Medicinal Plants in the Treatment of Colitis: Evidence from Preclinical Studies

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Key words

ulcerative colitis, medicinal plant, phytotherapy, flavonoid, terpene

received November 11, 2016
revised January 17, 2017
accepted February 20, 2017

Bibliography

DOI http://dx.doi.org/10.1055/s-0043-104933
Published online March 14, 2017 | Planta Med 2017; 83: 588–614 © Georg Thieme Verlag KG Stuttgart · New York | ISSN 0032-0943

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ABSTRACT

Ulcerative colitis is a chronic inflammatory condition whose treatment includes aminosalicylates, corticosteroids, and immunomodulators. Medicinal plants seem to be an important alternative treatment for this condition. They have been the subject of a great number of studies in recent years. This study was conducted to systematically review the medicinal plants tested in experimental models of ulcerative colitis. We conducted a systematic literature search through specialized databases (PUBMED, SCOPUS, EMBASE, MEDLINE, LILACS, SCIELO, and SCISEARCH) and selected articles published between January 2000 and June 21, 2016 by using "medicinal plants" and "ulcerative colitis" as key words. Sixty-eight studies were included, and the families Asteraceae and Lamiaceae presented the largest number of studies, but plants from several other families were cited; many of them have shown good results in experimental animals. However, only a few species (such as *Andrographis paniculata* and *Punica granatum*) have undergone clinical tests against ulcerative colitis, and the observation that many preclinical studies reviewed are purely descriptive has certainly contributed to this fact. Chemical constituents (mainly flavonoids and terpenes) seem to play a role in the effects of the plants. Thus, the data herein reviewed reinforce the potential of medicinal plants as a source of alternative approaches to the treatment of ulcerative colitis.

Introduction

IBDs mainly comprise two different clinical conditions, UC and Crohn's disease, that bear distinct characteristics, since UC is restricted to the colon and rectum and Crohn's disease may affect any region of the gastrointestinal tract [1]. The main symptoms of UC include diarrhea, abdominal cramps, and rectal bleeding, while Crohn's disease causes abdominal pain, diarrhea, fatigue, weight loss, and occasional bleeding as common symptoms.

Although there are few epidemiologic data from developing countries, the incidence and prevalence of UC has been increasing over the decades and in different regions worldwide, indicating its emergence as a global disease. In Brazil, Parente et al. [2] demonstrated a predominance of UC in people who are under 40 years old, mixed-race, or low-income in the geographic area of Northeastern Brazil.

The symptoms of UC emerge from gastrointestinal tract inflammation that leads to chronic tissue damage in susceptible individuals exposed to environmental risk factors. The etiology remains unknown, although alterations in innate and adaptive immune pathways seem to be involved in this process [3].

In addition, an imbalance in proinflammatory cytokines, such as TNF-α, IFN-γ, IL-1, IL-6, and IL-12, and anti-inflammatory cytokines, including IL-4, IL-10, and IL-11, is suggested to be crucial in the modulation of the inflammatory process [4]. A significant number of studies support this hypothesis in experimental models of intestinal inflammation that have been generated [5].

The ideal therapeutic strategies for patients with UC should not only induce remission, but also maintain long-term remission as well as reduce abnormal colon inflammation, diarrhea, rectal bleeding, and abdominal pain. Generally, anti-inflammatory drugs, such as 5-aminosalicylic acid, corticosteroids (dexamethasone), immunosuppressive drugs, 6-mercaptopurine, and aza-

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ABBREVIATIONS

CAT	catalase
COX	cyclooxygenase
DAI	disease activity index
DSS	dextran sulfate sodium
GPx	glutathione peroxidase
GSH	glutathione
IBDs	inflammatory bowel diseases
IFN-γ	interferon gamma
IL	interleukin
iNOS	inducible nitric oxide synthase
JNK	c-Jun N-terminal kinase
LDH	lactate dehydrogenase
MAPK	mitogen-activated protein kinases
MDA	malondialdehyde
MPO	myeloperoxidase
NF-κB	nuclear factor-κB
NO	nitric oxide
PGE_2	prostaglandin E_2
PI3K	phosphatidylinositol 3-kinases
p-JNK	phosphorylated c-Jun N-terminal kinase
p-p38	phosphorylated p38 kinase
SOD	superoxide dismutase
STAT	signal transducer and activator of transcription
TNBS	2,4,6-Trinitrobenzenesulfonic acid
TNF-α	tumor necrosis factor-α
UC	ulcerative colitis

thioprine, are used [6]. Another alternative for the treatment of UC is the use of biological agents, such as anti-TNF-α agents, which were the first biological agents applied to treat UC. Other examples include infliximab and adalimumab, which are currently in use for treating UC. Recently, golimumab, another anti-TNF-α agent, and vedolizumab, an anti-adhesion therapy, have been approved for UC treatment [7].

Because of potential adverse events and the lack of effectiveness of standard therapies, a widespread search has been launched to identify new therapies from natural sources to replace or complement actual drug options for UC treatment. In this way, medicinal plants are considered a potential resource to control various diseases, including UC. Many articles have reported the importance of medicinal plants in the treatment of UC [8–10].

