL-1 β, iNOS, IL-12, and IL-17 in vivo.	Non colitic; Control colitic	DNBS (dinitrobenzene sulphonic acid)	Male CD1 mice, weighing (25–30 g)	25mg/kg; 50mg/kg; 100 mg/kg, AFC	AFC exerted intestinal anti-inflammatory effects in DNBS-induced mouse colitis.	AFC: Ameliorated bodyweight loss; Promoted the recovery of the colonic histology; ↓ the expression of IL-1 β, TNF α, IL-6, IL-12, and IL-17; ↓ the expression of iNOS, MMP-9, ICAM-1 proteins.	In the CMT93 cell line, AFC down-regulated some inflammatory mediators (TNF α, IL-6, IL-17, and IL-1 β, and up-regulated the expression of proteins like the mucin MUC-2 and ZO-1.	[51]
Prunella vulgaris	Monofloral honey from Prunella vulgaris (PVH)	The precise mechanism deserves further clarification.	Regular control group; DSS group.	DSS (Dextran sodium sulfate)	Sprague Dawley (SD) rats (male, 190–220 g)	5 g per kg, p.o. PVH	PVH from Prunella Vulgaris protected against DSS-induced ulcerative colitis in rats.	PVH: ↓ DAI; ↓ histological scores; Modulated the gut microbiota composition.	n/a	[52]

Morinda citrifolia (Noni)	Noni-polysaccharides (PLS) extraction	The precise mechanism deserves further clarification.	0.9% saline (negative control); Acetic acid (positive control)	Acetic acid	Male Swiss mice (25–30 g)	0.1mg/kg; 0.3mg/kg ; 3.0 mg/kg, i.p; Noni-PLS	Noni-PLS exhibited an anti-inflammatory effect in an experimental model of UC induced by acetic acid.	Noni-PLS: ↓ lesion scores; ↓ colonic wet weight; ↓ the loss of mucosal architecture, cell infiltration, thickening of muscular layer, abscess formation in the crypt, and depletion of goblet cells; ↓ MPO, MDA, NO3/NO2 levels; ↓ IL-1β and TNF-α concentrations; ↓ COX-2 and iNOS expression; Restored GSH concentration.	n/a	[53]
Glycyrrhiza glabra	Glycyrrhizin natural preparation (GL-p)	GL-p is thought to have a therapeutic potential in inflammation suppressing MPO activity in a dose-dependent manner.	1 mL saline	DSS (Dextran sodium sulfate)	Male Wistar rats (~250 g, 8 wk old)	1 mL GL-p or 0.2% GL	GL-p ameliorated the extent of DSS-induced colitis in rats.	GL-p: ↓ the level of pro-inflammatory cytokines and chemokines in the colonic mucosa; ↓ MPO activity; No significant therapeutic differences between GL alone and GL-p.	GL-p dose-dependently inhibited MPO activity in mucosal tissue and purified human MPO enzyme.	[54]
Mentha piperita (Peppermint)	Menthol solution	Peppermint oil causes a relaxing effect by interacting with smooth Muscle calcium channels.	Carboxym ethyl cellulose (CMC)	Acetic acid	Male albino Wistar rats (225-240 g)	Menthol 50 mg/kg	Menthol has a significant anti-inflammatory effect in the acetic acid-induced IBD model.	Menthol: Improved bodyweight reduction and macroscopic/microscopic ulcer scores; ↓ MPO activity and MDA levels; ↑ GSH level; ↓ IL-1, IL-23 levels, and TNF-α; Ameliorated LPO and oxidative stress.	n/a	[55]
Forsythia koreana, Corydalis Saxicola, Semiaquilegia adoxoides, Taraxacum officinale, Chrysanthemum coronarium, Glycyrrhiza inflate, Lonicera japonica	Herbal aqueous extract	The exact mechanisms of the herbal extract treatment are not known.	Vehicle control PBS (Phosphate buffered saline)	DSS (Dextran sodium sulfate)	Female Swiss-Webster mice (6–8 weeks old)	228.5 pg/ml po, 165.7 pg/ml pr Herbal extract	Herbal concoction led to amelioration of the murine-induced model of DSS colitis.	The Herbal Extract: ↓ DAI Compared to the Control Mice; ↓ Colonic Ulceration; ↓ Neutrophil Sequestration in the Colonic Mucosa.	n/a	[56]
Zingiber officinale, Terminalia chebula, Aucklandia lappa	KM1608 herbal formulation	KM1608, composed of 3 plants, shows a potent synergism due to multiple target network mechanisms and greater efficacy.	Normal control; Colitis control.	TNBS (2,4,6-trinitrobenzene sulfonic acid)	ICR mice	200, 400, and 600 mg/kg of KM1608	KM1608 herbal formulation ameliorates the symptoms of colitis and the inflammatory responses.	KM1608: Improved minimal the colon length; ↓ the DAI and the colon weight/length ratio in a dose-dependent way; At 600 mg/kg ↓ MPO activity and TNF-α level and slightly ↓ IL-6 level in the colon tissue lysate; 600 mg/kg dose resulted in better parameters for many of the indices used for colitis evaluation than 5-ASA and prednisolone.		[57]

Note: 5-ASA: Aminosalicylic acids; AFC: Alkaloid extract of Fumaria capreolata L.; ANA-1 cells: Mouse macrophage cells; AP:-1 -activator protein-1; Bcl-2: B-cell lymphoma 2; BMDCs: bone marrow-derived dendritic cells; Caco-2 cells: cell line derived from a colon carcinoma; CaCo2 cells: immortalized cell line of human colorectal adenocarcinoma cells; CMC: carboxymethyl cellulose; CMC: Sodium Carboxymethyl Cellulose; CMT93 cell line: a cell line from an induced carcinoma of mouse rectum; C-MYC - c-Myc: oncoprotein; COX-2: Ciclo-oxigenase-2;

cyclin D1: a protein required for progression through the G1 phase of the cell cycle; DAI: disease activity index; DCs: Dendritic cells; DNBS: dinitrobenzene sulphonic acid; DSS: Dextran sodium sulfate; EGb 761:Ginkgo biloba extract; GCE: Garcinia cambogia extract; GDNPs: Ginger-derived nanoparticles; GELNs: Grape exosome-like nanoparticles; GG: Guggulsterone; MCP-1: Monocyte chemotactic protein-1; GL-p: Glycyrrhizin natural preparation; GSH: Glutathione; GSPE: Grape seeds proanthocyanidins extract; GTE: Green tea extract; HO-I: hypoiodous acid; HT-29 cell line: human colon adenocarcinoma cell line; ICAM-I: Intercellular Adhesion Molecule 1; IECs: Intestinal epithelial cells; IKK - inhibitor of nuclear factor-κB (IκB) kinase; IKK: IkappaB kinase; C57BL/6 mice: laboratory mouse inbred strain; IL: interleukin; iNOS: inducible nitric oxide synthase; IRBSV25/B cell: Syringa vulgaris cell line; IκBα: inhibitor of nuclear factor kappa B; KM1608 herbal formulation: Zingiber officinale, Terminalia chebula and Aucklandia lappa; LDH: Lactate dehydrogenase; LN: lipid nanosphere; LPO: Lipid Peroxidation; LPS: lipopolysaccharide; MAP: Modified apple polysaccharides solution; MCA-38: Cell Line derived from C57BL6 murine colon adenocarcinoma cells; MDA: lipid peroxidation; MMP-9: Matrix metallopeptidase; MPO: neutrophil infiltration; MUC-2: Human mucin-2; NF-κB: nuclear factor kappa light chain enhancer of activated B cells; NF-κB: Nuclear factor-kB activation; NO: nitric oxide; NO3/NO2 levels: nitrate and nitrite levels; NS: Saline-treated colitic group; O^{2-} : Superoxide; PBS: phosphate buffered saline; PBS: phosphate-buffered saline; PCur: Polycurcumin; PGE2: Prostaglandin E2; PLS: Noni- polysaccharides; P-selectin: granular membrane protein and a cellular adhesion molecule; p-STAT3: Phosphorylated signal transducer and activator of transcription; PVH: Prunella vulgaris honey; RAW 264.7 cells: monocyte/macrophage cell line; ROS: reactive oxygen species; SASP: sulphasalazine; SCFA production: Short-chain fatty acids;SIRT1:silent mating type information regulation-1; STAT3: Signal transducer and activator of transcription 3; TMP: Tetramethylpyrazine; TNBS: 2,4,6-trinitrobenzene sulfonic acid; TNF-α: Tumor necrosis factor; VB:Verbascoside extract; ZO-1:Zonula occludens-1 protein.

5.2.1 *Allium cepa L., quercetin-loaded microcapsules*

Quercetin is a flavonoid found in plants such as white onion bulls, spring onion leaves, skin apple peel, and *Hypericum perforatum* leaves [26]. Many health benefits are antiviral, antioxidant, anticarcinogenic, cardioprotective, anti-inflammatory, and other properties [58]. However, these benefits cannot be achieved satisfactorily in the experimental model of UC [25] when quercetin is administrated alone due to its loss in the stomach, small intestine, and blood circulation. However, the quercetin concentration that reaches the colon does not exert its properties [59]. Of particular interest is the quercetin-loaded microcapsules formulation, studied in acetic acid-induced colitis in male mice [25].