Some systematic reviews have been conducted in order to evaluate the efficacy of herbal therapy in the treatment of patients with IBDs, including UC [11, 12]. These studies have shown a great need for randomized, controlled trials with less limitation and heterogeneity in spite of the promising effects found in preclinical studies on medicinal plants in UC. Thus, the aim of the present study was to develop a systematic review to analyze whether medicinal plants have efficacy in the treatment of UC in experimental studies, which represents an important step for making decisions on translational advances.

Search Strategy

A systematic review was carried out through a literature search performed in June 2016 and included articles published over a period of 16 years (from January 2000 to June 21, 2016). This literature search was performed through specialized databases (PUBMED, SCOPUS, EMBASE, MEDLINE, LILACS, SCIELO and SCISEARCH) using different combinations of the following MeSH terms: medicinal plants and ulcerative colitis. The inclusion criteria used for manuscript selection considered original articles published in English, Spanish, and Portuguese, articles with the key words in the title, abstract, or full text, and studies that used plants for treating UC. Studies targeting only isolated secondary metabolites, combinations of two or more plants, or other associated types of pathology (like colon carcinogenesis) were excluded from the search.

For the selection of the manuscripts, two independent investigators (M. T. S. S. and L. M. C.) first selected the articles by analyzing the titles. The abstracts of the selected articles were then analyzed, and finally the full texts of the articles were evaluated. Any disagreement was resolved through a consensus between the investigators. The resulting articles were manually reviewed with the goal of identifying and excluding the studies that did not fit the criteria described above. The selected studies were submitted to a hand search, and the cited references that met the inclusion criteria were also included.

All the selected studies were submitted to data extraction by two collaborators (L. M. C. and M. T. S. S.) using a standardized form and were verified for their quality and accuracy by a third collaborator (E. A. C.). The information extracted included the species and family of the plants, the part of the plant used, the dose and route used, the animal model of colitis, a summary of the results, the bioactive compounds found, the study selected, and the reference.

To guide the discussion of data, the selected articles were divided according to the families of plants and were also submitted to additional analysis that considered the following: i) whether the effect of the medicinal plant on colitis was not purely descriptive and was accompanied by any evidence about the mechanism underlying the effect and ii) whether any isolated compound was described for such plants and was related to the beneficial effect on colitis by the selected study itself or other studies presented in the literature.

Data evaluation and outcomes

This review searched for plants with anti-inflammatory activity on UC over the past 16 years. The primary search identified 379 articles (93 from PUBMED, 180 from SCOPUS, 31 from EMBASE, 56 from MEDLINE, 17 from SCISEARCH, 1 from SCIELO, and 1 from LILACS).

After the initial screening of titles, abstracts, and full text and the exclusion of repetitions, 43 articles were selected. The hand search in the references of the selected articles allowed for the identification of 25 additional articles that met the inclusion crite-

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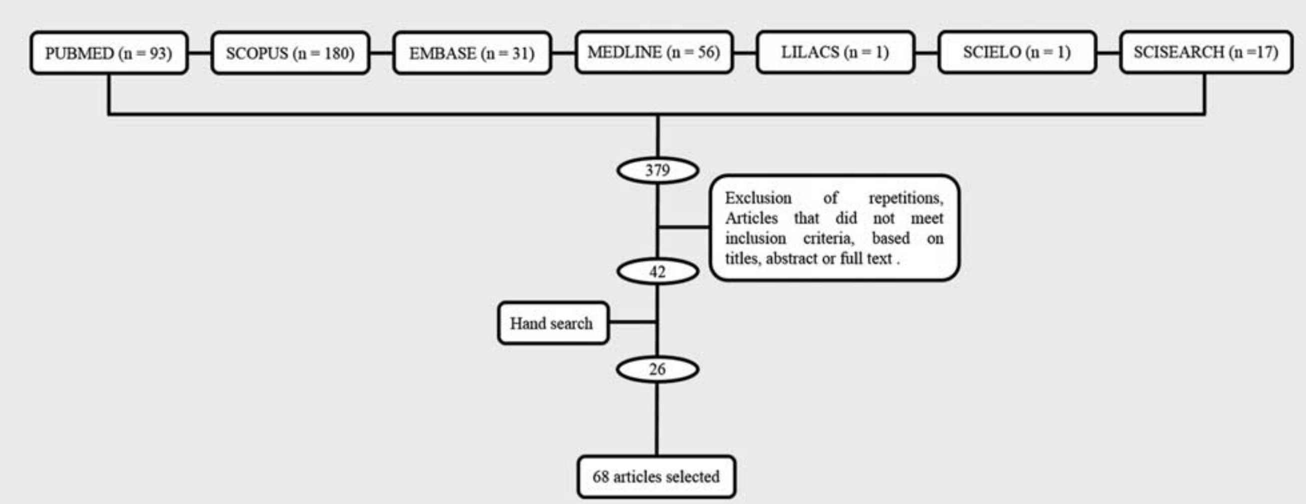

▶ **Fig. 1** Flow chart for the results of the search conducted in the study.

ria. Therefore, 68 studies were included in this review. A flowchart illustrating the study selection process is shown in ▶ **Fig. 1**.