In this experiment, the oral administration of 100 mg/kg quercetin-loaded microcapsules reduced neutrophil influx, edema, histological and macroscopical damage scores in the colon, decreased the levels of IL-1β and IL-33, prevented the reduction of IL-10, and maintained the endogenous antioxidant levels [25]. So, this novel formulation impeded pro-inflammatory cytokine production and sustained the antioxidant defenses and the anti-inflammatory cytokine IL-10. Further investigations are needed to benefit more from the mechanism of natural compounds inserted into modified released systems [25].

5.2.2 *Curcuma longa, curcumin emulsion, polycurcumin, nanoparticle curcumin*

Curcuma longa. L. (Turmeric) is a plant that belongs to the ginger family (Zingiberaceae). It has sterile yellow-white flowers that do not produce seeds. However, the only way to reproduce turmeric is through rhizomes. Turmeric is native to southeastern India and has been used for thousands of years to treat diseases like blood disorders, gastro-hepatic conditions, inflammation, and infection [60]. Noteworthy is the impact of turmeric on TNBS and DSS-induced UC in mice. In a study by Ukil, et al. [27], curcumin was emulsified in 2.5% carboxymethyl cellulose and administered orally for ten days to TNBS-induced colitis mice. Some of the benefits of this treatment were: improvement of the appearance of diarrhoea and the disruption of colonic architecture, reduction of neutrophil infiltration (MPO) and lipid peroxidation (MDA), a decline of serine protease activity, reduction of nitric oxide (NO) and O^{2-}levels, repression of the nuclear factor-kB activation [27].

Another study by Qiao, et al. [28] focused on the benefits of curcumin, this time as a polymer (PCur) made of hydrophilic polyethylene glycol (PEG) and hydrophobic curcumin (Cur) linked by a disulfide bond in DSS-induced colitis model. This study intended to recognize more about the response of PCur to the bacterial reducing environment in the colon. This last phenomenon

is one of several limitations of treatment in this region. It was seen that 50 mg/kg of PCur administered orally in vivo improved intestinal absorption and plasma drug concentration compared with Cur suspension. In addition, *in vivo*, similar benefits were achieved as in the study of Ukil, et al. [27]. Whereas *in vitro*, the cytotoxicity of PCur in CaCo2 cells was analyzed. As a result, it did not originate any notable change in cellular viability.

Recently of great interest is the development of nanoparticle curcumin (Theracurmin). The oral bioavailability of Theracurmin was 27-fold higher than that of curcumin powder [30]. Ohno et al. (2017) reported that in a DSS-induced colitis model, Theracurmin in vivo ameliorated body weight loss, DAI, histological colitis score, and mucosal permeability, inhibited NF-κB activation in colonic epithelial cells, suppressed mucosal mRNA expression of inflammatory mediators, increased the butyrate-producing bacteria and fecal butyrate level, increased extension of CD4+ Foxp3+ regulatory T cells and CD103+ CD8α− regulatory dendritic cells in the colonic mucosa [29]. *In vitro* nanoparticles, curcumin instantly blocked NF-κB activation in intestinal epithelial cells, as shown in the HT-29 cell line [29]. These positive results in suppressing mucosal inflammation make nanoparticle curcumin one of the competitor formulations for UC treatment. However, further studies are needed to define the most beneficial formulation of curcumin better.

5.2.3 Grapes, resveratrol solution, grape seeds proanthocyanidins extract, grape exosome-like nanoparticles

Grapes are a fruit that grows in a cluster. Since ancient times they have been known as the fruit with the healing power. Two crucial parts of it, the skin and seed, hold many nutritional and medicinal values because of polyphenolic antioxidants [61]. Grape seeds are rich in vitamin E, linoleic acid, flavonoids, and proanthocyanidins. In a lower concentration, skin also contains these values. However, it is more distinguished for the presence of resveratrol, a compound that is not found in seeds [61]. Resveratrol is reported for its essential role in preventing and treating chronic inflammatory disease and autoimmune disorders [32].

In a TNBS-induced model of UC [31], the administration of 100 mg/kg of resveratrol played an essential role in increasing the colon length, decreasing inflammatory biomarkers level and tissue disruption, reducing cellular infiltration, improving disease parameters, promoting the production of anti-inflammatory T cell subsets and altering the gut microbiome composition and increases the SCFA production. These responses make resveratrol a promising polyphenol in modulating intestinal microbiota and treatment of colitis.

Another study by Li, et al. [34] analyzed the role of proanthocyanidins in grape seeds proanthocyanidins extract (GSPE). Low, medium, and high doses of GSPE were administered

intragastrically to previously TNBS-induced male Wistar rats. Sulfasalazine (SASP) functioned as a positive control. GSPE, due to its potent antioxidant properties, increased body weight, showed an anti-inflammatory effect in the intestine, restored histologic lesions gradually, and reduced neutrophil infiltration by reducing MPO activity, MDA, and IL-1β production increased IL-2 and IL-4 levels. Of interest was the outcome that SASP and GSPE had no remarkable difference therapeutically.

Ju, et al. [35] studied grape exosome-like nanoparticles (GELNs). Exosomes are nanosized microvesicles that serve as a messenger in intracellular communication transporting proteins, lipids, mRNAs, and microRNAs to destiny cells. Though GELNs have specific biological activity and transport properties [35]. The experiment was conducted *in vivo* in a DSS model-induced colitis in mice and in vitro in Lgr5-EGFPhi stem cells isolated from crypts of Lgr5EGFP-IRES-CreERT2 mice. *In vivo*, GELN can migrate to intestinal mucus, be captured by mouse intestinal stem cells, and stimulate the proliferation of intestinal stem cells in the induced colitis model. Also, GELN can promote a quick restoration of the intestinal architecture. In vitro GELNs (40 μg/ml) directly promote Lgr5-EGFPhi intestinal stem cells' proliferation and accelerate organoid structure formation.

5.2.4 Embelia ribes Burm, suspension, lipid nanospheres

Embelia Ribes (Embelin), also known as false black pepper due to its appearance, is a plant that belongs to the Primulaceae family. Many studies reported embelin for its various medical benefits as an anti-inflammatory, analgesic, and antitumoral effects [36,37,62].

Thipeswamy and his colleagues focused on embelin suspension in an acetic acid-induced model of UC in mice. Three different groups of rats received before the induction of colitis, for five days, 25, 50 mg/kg, p.o of embelin and 100 mg/kg, p.o of sulfasalazine, respectively. After the induction of colitis, the treatment continued for seven days [36]. The results showed that embelin suspension at both doses (25 and 50 mg/kg) decreased the clinical activity scores, gross lesion score, percent affected area, and wet colon weight, decreased MPO, lipid peroxides, and LDH. Embelin suspension (25 and 50 mg/kg) augmented the GSH level. At 50 mg/kg showed remarkable recovery of colonic mucosa previously damaged from induced colitis [36]. Although this experiment had a positive contribution to understanding the role of embelin suspension in non-UC rats and its prolongation in the same rats UC induced, post-treatment centralized studies are needed in different models of UC.

Researchers have recently investigated embelin integrated into lipid nanospheres (LNs) [38]. Nanoparticles can accumulate in the inflamed intestinal regions by ameliorating IBD therapy. A carrier system that delivers the drug directly to the inflamed area after being taken orally

would be advantageous because of its prolonged drug release and lower side effects and dosage [63]. Badamaranahalli, et al. [38] investigated acetic acid-induced colitis in male Wister rats using a sodium CMC control mechanism. The results demonstrated that LNs of embelin could decrease MPO, LDH, and LPO levels, improve reduced GSH levels, and improve edema, necrotic destruction, inflammatory cellular infiltration, and hemorrhages. So further reflections and studies on embelin LNs could be advantageous in treatment of IBD.

5.2.5 Zingiber officinale, ginger-derived nanoparticles

Zingiber officinale (Ginger) is a flowering plant with a rhizome commonly used as a spice and folk medicine. Many types of research have shown the interrelation between ginger and IBD [39,64]. The most promising ones are those centralized on nanoparticles with colon targeting properties.

Zhang, et al. [39] investigated *in vivo* and *in vitro* the potential of ginger-derived nanoparticles, of which GDNPs-2 came out to have the highest concentration of gingers' potent components. GDNPs were administered to DSS-induced UC mice, and GNDPs-2 developed remarkable results. GDNPs-2 could reduce acute colitis, enhance intestinal repair, and prevent chronic colitis and colitis-associated cancer. GDNPs-2 increased the survival and proliferation of IECs, increased the anti-inflammatory, and decreased the pro-inflammatory cytokines (TNF-a, IL-6, and IL-1b).

In vivo, Zhang et al. (2016) observed that GDNPs-2 did not alter the viability of colon-26 and RAW 264.7 cells for 24h. Therefore, GDNPs-2, with its non-toxic delivery system features, are very promising in healing the intestinal mucosa.

5.2.6 Commiphora mukul, guggulsterone-52 solution

Commiphora mukul is a flowering plant that belongs to the Burseraceae family. It produces a plant sterol and an active compound called guggulsterone that has been used for thousands of years in Indian folk medicine [65]. Nevertheless, guggulsterone can potentially cause consequential side effects in blood, even if administrated orally or rectally. In order to deal with this limitation, JM Kim et al. (2010) integrated four guggulsterone derivatives, from which GG-52 resulted from the most successful. In vivo, a 200 mg/kg dose of GG-52 administered in a DSS-induced colitis model could ameliorate colitis by reducing clinical and macroscopic inflammatory indices. Remarkable was the result that GG-52 had an efficacy equal to that of sulfasalazine and prednisolone. Whereas in vitro, GG-52 could exert anti-inflammatory effects by blocking IKK(IkB kinase) activity in intestinal epithelial cells [41].

Another study by Kang, et al. [40] administered two different dosages of GG-52 in a piroxicam-induced model of colitis. It was observed that GG-52 at 200 mg/kg reduced inflammatory lesions and ulceration, reduced the expression of TNF-α and IL-12p40 mRNA, and attenuated histological scoring. They used bone marrow-derived dendritic cells to test GG-52 properties *in vitro*, where GG-52 intervened in NF-κB inhibition. In conclusion, GG-52 could be a possible molecule in treating IBD.

5.2.7 Aster tataricus, astin C extract

Aster tataricus is a plant that belongs to the family Asteraceae. Astin C (a cyclopeptide found in *Aster tataricus*) can induce activated T-cell apoptosis via the mitochondria-mediated pathway [42]. Shen and his colleagues studied the effect of astin C in a TNBS model of colitis. The results showed that this cyclopeptide could reduce the weight/ length ratio to 2 and 4 mg/kg. Whereas 4 mg/kg of astin C ameliorated the sign of colitis, decreased TNF-α levels, and decreased IL-4 and IL-17 levels. They also observed the role of astin C *in vitro* using lymph node cells isolated from C57BL/6 mice. They realized that it could suppress the proliferation and induce apoptosis in activated T cells [42]. Because of its way of action, the astin C molecule is promising in inflammatory intestinal diseases.

5.2.8 Syringa vulgaris, verbascoside extract

Syringa vulgaris is a flowering plant that belongs to the Oleaceae family. *Syringa vulgaris* IRBSV25/B cell cultures are utilized to obtain biotechnologically verbascoside (VB). Several studies are done on this promising molecule to uncover the truth about its anti-inflammatory properties [43,66] and the effect on oxidative stress-related neurodegenerative diseases [19], among others.

Mazzon, et al. [43] observed the effect of verbascoside extract in a DNBS-induced model of UC in Sprague–Dawley male rats. The effect of two different VB dosages (2 and 0.2 mg/kg) was analyzed. The results demonstrated that VB reduced the extent and severity of the signs of colon injury and attenuated body weight loss. VB at 2mg/kg had a better effect in reducing TNF-α and IL-1β levels. At 2 mg/kg, VB reduced ICAM-I, P-selectin, iNOS, and nitrotyrosine staining. VB reduced the loss of IκB-α levels in the colon and NF-κB p65 nuclear levels. Furthermore, VB could suppress DNBS-induced MMP-9expression.

VB interrupts the tissue injury cycle at the level of NF-κB activation and cytokine release. VB is proposed to function as an intracellular radical scavenger; it can be profitable if used in therapy-related internal or external inflammation [43].

5.2.9 *Ligusticum wallichii, tetramethylpyrazine solution*

Ligustiicum wallichii is a plant that belongs to the family Apiaceae. Its importance has been raised due to the natural compound isolated from it named tetramethylpyrazine (TMP). TMP is an effective multitargeting product studied for its potential as an anti-inflammatory, antioxidant, antiplatelet, and antiapoptosis [67].

The study of Lu, et al. [44] is of interest to the role of TMP solution in oxazolone-induced colitis model in male KM mice. TMP solution was administered at 80 mg/kg/day to previously induced colitis mice than the sulphasalazine positive control. The results showed that TMP solution promotes the recovery of the intestinal cytoarchitecture, reducing ulceration and edema. Moreover, promotes the depletion of mucus in the submucosal layers. TMP decreases the nucleus translocation of NF-κB and the downstream signaling, such as C-MYC, iNOS, and COX-2.

In vitro, TMP inhibits NF-κB translocation and its downstream production of inflammatory factors, such as TNF-α, IL-6, IL-8, and ROS production induced by LPS in Caco-2 cells [44]. Attractive is the synergic effect of TMP and sulphasalazine when combined for the beneficial treatment of ulcerative colitis in the mice model [44]. However, in order to diminish the toxicity and reach maximum therapeutical usefulness, more studies are required.

5.2.10 *Ginkgo biloba, ginkgo biloba extract*

Ginkgo biloba is a tree native to China; it belongs to the Ginkgoaceae family. The variety of active ingredients that ginkgo contains brings to a number of the mechanism of action of this plant. Many studies propose different effects of ginkgo, such as a vaso-regulatory effect, changes in nerve cell metabolism in an animal study, deterrence of cell membrane harm from free radicals, and antagonism of platelet activation factor [68]. Leaf extracts of Ginkgo biloba have been used for years in traditional medicine. Of interest is standardized EGb 761, which looks promising in ameliorating ulcerative colitis in mice through its antioxidant and free radical scavenging actions [17].

Kotakadi, et al. [17] studied the effect of EGb 761 in vivo in DSS-induced colitis in mice and in vitro ANA-1 cell line. 3.5 g of EGb 761 were administrated in C57BL/6 type mice after induction of colitis. The results showed that EGb 761 ameliorated systemic stress, lowered levels of TNF-alpha, and reduced to normal the levels of iNOS, Cox-2, TNF-alpha, p53, and p53-serine 15 phosphorylation. EGb 761reduced the colonic cell numbers as CD4+/CD25-/Foxp3- T and drove apoptosis of activated CD4+ effector T cells upstream of the colon. In vitro, EGb 761 extract attenuates pro-inflammatory protein iNOS in a dose-response manner

[17]. Further studies are required to understand the beneficiaries of EGb 761 in ulcerative colitis treatment.

5.2.11 Corydalis dubia, capnoidine solution

Corydalis dubia is a yellow flowering herb that belongs to the Fumariaceae family. Its origin is Bhutan, India. It is used in their traditional medicine as a febrifuge and for treating blood, liver, and bile infections [69]. Attractive is the anti-inflammatory property of a compound isolated from *Corydalis dubia*, named capnoidine. Even though the exact mechanism of action of capnoidine is not precisely known, the response of capnoidine solution in TNBS-induced colitis in mice is significant [46]. The dosage of capnoidine administered could improve body weight loss, mobility, piloerection, and faecal consistency. It reduced adhesion, oedema, ulceration, colon length, altered inflammatory cytokines levels, and reduced levels of p-IκB-α (Ser32) and pNF-κB p65 (Ser536). The mentioned study results make capnoidine a strong candidate for future ulcerative colitis treatment.

5.2.12 Camellia sinensis, green tea extract

Camellia sinensis is a plant that belongs to the family of Theaceae. It is famous for producing green tea, one of the most popular beverages in the world. Green tea has a multiplex composition and contains proteins, amino acids, carbohydrates, lipids, sterols, vitamins, minerals, xanthic bases, pigments, and volatile compounds [70]. Many studies have also pointed out the potential benefits of green tea in animals and humans, such as preventing hepatoxicity, oxidative stress, neurological problems, and antitumorigenic effect [71]. The effect of green tea extract (GTE) on ulcerative colitis is noteworthy. In a study by Mazzon, et al. [47] where ulcerative colitis in Male Sprague-Dawley rats by DNBS, the outcomes of administration of 50 mg/kg of GTE were observed. GTE could attenuate diarrhea and body weight loss, ameliorate the colonic architecture disruption, and reduce MPO and TNF-α production. GTE could reduce the appearance of nitrotyrosine immunoreactivity in the colon and reduce the up-regulation of ICAM-1[47]. Subsequently, GTE can be beneficial in inflammation-related diseases.

5.2.13 Malus domestica "Fuji," modified apple polysaccharide solution

Malus domestica, apple, is an edible fruit that belongs to the Maloideae subfamily and the Rosaceae family. The apple is considered one of the most produced mild temperature tree crops and delineates 25-30 species [72]. The importance of apples in medicine has increased due to

phytochemicals such as polyphenols [49,72,73]. Excessive focus is recently shown on polyphenols and their antioxidant properties, reportedly stronger than vitamin C [73]. Besides this, the importance of another product, modified apple polysaccharides (MAP), has increased. Li, et al. [48] concentrated on the mechanism of modified apple polysaccharides.