A considerable number of articles were found in the hand search. This was caused by the inhomogeneity or inconsistence in the key words used by a number of studies, which made the identification of these studies difficult. This fact highlighted the need for choosing the study key words carefully, considering the MeSH terms or other database language, in order to optimize the identification of the study in the databases and avoid the risk that it will not be found by other researchers [13, 14].

In the articles found by the present review, plants from 32 families were investigated for their effects on colitis. The families Asteraceae and Lamiaceae presented the largest number of studies, comprising a total of ten studies each. In the families Fabaceae and Rosaceae, we found seven and six studies, respectively. The family Zingiberaceae presented four studies, the families Malvaceae and Araliaceae presented three studies each, and the families Apocynaceae, Boraginaceae, Euphorbiaceae, Moraceae, Moringaceae, Polygonaceae, and Solanaceae presented two studies each. For other families, we found only one study each.

Due to the high diversity of species used in the studies selected, we found that many parts of the plants were used, mainly leaves, aerial parts, barks, and fruits, besides other parts. The main route used to administer the plant extracts was the oral route, followed by rectal administration. The details of the studies are shown in ▶ **Table 1**. Regarding the model of colitis, as shown in ▶ **Table 2**, 51.3 % (n = 39) of the studies utilized the model of acetic acid-induced colitis, 23.7 % (n = 18) utilized TNBS-induced colitis, 19.7 % (n = 15) used DSS-induced colitis, and 5.3 % (n = 4) used other models to induce colitis. These studies were conducted in rats (65.8 %) or mice (34.2 %).

The acetic acid model is commonly employed because of its low cost and the easy induction of colitis in both rats and mice. The intrarectal injection of acetic acid bears a close resemblance to colitis in terms of histopathological features and the profile of mediators presented in the acute response of colon inflammation [15]. However, murine models of intestinal inflammation have been improved by knowledge of mucosal immunity, thus increasing our ability to interpret the complex pathophysiology of colitis. The DSS model is the most traditional when one desires to evaluate the characteristics of UC. Administration of DSS in the drinking water has also been extensively used along with azoxymethane to study colon cancer. However, intracolonic injection of TNBS results in intestinal inflammation and has been broadly used to investigate immunologic features that are suggested to mimic the alterations found in Crohn's disease in humans but has some limitations, such as the fact that in Crohn's disease, many parts of the digestive tract can be inflamed, while in the model of TNBS, the route of administration favors colonic inflammation [1, 16].

The articles were evaluated in search of information about the efficacy of the plants to treat colitis, the likely mechanism involved in this effect, and whether isolated compounds were identified for such plants by the selected study itself or by others. Based on this information, some articles are summarized below in more detail. Information about the other articles can be found in ▶ **Table 1**.

Family Asteraceae

Asteraceae (previously known as Compositae) is one of the largest families of plants, comprising approximately 1600 genera and 23 000 species all over the world, which may have contributed to the high number of studies selected with plants from this family.

Among the species from this family cited in the selected studies (▶ **Table 1**), we highlight the effect of *Arctium lappa* L., *Baccharis dracunculifolia* DC, and *Ixeris dentata* (Thunb. ex Thunb.) Nakai on UC in experimental animals.

A. lappa L. is a plant that contains more polysaccharides and residues than other vegetables and is easily obtained throughout the year. Wu et al. [17] evaluated the beneficial effects of the ethanol extract, petroleum ether fraction, *n*-butanol fraction, and water fraction of the fruit of *A. lappa*, in doses varying from 25 to 100 mg/kg (p. o.), on colitis induced by DSS (3.5 %) in mice.

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▸ **Table 1** Data about the plants discussed in the studies selected through systematic evaluation of the literature.

Family	Species	Extract and part of the plant	Dose and route	Model of colitis/animal used	Summary of results	Bioactive compounds or classes of compounds found in the study	Reference
Acanthaceae	*Andrographis paniculata* (Burm.f.) Nees	A patented extract of the plant (HMPL-004)	300 mg/kg; p. o.	T cell transfer model/B6 $Rag1^{-/-}$ mice	Treatment with the extract inhibited weight loss, intestinal inflammation, and TNF-α, IL-1β, IFN-γ, and IL-22 expression in the colon. It also prevented early proliferation of $CD4^+$ T cells *in vivo* and concomitant differentiation into Th1/Th17 effector T cells.	None	[147]
Amaranthaceae	*Amaranthus roxburghianus* H. W. Kung	Hydroalcoholic extract of roots alone or in combination with piperine	50 and 100 mg/kg; p. o.	Acetic acid/Swiss mice	Treatment with the extract (100 mg/kg) decreased morphological alterations, MPO activity, and MDA concentration in the colon. Combination with piperine increased the protective effect.	4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl; eugenol; benzene, 1-(1,5-dimethyl-4-hexenyl)-4-methyl	[194]
Amaryllidaceae	*Allium sativum* L.	Garlic formulation (garlic bulbs initially extracted with water)	250 mg/kg; p. o.	Acetic acid/Wistar rats	Garlic decreased colon weight and length, MDA levels, histological alterations and serum nitrate. It also increased colon GSH levels and CAT and SOD activity.	Allicin, ajoene, N-α-(1-deoxy-D-fructos-1-yl)-L-arginine (Fru-Arg), S-allyl-L-cysteine and S-allylmercapto-L-cysteine	[153]
Apiaceae	*Kelussia odoratissima* Mozaff.	Hydroalcoholic extract of aerial parts	125, 250, and 500 mg/kg; p. o.	Acetic acid/Wistar rats	Treatment with the extract (125 and 250 mg/kg) ameliorated macroscopic parameters, histological alterations, and MPO activity in the colon.	None	[163]
Apocynaceae	*Gymnema sylvestre* (Retz.) R.Br. ex Sm.	Ethanol extract of the leaves	50, 100, and 200 mg/kg; p. o.	Acetic acid/Wistar rats	The extract maintained the cytoarchitecture of the entire colon and increased mucus content. It also diminished levels of MDA, sulfhydryl content, and concentrations of IL-1β, IL-6, TNF-α, PGE_2, and NO in colon tissues and increased the activity of SOD and CAT.	Triterpenoid saponins (gymnemic acids I–V, VII, XI, XIII, XVII and XVIII – X), deacylgymnemic acid and gymnemasin B	[120]
	Solenostemma argel (Delile) Hayne	Hydroalcoholic extract of aerial parts	125, 250, and 500 mg/kg; p. o.	Acetic acid/Wistar Rats	All doses of the extract reduced the signs of colitis and colonic lipid peroxidation, plasma levels of TNF-α, catalytic activity of hG-IIA $sPLA_2$ (but not DrG-IB $sPLA_2$), and protease activity.	Flavonoids and terpenoids	[195]
Araliaceae	*Panax quinquefolius* L.	Hydroalcoholic extract of the root	11.9 mg/kg; p. o.	DSS or oxazolone/C57BL/6 mice	The extract reduced inflammation and ulceration as well as COX-2, iNOS, and NF-κB expression. Additionally, it attenuated the activation of macrophages and provided protection against DNA damage.	None	[95]
	Panax quinquefolius L.	Different fractions of aqueous extract of the root (butanol, hexane, ethylacetate, dichloromethane and water fractions)	11.9 mg/kg; p. o.	DSS/C57BL/6 mice	The hexane fraction suppressed colitis and prevented colon cancer associated with colitis.	Fatty acids, polyacetylenes (panaxynol, panaxydol, panaxydiol) and ginsenosides	[97]
	Panax quinquefolius L.	Hexane fraction of aqueous extract of the root	11.9 mg/kg; p. o.	DSS/C57BL/6 p53 −/− and C57BL/6 p53+/+ mice	The hexane fraction was effective in targeting inflammatory and cancer cells and mitigating the histological score in mice with colitis through mechanisms both dependent and independent of the expression of p53.	None	[96]

continued

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Table 1 *Continued*

Family	Species	Extract and part of the plant	Dose and route	Model of colitis/ animal used	Summary of results	Bioactive compounds or classes of compounds found in the study	Reference
Asteraceae	*Achillea fragrantissima* (Forssk.) Sch.Bip.	Nonpolar (dichloromethane : methanol) or polar (70% aqueous methanol) extracts of leaves	200 and 400 mg/kg; p. o.	Acetic acid/ Wistar rats	Nonpolar and polar extracts reduced acetic acid-induced damage to colon.	None	[196]
	Arctium lappa L.	Hydroethanolic extract and petroleum ether, ethyl acetate, butanol and aqueous fractions of the fruit	25, 50, 100 mg/kg; p. o.	DSS/C57BL/6 mice	The ethyl acetate fraction (100 mg/kg) is the main active fraction and arctigenin is the active compound in the fruit of *A. lappa*. The abovementioned extracts, fractions, and compounds decreased markers of inflammation and histological alterations in the colon.	Arctigenin and arctiin	[17]
	Arctium lappa L.	Chloroform fraction from hydroalcoholic extract of the leaves	25 and 50 mg/kg; p. o.	TNBS/Wistar rats	All doses reduced the macroscopic parameters and morphological alterations and increased mucus secretion. Additionally, they reduced MPO activity, TNF-α levels, and COX-2 expression.	Onopordopicrin	[20]
	Arctium lappa L.	Powder of burdock	100 mg/kg; p. o.	DSS/BALB/c mice	The treatment reduced DAI, histological parameters, and IL-6 and TNF-α levels.	None	[21]
	Baccharis dracunculifolia DC.	Ethyl acetate extract of aerial parts	5, 10, 25, 50, 100, and 200 mg/kg; p. o.	TNBS/Wistar rats	The extract (5 and 50 mg/kg) attenuated colonic damage as evidenced by the reduction of oxidative stress and MPO activity.	Caffeic acid, *p*-coumaric acid, aromadendrin-4-O-methyl ether, 3-prenyl-*p*-coumaric acid (drupanin), 3,5-diprenyl-*p*-coumaric acid (artepillin C) and baccharin	[24]
	Calendula officinalis L.	Hydroalcoholic extract of flowers	1500 and 3000 mg/kg p. o.; 10 and 20% gel i. r.	Acetic acid/ Wistar rats	The extract gel formulation or oral administration decreased tissue MDA levels and MPO activity, and a histopathological evaluation indicated a reduction in inflammation.	None	[197]
	Conyza dioscoridis (L.) Desf.	Hydroalcoholic extract of aerial parts	125, 250, and 500 mg/kg; p. o.	Acetic acid/ Wistar rats	All doses of the extract reduced the signs of colitis and levels of inflammatory mediators.	Carbohydrates, flavonoids, tannins, unsaturated sterols, proteins, lactones and alkaloids.	[195]
	Helichrysum oligocephalum DC.	Hydroethanolic extract of aerial parts	100, 200, and 400 mg/kg; p. o. or i. p.	Acetic acid/ Wistar rats	The extract (100 mg/kg) decreased ulceration, MPO activity, and TNF-α levels in the colon.	None	[198]
	Ixeris dentata (Thunb. ex Thunb.) Nakai	Aqueous extract of the whole plant	100 mg/kg; p. o.	DSS/BALB/c mice	The extract reduced the signs of colitis and the levels of inflammatory mediators.	3,4-dihydroxycinnamic acid (caffeic acid)	[30]
	Matricaria aurea (Loefl.) Sch.Bip.	Hydroalcoholic extract of flowers	200, 400, 800 mg/kg; p. o. or i. r.	Acetic acid/ Wistar rats	Protective effect of the extract at 400 and 800 mg/kg (p. o.) and at 800 mg/kg (i. r.) on macroscopic and histological alterations.	None	[199]