They administrated 0.5 mg/mL MAP to a model of DSS-induced mice colitis. The results demonstrated that MAP was potentially protective against intestinal toxicity caused by DSS. Also, it ameliorated colon length shortening and body weight, reduced IL-22 serum level, and decreased the expression of p-STAT3, Bcl-2, and cyclin D1. In addition, they studied the effect of MAP in vitro in two types of cell lines. It was reported that MAP could suppress IL-22-induced activation of STAT3 in MCA-38 cells and up-regulation of the expression of IL-22BP in DC2.4 cells. These results [48] indicate that MAP can be beneficial in treating inflammatory bowel diseases.

5.2.14 Garcinia cambogia, garcinia cambogia extract

Garcinia cambogia is a small or medium-sized tree located initially in South-eastern Asia. From the outside, its fruit looks like a pumpkin. Besides being broadly presented for its weight loss property, it is also ethnobotanically known for treating rheumatism, bowel disorder, and intestinal parasites [74]. Focusing on the bowel remedy of *Garcinia cambogia*, an experimental study in TNBS/ethanol-induced colitis rats was performed *in vitro* and *in vivo* using its extract [50]. *In vivo*, garcinia cambogia extract (0.5 and 1 g/kg) led to a slight weight gain, which was not statistically significant and reduced MPO activity.

Meanwhile, at 1g/kg, it reduced colonic IL-1β expression, inhibited the iNOS colonic expression, and prevented the DNA damage induced by TNBS. *In vitro*, specifically in isolated colonocytes of colitis, garcinia cambogia extract showed the impact at a 1 g/kg dose, preventing DNA damage induced by TNBS/ethanol. Hence, garcinia cambogia extract carries a noteworthy potency in investigating and progressing compounds to treat inflammatory bowel disease.

5.2.15 Fumaria capreolata L., alkaloid extract

The genus *Fumaria* (Fumariaceae) exists in 46 species worldwide. They have various properties such as antihypertensive, diuretic, and potency to treat gastrointestinal and hepatobiliary diseases [75,76]. Important to detach from these 46 species is *Fumaria capreolata*, more specifically, the aerial parts of this plant (AFC). Bribi, et al. [51] studied the anti-inflammatory effects of total alkaloids of *Fumaria capreolata*. The experiment observed the

role of alkaloid extract of aerial parts of this plant in *vitro* and *vivo* in DNBS-induced mouse colitis. In vivo, the experiment results showed that AFC alkaloid extract ameliorated body weight loss, promoted colonic histology recovery, and reduced IL-1 β, TNF α, IL-6, IL-12, and IL-17. Also, it reduced the expression of iNOS, MMP-9, and ICAM-1 protein. Meanwhile, in vitro, in the CMT93 cell line, AFC alkaloid extract down-regulated some inflammatory mediators (TNF α, IL-6, IL-17, and IL-1 β. It up-regulated the expression of proteins like the mucin MUC-2 and ZO-1. This experiment and others that focus on the intestinal anti-inflammatory effect of fumaria capreolata give light to the importance of further, more specific studies.

5.2.16 Prunella Vulgaris, monofloral honey from Prunella vulgaris

Prunella vulgaris, known differently as "self-heal," is a medicinal plant that belongs to the Lamiaceae family. It has purple color flowers that bloom mainly from the end of May to August. The immense importance of this plant is related to its property in treating the common cold, sore throat, and headache, among others [77,78]. The gastrointestinal protective effect of monofloral honey derived from *Prunella vulgaris* (PVH) is significant. In a DSS-induced model of acute colitis in Sprague Dawley male rats, the role of PVH was observed.

The administration of 5 g/kg of PVH decreased DAI, lowered histological scores, and modulated the gut microbiota composition reversing the increase in the Bacteroidetes/Firmicutes ratio and re-establishing *Lactobacillus* spp. populations. This study by Wang, et al. [52] indicates the importance of the anticolitis effect of PVH. It reinforces the perspective of natural honey as an effective food for preventing IBD.

5.2.17 Morinda citrifolia, noni-polysaccharides extraction

Morinda citrifolia, commonly known as Noni, is a shrub or small tree that belongs to the Rubiaceae family. It is native to South Asia but grows all around the tropics [79,80]. In traditional medicine, every part of Noni is used to obtain therapeutical properties. Noni is widely known for its anti-inflammatory, analgesic, antimicrobial, anticancer, hypotensive, antitumor, anthelmintic, antibacterial, antiviral, antifungal, and immunostimulatory properties. The usage of Noni polysaccharides (PLS) and their effect on treating inflammatory bowel diseases such as colitis are of great importance for our topic.

Polysaccharides are a group of complex and heterogeneous macromolecules found in plants. They are important for their low toxicity and a broad spectrum of activities *in vitro* and *in vivo*. Their effect was evaluated in an acetic acid-induced UC in mice. From three different dosages of Noni-PLS extraction studied (0.1, 0.3, and 3.0 mg/kg), 3.0 mg/kg revealed the most

significant results by reducing lesion scores, colonic wet weight, the loss of mucosal architecture, cell infiltration, thickening of muscular layer, abscess formation in the crypt, and depletion of goblet cells. Also, Noni-PLS extraction reduced MPO, MDA, NO3/NO2 levels, reduced IL-1β, TNF-α concentrations, COX-2, and iNOS expression, and restored GSH concentration [80]. Thus, Noni-PLS extraction has significant potential in the treatment of ulcerative colitis.

5.2.18 Glycyrrhiza glabra, glycyrrhizin natural preparation

Glycyrrhiza glabra is a plant that belongs to the Fabaceae family. It is native to Mediterranean areas but is nowadays also found in Russia, China, and India. Among the pharmacological activities of *Glycyrrhiza glabra* can be mentioned its antioxidant, anti-inflammatory, anti-ulcerative, expectorant, antitussive, sedative, neuroprotective, antimicrobial, and antiviral activities [81].

In a study published in 2011, Kudo, et al. [82] evaluated the effectiveness of Glycyrrhizin natural preparation, GL-p, in dextran sodium sulfate-induced ulcerative colitis in male Wistar rats [82]. The results showed that GL-p *in vivo* reduced pro-inflammatory cytokines and chemokines in the colonic mucosa and reduced MPO activity. Meanwhile, no significant therapeutic differences were observed between GL alone and GL-p. *In vitro*, GL-p dose-dependently inhibited MPO activity in mucosal tissue and purified human MPO enzyme. More studies are needed to define the right scheme of administration of GL-p to obtain more and fewer side effects.

5.2.19 Mentha piperita, menthol solution

Mentha piperita (Peppermint) is a plant that belongs to the family Lamiaceae. Its origin is Europe and the Middle East but now is expanded and grown in different world regions. It is famous for its various forms and effects. Apart from being used in pharmaceuticals products, the food industry, and cosmeceuticals [83], there are different results related to peppermint's potential in treating irritable bowel disease. Menthol is one of the main components of peppermint.

In an acetic acid-induced UC model [55], menthol solution positively impacted bodyweight reduction and macroscopic/microscopic ulcer scores. Menthol solution reduced MPO activity and MDA levels, increased GSH levels, reduced interleukin-1, interleukin-23 levels, and tumor necrosis factor-α. It ameliorated lipid peroxidation and oxidative stress. Peppermint has also

been studied in clinical trials [84], but more extended studies are required to obtain favorable results.

5.3 Some herbal formulations

Inflammatory bowel diseases such as ulcerative colitis and Crohn's disease are very complex to be controlled by just one target therapy. Many trials aiming at just one single target agent have failed to succeed. Future studies should focus on multiple target therapy, hoping the synergistic combination can bring brighter results.

Some studied plants individually hold anti-inflammatory properties (as in sections 5.3.1 and 5.3.2), which can have significant potential in treating IBD. Below will be presented two different herbal formulations, 5.3.1 and 5.3.2, respectively.

5.3.1 Forsythia koreana, Corydalis Saxicola, Semiaquilegia adoxoides, Taraxacum officinale, Chrysanthemum coronarium, Glycyrrhiza inflate, Lonicera japonica

An herbal aqueous extract comprises seven herbs: Forsythia koreana, Corydalis Saxicola, Semiaquilegia adoxoides, Taraxacum officinale, Chrysanthemum coronarium, Glycyrrhiza inflate, Lonicera japonica, which individually has anti-inflammatory properties, was studied in vivo and induced DSS model of murine colitis in Female Swiss-Webster mice. Two groups of mice with herbal extract doses of 228.5 pg/ml po and 165.7 pg/ml pr, respectively, were analyzed.

The results showed that the herbal extract, compared to the control mice for both groups, decreased DAI, colonic ulceration, and neutrophil sequestration in the colonic mucosa [85]. Further studies are needed to outline the exact compound found in this herbal formulation, responsible for the favorable effects in ameliorating DSS-induced colitis.

5.3.2 Zingiber officinale, Terminalia chebula, and Aucklandia lappa

KM1608 is an herbal formulation composed of 3 plants: *Zingiber officinale, Terminalia chebula*, and *Aucklandia lappa*, whose remarkable anti-inflammatory activities were previously studied. The purpose of bringing these three plants together was to evaluate their synergistic anti-inflammatory potential in a TNBS-induced model of colitis [86].

Three different doses of KM1608 herbal formulation, 200, 400, and 600 mg/kg, were administered to three groups of TNBS-induced ICR mice. The outcome of this study demonstrated that *in vivo* KM1608 improved very little the colon length and decreased the DAI

and the colon weight/length ratio in a dose-dependent way. At 600 mg/kg decreased, MPO activity and TNF-α levels and slightly decreased IL-6 levels in the colon tissue lysate. Of great importance is the result obtained from a 600 mg/kg dose of KM1608. It manifested much better parameters for many of the indices used for colitis evaluation compared to 5-ASA and prednisolone.

Overall, the therapeutic outcome obtained from KM1608, composed of 3 plants, was more potent when compared to the outcome of each of these two plants individually or when they formed an herbal formulation that consisted of just two plants. Since KM1608 alleviated colitis symptoms in this TNBS-induced model, optimistically, it can be beneficial in the schemes of IBD treatment.

5.4 Plant and plant products in clinical trials

Table 2 summarizes some important plant and plant products studied in clinical trials from 2003 to 2020, mostly from the last ten years. In contrast to Table 1., Table 2 has a limited number of trials that helps us understand the narrow number of human studies. The four plants/plant products selected here have just one target agent. Regarding the mechanism of action, Germinated barley foodstuff prebiotic has an almost clear mechanism of action. In contrast, the other three`s mechanism of action is unknown or needs to be defined by evaluating the proposed mechanisms. The selected clinical trials are double-blind or open-label trials. The maximum number of patients who participated in these clinical trials is 59. In most of them, a placebo is used as a control, and just in one of them, baseline treatment (5-ASA/steroids) is used.

These clinical trials are performed on mild to moderate UC patients. The most significant outcomes are registered briefly as below in Table 2. Favorably there are very few adverse effects noted during these clinical trials.

Table 2. Summary of the Plant and plant products in clinical trials.

Name of plant	Plant product	Mechanism of action (potential)	Control	Dosage	Study in humans	Clinical trials (nr)	Success in humans	Outcome	Side effects	Reference
Zingiber officinale (Ginger)	Ginger capsules	Some mechanisms of action are proposed, but yet further studies are required.	Placebo	Four capsules (4 x 500 mg dried ginger powder)	A randomized, double-blind, placebo-controlled trial.	46 patients with active mild to moderate UC	Ginger capsules can ameliorate the treatment of patients with UC	Ginger: ↓ MDA and improved the severity of disease activity scores; however, it did not affect serum total antioxidant capacity (TAC); it Improved the life quality of patients.	Heartburn in some patients that took ginger capsules with an empty stomach. Some other patients expressed dissatisfaction because of the foul-smelling of ginger in the digestive tract.	[87]
Mentha piperita (Peppermint)	Enteric-coated peppermint oil capsules	Peppermint oil causes a relaxing effect by interacting with smooth Muscle calcium channels.	Placebo (225mg of maltodextrin with mint flavor) 26 patients	2 enteric-coated capsules (1 caps=225mg of peppermint oil + 45mg of Natrasorb) 24 patients	Double-blind placebo-controlled randomized trial	50 Patients	The positive effect of peppermint oil lasts one 1month after the therapy in more than 50% of treated patients.	Peppermint oil capsules ↓ notably IBS symptoms after four weeks of treatment.	Intense heartburn led to 1 patient's withdrawal.	[84,88]
Hordeum vulgare (Barley)	Germinated barley foodstuff prebiotic (GBF)	GBF alternates the diffusion of microflora and increases the colonic butyrate content. The augmentation of butyrate has an anti-inflammatory effect because it impedes the production of pro-inflammatory cytokines. Also, the water-holding capacity of GBF, which is noticeable high, improves bowel movement, serving as a second mechanism.	It was challenging to set up a control substance (placebo) that does not influence the intestinal tract due to GBF's bulky and insoluble properties.	20-30 g of GBF daily + baseline treatment for six months.	Open-label trial	21 Patients (mild to moderate UC)	GBF was securely administered without any dietary limitations and positively impacted UC patients during the 6-month administration.	GBF (after six months): ↓ visible blood in the stool and the presence of nocturnal diarrhea; ↓ the total clinical score compared with the scores for 0 and 3 months; Ameliorated erythema, granularity, and erosion intensely.	No febrile or allergic reactions and no side effects in any patients. The administration of GBF was accepted well by patients with active UC.	[89-91]
	Germinated barley foodstuff prebiotic (GBF)		Baseline treatment (5-ASA or steroids)	20 g of GBF (21.8-23.6 g/day) + baseline treatment daily for 12 months.	Open-label trial	59 patients (in clinical remission stage with low-level UC disease activity)	GBF was securely administered without any dietary limitations and contributed positively to UC remission stage patients during 12-month administration.	In the GBF group: CAI was improved at 3, 6, and 12 months; In the GBF+ steroid group: The cumulative recurrence rate was lower; GBF administration was well tolerated, and it seems adequate maintenance therapy to attenuate steroid dose.	No patient experienced side effects.	[92]

Name of plant	Plant product	Mechanism of action (potential)	Control	Dosage	Study in humans	Clinical trials (nr)	Success in humans	Outcome	Side effects	Reference
Strobilanthes cusia	Indigo Naturalis (IN) capsules	The mechanism of action remains unknown.	Placebo (19 patients)	500 mg IN capsules (23 patients)	Multicenter, double-blind clinical trial	42 patients with mild to moderately active UC	Indigo Naturalis (IN) was highly influential in short-term administration.	IN: improved albumin level and the Lichtiger index in 2 weeks.	Five patients experienced mild headaches in the IN group and one in the placebo group. No profound adverse effect in 2 weeks.	[93]

Note: GBF: Germinated barley foodstuff prebiotic; IBS: inflammatory bowel disease; IN: Indigo Naturalis capsules; TAC: serum total anti-oxidant capacity; UC: ulcerative colitis.

5.4.1 Zingiber officinale, ginger capsules

In a randomized, double-blind placebo-controlled study where 46 patients with active mild to moderate UC participated, ginger in capsules (each capsule was composed of 500 mg dried ginger powder) remarkably improved patients' quality of life in the third month of treatment. Furthermore, four capsules/day of administration could improve disease activity and decrease MDA. Nevertheless, this dosage and timespan could not influence TAC [87]. Consequently, more studies with different dosages and timespan are needed to achieve solid conclusions.

5.4.2 Mentha piperita, enteric-coated peppermint oil capsules

In a double-blind placebo-controlled randomized study [84], where 50 patients with IBS symptoms participated, the potency of enteric-coated peppermint oil capsules were observed. Enteric-coated peppermint oil capsules (each capsule composed of 225mg of peppermint oil and 45 mg of Natrasorb starch) taken 2/day in a four-week treatment had a positive effect in reducing the abdominal symptoms, for one month after the therapy in more than 50% of treated patients compared to the placebo group [84]. However, a four-week duration of treatment is considered short, though more extended studies are required at this point.

5.4.3 Hordeum vulgare (Barley), germinated barley foodstuff prebiotic

Hordeum vulgare (Barley) is a crop that belongs to the grass family. Besides its importance in the food industry, barley is being studied for its favorable impact on health due to Germinated Barley Foodstuff GBF [94]. This byproduct contains mainly aleurone and scutellum [90]. In two open-label trials [90,92], GBF was administered to patients with mild to moderate UC associated with baseline treatment for 6 and 12 months. After six months of treatment GBF reduced visible blood in the stool, decreased total clinical score, and ameliorated erythema, granularity, and erosion. Meanwhile, the 12-month trial study [92] reported a lower cumulative recurrence rate. GBF administration was well tolerated and seemed adequate as a maintenance therapy to attenuate baseline treatment dosage.

5.4.4 Indigo Naturalis, capsules

Indigo Naturalis IN is a blue pigment found in plants like *Strobilanthes cusia*, *Indigofera bungeana Walp*, and *Isatis tinctoria*. In a multicentre, double-blind clinical trial [93], 42 patients

with mild to moderately active UC were analyzed for two weeks. The trial was organized in two groups, taking 500 mg of placebo and IN capsules. At the end of two weeks, the group that took IN capsules improved the albumin level and Lichtiger index. Although no serious side effects were observed, the short-term trial could not state long-term benefits or threats [93]. However, further studies are required for better beneficial uses of IN.

6. Discussion

The literature review affirmed that numerous studies were performed on plant and plant products using the experimental model of UC. The vast majority of these plants were selected due to their strong background in traditional medicine and proven success for centuries. Most of the studies in this literature review were performed *in vivo* in different induced models of UC in mice and *in vitro* in various cell lines.

Different pharmaceutical plant products developed and administrated in the experimental colitis mice model demonstrated their potential to increase efficacity and ameliorate UC. More specifically, microcapsules were demonstrated to be more favorable to inflamed colon and have a modified released system. Another competitive product is GELN [35]. These grape exosome-like nanoparticles successfully stimulate the proliferation of intestinal stem cells *in vivo* and *in vitro*. In addition, another nanoparticle, GDPN2 [39], ginger-derived nanoparticles, is very promising in improving IBD.