continued

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▶ **Table 1** *Continued*

Family	Species	Extract and part of the plant	Dose and route	Model of colitis/ animal used	Summary of results	Bioactive compounds or classes of compounds found in the study	Reference
Berberidaceae	*Berberis vulgaris* L.	Hydroalcoholic extract of the fruit	375, 750, and 1500 mg/kg; p. o. and i. r.	Acetic acid/ Wistar rats	The doses of 750 and 1500 mg/kg (p. o. and i. r.) decreased macroscopic parameters, but histopathologic parameters were decreased only by 1500 mg/kg (p. o.).	None	[165]
Bignoniaceae	*Oroxylum indicum* (L.) Kurz	Aqueous extract of the root bark	100, 200, and 400 mg/kg, p. o.	DNBS/Wistar rats	Treatment with the extract reduced both macroscopic and pathologic parameters. Additionally, it decreased MPO activity, MDA concentrations, and NO levels and increased the reduced GSH levels in the colon.	Baicalein, chrysin, biochanin-A and ellagic acid	[169]
Boraginaceae	*Cordia dichotoma* G. Forst.	Hydroalcoholic extract of the bark was fractioned into *n*-hexane, ethyl acetate and methanol fractions	50 mg/kg and 500 mg/kg; p. o.	Acetic acid/ Swiss mice	The methanol fraction and hydroalcoholic extract decreased microscopic damage in the colon and MPO activity and MDA levels in blood and tissue.	None	[126]
	Cordia dichotoma G. Forst.	Methanol fraction of methanolic extract of the bark and isolated apigenin	50 mg/kg; p. o.	Acetic acid/mice	The methanol fraction and isolated apigenin reduced histopathological damage in the colon and MPO activity and MDA levels in blood and tissue.	Apigenin	[127]
Brassicaceae	*Sisymbrium irio* L.	Hydroalcoholic extract of aerial parts	125, 250, and 500 mg/kg; p. o.	Acetic acid/ Wistar rats	All doses of the extract reduced the signs of colitis and the levels of inflammatory mediators.	None	[195]
Combretaceae	*Terminalia chebula* Retz.	Ethanol extract of fruit pulps	300, 600 and 1200 mg/kg; p. o.	Acetic acid/ Wistar rats	Treatment with the extract (600 mg/kg) increased SOD and CAT activity and GSH content, while it also reduced the lipoperoxidation, MPO activity, and histological damage in the colon.	Tannins, triterpenoids, phenolic compounds, carbohydrates, glycosides, amino acids, fixed oil, gum and mucilage	[200]
Dilleniaceae	*Dillenia indica* L.	Methanol extract of leaves; *n*-hexane and chloroform fractions	200, 400, and 800 mg/kg, p. o.; 100 and 200 mg/kg. p. o. (each fraction)	Acetic acid/ Swiss mice	The methanol extract (800 mg/kg) and *n*-hexane and chloroform fractions (200 mg/kg each) lowered the macroscopic score, colon weight, MPO activity, and MDA and TNF-α concentrations and augmented GSH levels and CAT and SOD activity.	None	[174]
Euphorbiaceae	*Euphorbia hirta* L.	Hydroalcoholic extract of aerial parts	125, 250, and 500 mg/kg; p. o.	Acetic acid/ Wistar rats	All doses of the extract reduced the signs of colitis and levels of inflammatory mediators.	None	[195]
	Emblica officinalis Gaertn.	Methanol extract of the fruit	100 and 200 mg/kg, p. o.	Acetic acid/ Wistar rats	Treatment with the extract decreased serum LDH and brought histopathological changes back to nearly normal levels.	None	[129]

continued

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▸ **Table 1** *Continued*

Family	Species	Extract and part of the plant	Dose and route	Model of colitis/ animal used	Summary of results	Bioactive compounds or classes of compounds found in the study	Reference
Fabaceae	*Abarema cochliocarpos* (Gomes) Barneby & J. W. Grimes	Butanolic fraction of the bark extract	100 and 150 mg/kg; p. o.	TNBS/Wistar rats	The fraction (150 mg/kg) decreased macroscopic and histological parameters, MPO activity, TNF-α production, expression of COX-2 and iNOS, and activation of JNK.	(+)-Catechins	[60]
	Abarema cochliocarpos (Gomes) Barneby & J. W. Grimes	Butanolic fraction of the bark extract	150 mg/kg; p. o.	TNBS/Wistar Rats	The fraction decreased macroscopic and histological parameters of chronic colitis and impaired changes in MPO activity, cytokine production, and iNOS, COX-2, IκBα, p-p38 and p-JNK expression in the colon.	None	[201]
	Bauhinia tomentosa L.	Methanol extract of the leaves	5, 10, and 20 mg/kg; i. p.	Acetic acid/ Wistar rats	The extract (20 mg/kg) decreased colon macroscopic and histological alterations, MPO activity, TNF-α concentration, NO levels, lipoperoxidation, iNOS expression, and LDH activity. It also increased GSH contents and SOD and GPx activity.	None	[63]
	Cassia obtusifolia L.	Aqueous extract of aerial parts	1 g/kg; p. o.	DSS/BALB/c mice	The extract reduced macroscopic signs of colitis, body weight loss, colonic IL-6 production, and expression of COX-2 and NF-κB.	Emodin	[202]
	Copaifera langsdorffii Desf.	Oleoresin from the bark	200 and 400 mg/kg; p. o. and i. r.	Acetic acid/ Wistar rats	All doses reduced macroscopic injury, MPO activity and MDA levels in the colon.	None	[203]
	Hymenaea stigonocarpa Hayne	Methanolic extract of the bark/ fruit pulp flour	100, 200, and 400 mg/kg; p. o./diet enriched with 5 and 10 %; p. o.	TNBS/Wistar rats	The extract (200 mg/kg) and fruit pulp flour (10 %) prevented colonic damage, decreased MPO activity and lipid peroxidation, and increased the reduced GSH content.	Flavonoids, tannins, terpenes and other phenolic compounds	[204]
	Retama monosperma (L.) Boiss	Aqueous extract of aerial parts	9 and 18 mg/kg; p. o.	TNBS/Wistar rats	The extract reduced macroscopic and microscopic signs of colitis and impaired the alterations induced by TNBS in MPO activity and iNOS, COX-2, IκBα, p-p38 and p-JNK expression in the colon.	Flavonoids (genistein, rutin, luteolin, apigenin, genistin and daidzein)	[72]
Hypericaceae	*Hypericum perforatum* L.	Hydroalcoholic extract of aerial parts	300 and 600 mg/kg, p. o.; 1 mL of 10 % and 20 % gel form, i. r.	Acetic acid/ Sprague Dawley rats	Treatment with the extract (600 mg/kg) ameliorated colon histopathological alterations and the MDA concentration.	None	[205]
Lamiaceae	*Phlomis lychnitis* L.	Hydroalcoholic extract of aerial parts	10 and 25 mg/kg; p. o.	TNBS/Wistar rats	The extract (both doses) reduced colonic damage, MPO activity, iNOS expression, mRNA expression of cytokines, and markers of epithelial integrity.	None	[37]
	Phlomis purpurea L.	Hydroalcoholic extract of aerial parts	10 and 25 mg/kg; p. o.	TNBS/Wistar rats	The extract (25 mg/kg) reduced colonic damage, MPO activity, iNOS expression, mRNA expression of cytokines, and markers of epithelial integrity.	None	[37]
	Origanum onites L.	Essential oil of the whole plant	0.1 and 1 mg/kg; i. p. and i. r.	TNBS/Sprague Dawley rats	The essential oil produced a protective effect against colonic injury.	None	[206]