Since nanoparticles derived from natural sources can overcome toxicity and can be produced on a larger scale are considered to be safe and cost-effective. Herbal formulations (for example, KM1608), thanks to their multiple biological characteristics, had a significant impact that left behind even the results of 5-ASA and prednisolone [86]. However, since herbal formulations hold many biological compounds, detailed studies are needed to fully understand the relationship between compounds, dosage, and pharmacological effects.

There are various remarkable outcomes in experimental colitis cases or clinical trials. Figure 11 presents all the outcomes of plants and herbal formulations that belong to our literature review, from the lowest to the highest. The overall outcomes of *Mentha piperita, Syringa vulgaris, Grape, and Curcuma longa* are prominent, with 11, 11, 13, and 15 total outcomes, respectively, highlighting the importance of further studies regarding these plants and a potential satisfactory herbal formulation if these four plants come together in a single product with a multiple target therapy. More detailed information on outcomes can be found in Table A. 1 in the appendix.

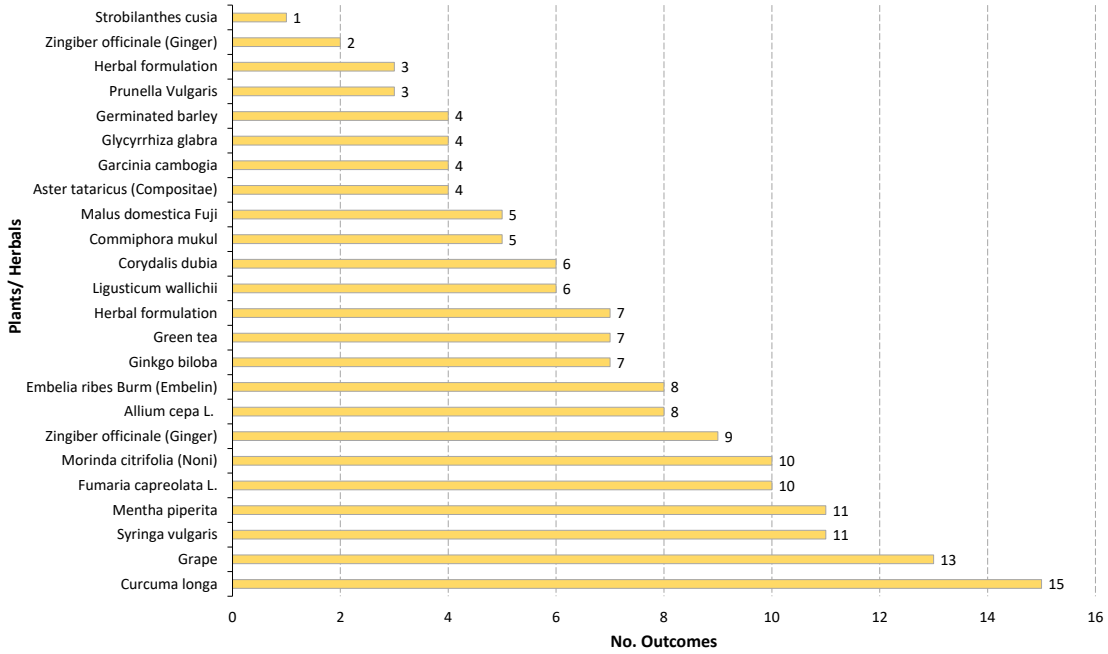


Fig. 11. Overall number of outcomes of plant products/ herbal formulations in experimental colitis or clinical trials ordered from the lowest to the highest.

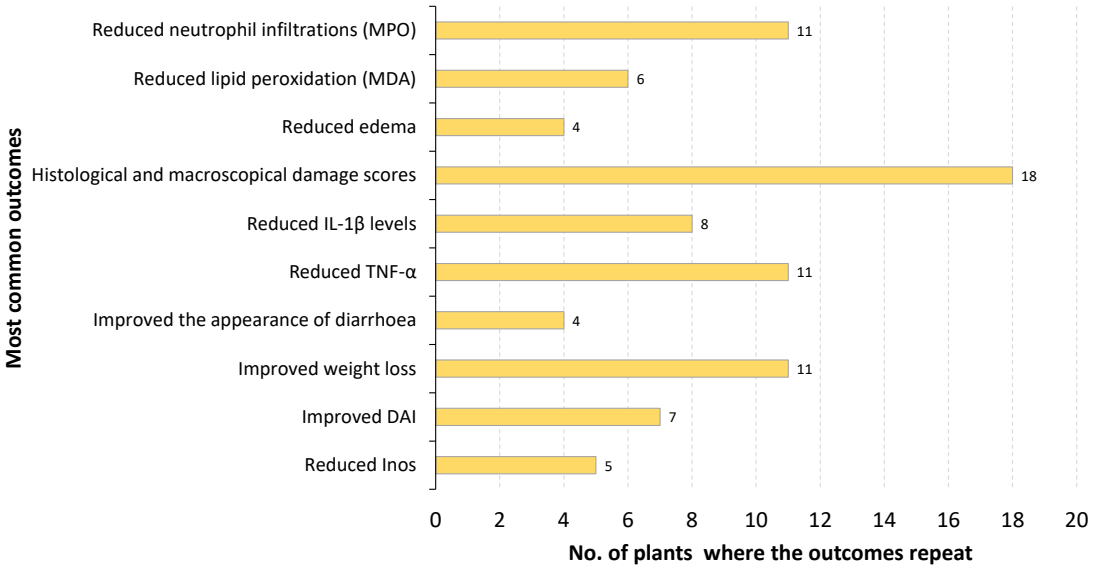


Fig. 12. The most common outcomes repeated in different plant products/herbal formulations.

Meanwhile, Figure 12. Represents the most common outcomes repeated in different plant products/herbal formulations, where reduced histological and macroscopical damage score is the most common outcome. This is followed by reduced neutrophil infiltration (MPO), reduced TNF-alpha, and improved weight loss. Considering overall outcomes for each plant and outcomes that repeat more (Figures 11 and 12), the plants with a significant number of outcomes

can be considered for a screening process. More detailed information can be found in Table A. 2. In the appendix.

Hence pharmaceutical industries and governmental agencies should invest more in this direction to speed up the research and find appropriate natural compounds that can control and cure IBD worldwide.

7. Future Research Recommendations

More clinical and pharmacological studies should be performed to reach concrete results in treating UC. More attention and investment should be given to natural nanoparticles since they target delivery into the colon and hold a huge potential in treating IBD. A combination of multiple natural exosomes in one single nanoparticle can be promising in the future as exosomes serve as good transporters of proteins, lipids, mRNAs, and microRNAs to destiny cells.

More clinical trials should analyze the nontoxicity of nanoparticles that target the colon.

More research should be done on herbal formulations since there are still gaps regarding the relation of components and dosage with the exact pharmacological effects.

UC conventional treatment holds a considerable cost; meanwhile, treatment with plant products is considered less expensive. So, the cost-effectiveness ratio of plant products should be evaluated in future studies.

8. Concluding Remarks

Various studies show the effectiveness of plants, plant products, and herbal formulations in ameliorating ulcerative colitis.

Several pharmaceutical plant products are developed in different studies like microcapsules, nanoparticles, nanospheres, solutions, emulsions, and extracts.

For example, in Table 1, Quercetin-Loaded Microcapsules are distinguished by reducing inflammation by impeding pro-inflammatory cytokine production, maintaining the antioxidant defenses, and the anti-inflammatory cytokine IL-10. Quercetin-Loaded Microcapsules showed to be superior to nonencapsulated quercetin. Thus, they are a good case that raises the importance of developing a modified released system for more efficacity when using natural compounds.

Another plant product, Embelin LNs, derived from *Embelia ribes Burm* (Embelin), has remarkable results in preventing induced UC in rats compared to embelin conventional suspensions. The slow release of Embelin LNs and the preferable ingestion from the inflamed colon remarks the future potential of this nanosphere.

Many plant products demonstrate the same anti-inflammatory properties; hence it would be good to focus more on the research of herbal formulation since the synergistic combination brings stronger and more resultative products.

For example, in Table 1, KM1608 herbal formulation composed of three plants, namely *Zingiber officinale, Terminalia chebula*, and *Aucklandia lappa*, eases the symptoms of colitis and the inflammatory responses better than 5-ASA and prednisolone. KM1608, composed of 3 plants, shows a potent synergism due to multiple target network mechanisms and greater efficacy.

Table 2 includes just four plant products studied in clinical trials, revealing the small number of plant products studied in humans. The small number of participants in each of these clinical trials is emphasized, as also their mild to moderate stages of ulcerative colitis. More research is needed, including severe stages of ulcerative colitis as well. The plant products were accepted well by the patients with active UC, except for some in the ginger capsules clinical trial. In the ginger capsule clinical trial, some patients complained of heartburn and foul-smelling ginger in the digestive tract. Another clinical trial based on enteric-coated peppermint oil capsules, a product derived from *Mentha piperita*, signalized intense heartburn in one patient who withdrew from the trial.

These plant products ameliorated ulcerative colitis in short-term administration. However, long-term studies are required to understand their effectiveness and adverse reactions better.

Generally, these plant products' work is not widely known, so more studies are needed to better understand their mechanism of action.

Conventional therapy of ulcerative colitis is not a cheap treatment. However, further studies are needed to calculate the cost of herbal therapy, which is expected to be smaller. Government agencies and pharmaceutical companies should contribute financially to promote the progress of clinical studies until a satisfactory solution is established.

Appendices

Appendix A

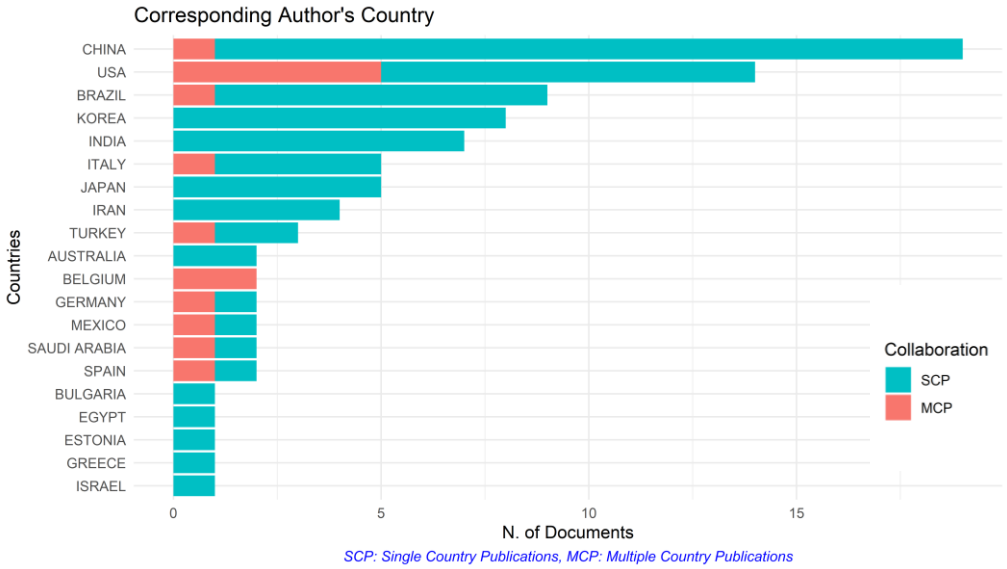


Fig. A 1. Type of collaboration among most contributing countries in ulcerative colitis studies.

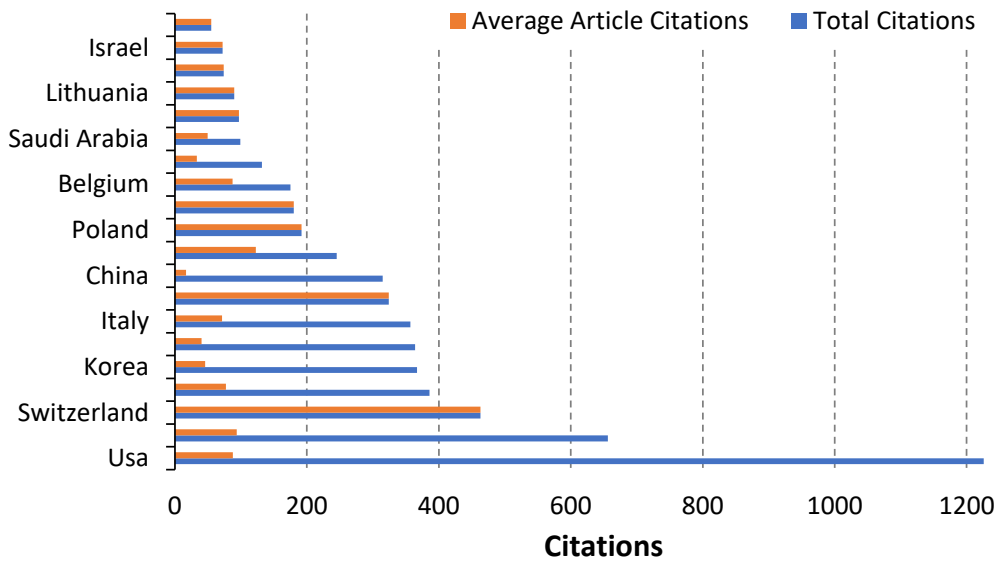


Fig. A 2. Publication's citations from the most contributing countries in ulcerative colitis studies.

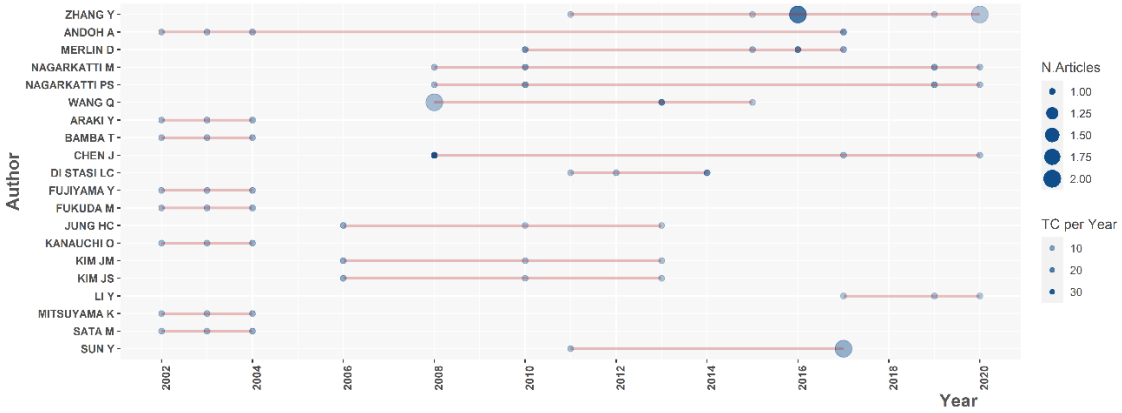


Fig. A 3. The most contributing authors in publications number and Total Citations (TC).

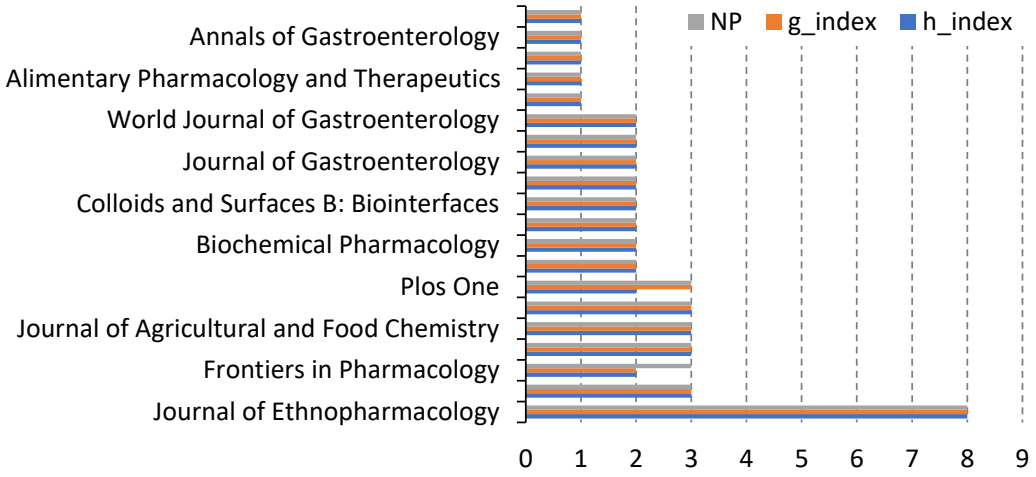
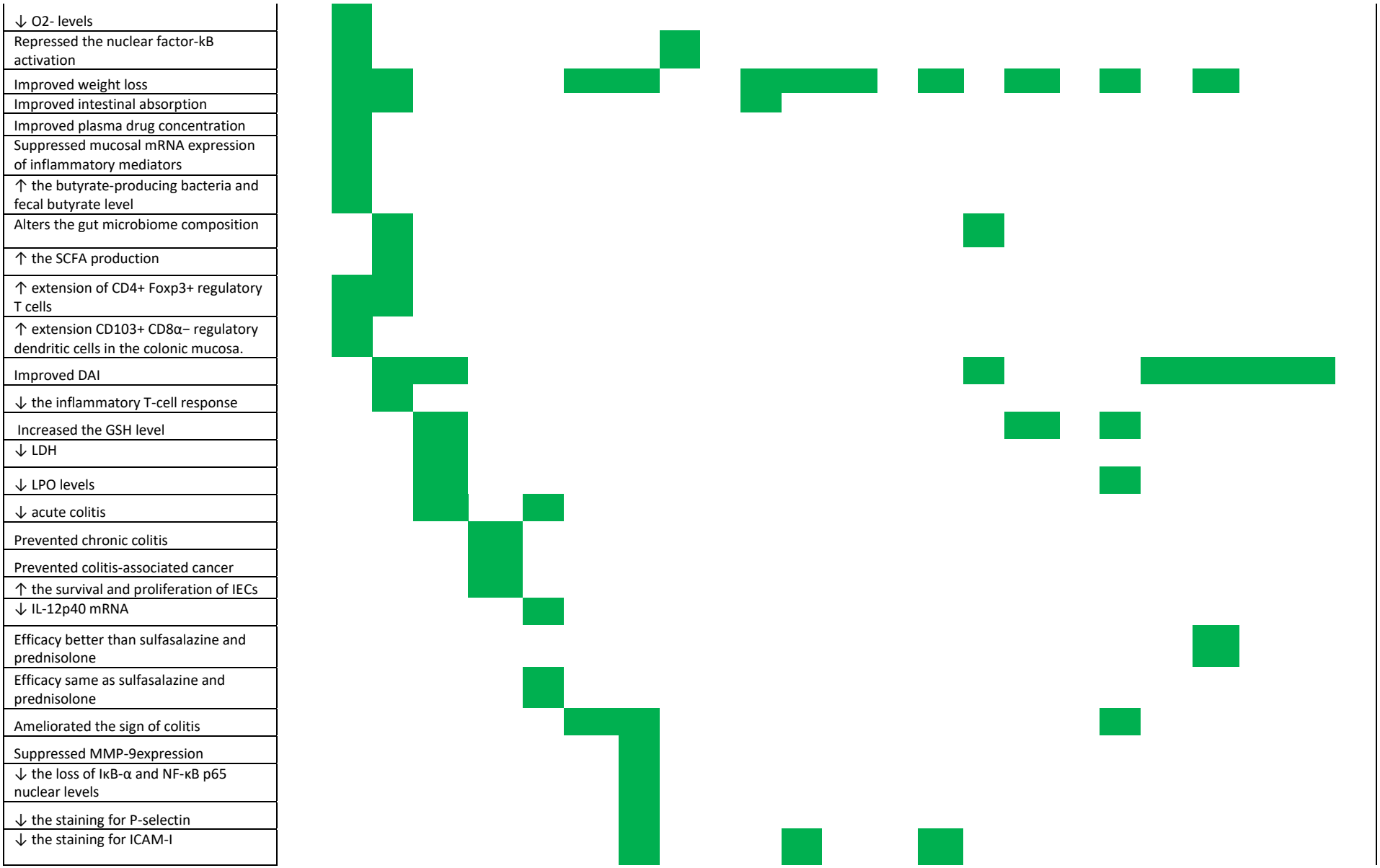