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Table 1 *Continued*

Family	Species	Extract and part of the plant	Dose and route	Model of colitis/animal used	Summary of results	Bioactive compounds or classes of compounds found in the study	Reference
	Origanum syriacum L.	Hydroalcoholic extract of aerial parts	125, 250, and 500 mg/kg; p. o.	Acetic acid/Wistar rats	All doses of the extract reduced the signs of colitis and levels of inflammatory mediators.	Flavonoids and terpenoids	[195]
	Rosmarinus officinalis L.	Hydroalcoholic extract and essential oil of leaves	100, 200, and 400 mg/kg (extract); 100, 200, and 400 µL/kg (oil); p. o. and i. p.	TNBS/Wistar rats	The extract and oil, at high doses, decreased the weight/length ratio, area, and severity of ulcers, and the severity and extension of inflammation and crypt damage.	α-Pinene and 1,8-cineole (in essential oil)	[44]
	Salvia lanigera Poir.	Hydroalcoholic extract of aerial parts	125, 250, and 500 mg/kg; p. o.	Acetic acid/Wistar rats	All doses of the extract reduced the signs of colitis and levels of inflammatory mediators.	Flavonoids and terpenoids	[195]
	Scutellaria baicalensis Georgi	Extract of roots (sequential extraction with hexane, acetone and methanol)	100 mg/kg; p. o.	DSS/Wistar rats	The extract reduced DAI and colonic macroscopic damage, histological parameters, and MPO activity.	None	[52]
	Vitex negundo L.	Ethanol and aqueous extracts of roots	100 mg/kg	Acetic acid/Swiss mice	The ethanol extract decreased histopathological alterations, MPO activity, and MDA levels in blood and tissue.	None	[207]
	Vitex negundo L.	Ethanol extract of the leaves	500 mg/kg; p. o.	Acetic acid/Wistar rats	The extract reduced macroscopic and microscopic lesions of the colon as well as MPO, CAT, and SOD activity and MDA levels.	None	[208]
	Ziziphora clinopodioides Lam.	Methanol extracts of aerial parts (including flower, stalk and leaf)	75, 150, and 300 mg/kg; p. o. (in the drinking water)	DSS/Swiss mice	The extract decreased lipid peroxidation and NO and TNF-α levels in the colon. Additionally, it increased total thiol contents, total antioxidant capacity, and SOD and CAT activity.	None	[55]
Lythraceae	*Punica granatum* L.	Ethanol extract and ellagic acid-rich fraction of ethanol extract of flowers	100 and 200 mg/kg (both extract and fraction); p. o.	DSS/Swiss mice	Extract or fraction diminished macroscopic and histological alterations, MPO activity, histamine concentration, and lipid peroxidation in the colon.	Ellagic acid	[179]
Malvaceae	*Hibiscus rosa-sinensis* L.	Hydroalcoholic extract of leaves	50, 100 and 200 mg/kg; p. o.	Acetic acid/Wistar rats	The extract lowered macroscopic and histological damage, MPO activity, and NO and TNF-α levels while increasing the GSH concentration and SOD activity.	Alkaloids, steroids, flavonoids and polyphenols	[209]
	Malva parviflora L.	Methanol and aqueous extract of leaves	100 and 200 mg/kg, p. o.	Acetic acid/Wistar rats	Both extracts reduced the colon weight/length ratio. The methanol extract (200 mg/kg) provided a better anticolitic effect than did the aqueous extract, which was confirmed by the histopathological findings.	Alkaloids, saponins, anthraquinones, glycosides, tannins, flavonoids and coumarins	[210]
	Thespesia populnea Sol. ex Correa	Aqueous and ethanol extract of heartwood. Ethanol extract was further partitioned with chloroform and ethyl acetate	100 and 200 mg/kg, i. r.	DNBS/Swiss mice	It reduced protease and MPO activity and MDA concentration in the tissue and blood of treated animals. The aqueous extract seemed to be the more effective one.	None	[211]