Fig. A 4. The Number of Publications (NP) and respective indexes for the most contributing journals in ulcerative colitis studies.

Table A. 1. Outcomes of plants and herbal formulations in experimental colitis and clinical trials.


↓ O2- levels
Repressed the nuclear factor-kB activation
Improved weight loss
Improved intestinal absorption
Improved plasma drug concentration
Suppressed mucosal mRNA expression of inflammatory mediators
↑ the butyrate-producing bacteria and fecal butyrate level
Alters the gut microbiome composition
↑ the SCFA production
↑ extension of CD4+ Foxp3+ regulatory T cells
↑ extension CD103+ CD8α− regulatory dendritic cells in the colonic mucosa.
Improved DAI
↓ the inflammatory T-cell response
Increased the GSH level
↓ LDH
↓ LPO levels
↓ acute colitis
Prevented chronic colitis
Prevented colitis-associated cancer
↑ the survival and proliferation of IECs
↓ IL-12p40 mRNA
Efficacy better than sulfasalazine and prednisolone
Efficacy same as sulfasalazine and prednisolone
Ameliorated the sign of colitis
Suppressed MMP-9expression
↓ the loss of IκB-α and NF-κB p65 nuclear levels
↓ the staining for P-selectin
↓ the staining for ICAM-I

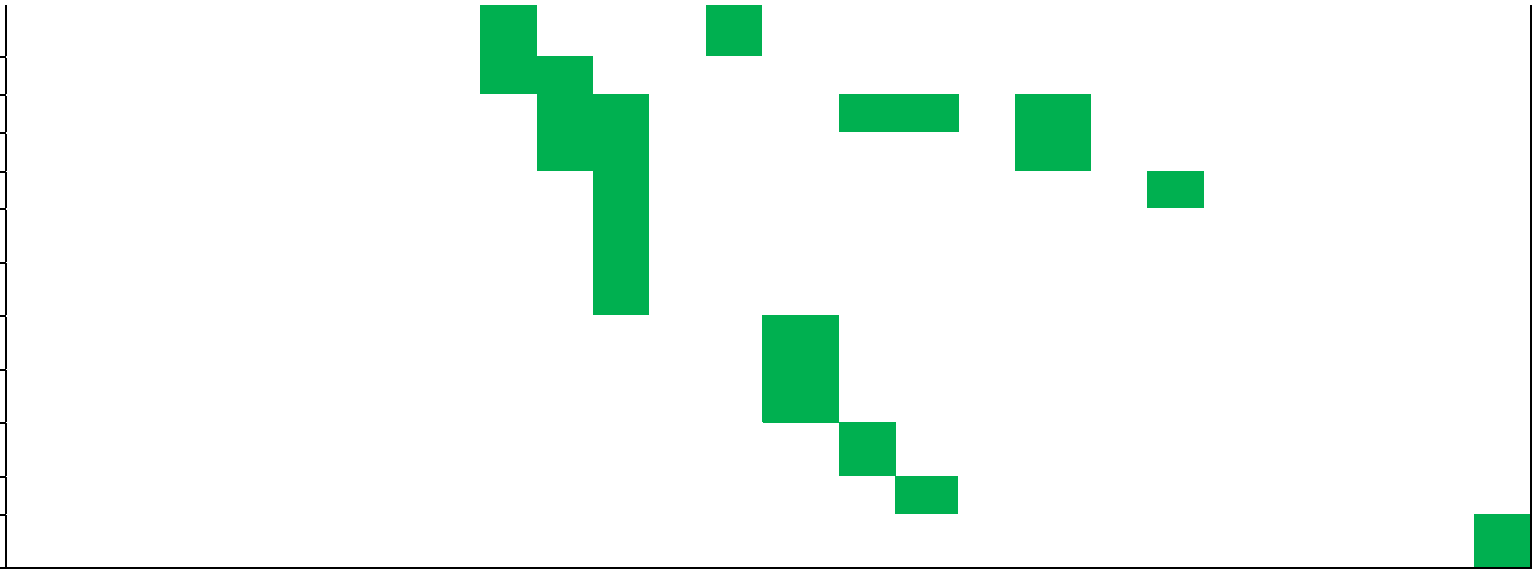
↓ the staining for iNOS and nitrotyrosine	
↓ C-MYC,	
↓ iNOS	
↓ COX-2	
Ameliorated systemic stress	
Drives apoptosis of activated CD4+ effector T cells upstream of the colon	
↓ the colonic cell numbers as CD4+/CD25-/Foxp3- T	
↓ the expression of p-STAT3, Bcl-2, and cyclin D1	
Protective against intestinal toxicity caused by DSS	
Prevent the DNA damage induced by TNBS	
↓ the expression of MMP-9	
Improved albumin level and the Lichtiger index	

Table A. 2. Plants with significant outcomes can be considered for screening.

15 Plants → Screening!!!

PLANTS/HERBAL FORMULATIONS / OUTCOMES THAT REPEAT MORE	Allium cepa L.	Curcuma longa	Grape	Embelia ribes Burm (Embelin)	Zingiber officinale (Ginger)	Commiphora mukul	Syringa vulgaris	Ligusticum wallichii	Ginkgo biloba	Corydalis dubia	Green tea	Fumaria capreolata L.	Morinda citrifolia (Noni)	Mentha piperita	KM1608	Zingiber officinale (Ginger)
OVERALL OUTCOMES FOR EACH	8	15	13	8	9	5	11	6	7	6	7	10	10	11	7	9
OUTCOMES THAT REPEAT MORE	5	5	6	4	3	3	4	3	2	4	5	5	7	5	6	2
↓ neutrophil infiltration (MPO)	■	■	■	■							■		■	■		
↓ lipid peroxidation (MDA)	■	■	■										■	■		■
↓ edema	■			■				■		■						
↓ histological and macroscopical damage scores	■	■	■	■	■	■	■	■		■	■	■	■	■		
↓ IL-1β levels	■		■		■		■					■	■			
↓ TNF-α					■	■	■		■		■	■	■	■		
Improved the appearance of diarrhoea		■								■	■					
Improved weight loss		■	■				■			■	■	■	■	■		
Improved DAI			■	■												■
↓ iNOS								■	■			■	■			
Efficacy better than sulfasalazine and prednisolone																
Efficacy same as sulfasalazine and prednisolone						■										

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