continued

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▶ **Table 1** *Continued*

Family	Species	Extract and part of the plant	Dose and route	Model of colitis/animal used	Summary of results	Bioactive compounds or classes of compounds found in the study	Reference
Moraceae	*Ficus benghalensis* L.	Aqueous extract of the stem bark	250 and 500 mg/kg; p. o.	TNBS/Wistar rats	All doses of the extract reduced the colonic mucosal damage index, DAI, and MPO activity, and MDA and NO in the colon and increased SOD activity	None	[135]
	Ficus benghalensis L.	Ethanol extract of the stem bark	250 and 500 mg/kg; p. o.	TNBS/Wistar rats	All doses of the extract reduced the colonic mucosal damage index, DAI, and MPO, MDA, NO in the colon and mast cell degranulation, and increased SOD activity.	None	[136]
Moringaceae	*Moringa oleifera* Lam.	Ethanol and aqueous extract of roots	100 and 200 mg/kg; p. o.	Acetic acid/Swiss mice	The highest dose of each extract reduced MPO activity and MDA levels in the blood and colon.	None	[140]
	Moringa oleifera Lam.	Hydroalcoholic extract of seeds and chloroform fraction of this extract	50, 100, and 200 mg/kg; p. o.	Acetic acid/Wistar rats	The hydroalcoholic extract reduced macroscopic damage, ulcer area and index, histological parameters, and MPO activity in the colon.	None	[141]
Myrtaceae	*Rhodomyrtus tomentosa* (Aiton) Hassk.	Methanol extract of the leaves	200 mg/kg; p. o.	DSS/C57BL/6 mice	Treatment with the extract reduced the shortening of the colon length.	Quercetin	[212]
Orobanchaceae	*Cistanche tubulosa* (Schenk) Wight	Commercially echinacoside-enriched-extract of non-identified part of the plant	120 µg/mL in drinking water (~ 20 mg/kg/day; p. o.)	DSS/C57BL/6J mice	Treatment with the extract protected the intestinal epithelium from inflammatory injury, but not against neutrophil infiltration, and induced an upregulation of transforming growth factor-β1 and increased Ki67+ proliferating cells in the colon.	Echinacoside (~ 90%), acteoside, tubuloside A and isoacteoside	[213]
Oxalidaceae	*Oxalis corniculata* L.	Petroleum ether, chloroform, ethyl acetate and methanol fractions of the extract of leaves	100 mg/kg; i. p.	Acetic acid/Swiss mice	Ethyl acetate and methanol fractions were the most effective at reducing the histopathological scores, ulcer index, MPO activity, and MDA levels in the colon.	None	[214]
Phyllanthaceae	*Phyllanthus niruri* L.	Spray-dried aqueous extract of aerial parts	25, 100, and 200 mg/kg, p. o.	Acetic acid/Wistar rats	Treatment with the extract prevented colonic GSH depletion, lipoperoxidation, and microscopic damage to tissues. It also reduced MPO activity and expression of TNF-α, IFN-γ, and p53 proteins.	None	[215]
Polygonaceae	*Rheum tanguticum* Maxim. ex Balf.	Ethanol extract of aerial parts enriched with polysaccharides	200 mg/kg; p. o.	TNBS/Sprague-Dawley Rats	The extract administration reduced clinical and macroscopic alterations, area of ulcers, MPO activity, and presence of CD4+ T lymphocytes in the colon. It also increased SOD activity in the colon.	Uronic acid	[216]
	Polygonum hydropiper L.	Methanol extract of the leaves	100 mg/kg; p. o.	DSS/C57BL/6 mice	The extract partially reverted the reduction of the colon length without altering body weight.	Quercetin	[113]

continued

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▸ **Table 1** *Continued*

Family	Species	Extract and part of the plant	Dose and route	Model of colitis/ animal used	Summary of results	Bioactive compounds or classes of compounds found in the study	Reference
Rhizophoraceae	*Rhizophora apiculata* Blume	Hydromethanolic extract of the whole plant	10 mg/kg; i. p.	Acetic acid/ Swiss mice	The extract inhibited serum NO concentrations, colonic weight, histopathologic alterations, lipoperoxidation, GSH levels, GPx activity, and iNOS, COX-2 and TNF-*α* expression. It also increased SOD activity in the colon.	Pyrrolidinyl, pentyl ester, derivates ketone, ethan-1-one, 3-bromophenyl 3,4-dimethylbenzene-1-sulfonate, 5-Bromo-2-thiophenecarboxaldehyde, thiophene-2-carboxamide and 1,3-thiazolidine-2,4-dione	[217]
Rosaceae	Cydonia oblonga Mill.	Fruit (quince) juice or hydroalcoholic extract of the fruit	200, 400, and 800 mg/kg for juice and 200, 500, and 800 mg/kg for extract; p. o. and i. p.	TNBS/Wistar rats	Quince juice or extract diminished colonic inflammation.	None	[76]
	Fragaria × ananassa (Duchesne ex Weston) Duchesne ex Rozier	Hydroalcoholic extract of the fruit	200 and 400 mg/kg, p. o.; 2 mL of 10 % and 20 % gel form, i. r.	Acetic acid/ Sprague Dawley rats	The extract reversed the alterations caused by acetic acid to the tissue histopathology and MDA levels.	None	[218]
	Fragaria vesca L.	Ethanol extract of the fruit	500 mg/kg; p. o.	Acetic acid/ Wistar rats	The extract decreased macroscopic damage, DAI, microscopic parameters, and MPO activity. It also increased SOD and CAT activity.	None	[219]
	Malus domestica Borkh.	Methanol extract of fruit (apple)	10^{-4} mol/L (catechin equivalent); i. r.	TNBS/Wistar rats	The extract presented anti-inflammatory and healing effects through the reduction of COX-2, TNF-*α*, and calpain expression and an increase in tissue transglutaminase expression.	None	[86]
	Prunus armeniaca L.	Aqueous extract or aqueous extract mixed with oil of apricot kernel	100, 200, and 400 mg/kg; p. o. or i. p.	TNBS/Wistar rats	Apricot extract and extract plus oil reduced colonic inflammation.	None	[220]
	Rosa × damascena Herrm.	Hydroalcoholic extract of flowers and volatile oil	250, 500, 1000 mg/kg (p. o.) and 125, 250, 500 mg/kg; (i. p.) for extract; 100, 200, and 400 µL/kg (p. o.) for oil	Acetic acid/ Wistar rats	The oil at 100 and 200 mg/kg decreased macroscopic parameters of colitis. However, all doses diminished the MPO activity. For the extract, all doses decreased macroscopic parameters, and microscopic and MPO activity. However, via i. p. administration, only the lowest dose produced a beneficial effect.	Gallic acid	[89]
Rubiaceae	*Oldenlandia diffusa* (Willd.) Roxb.	Aqueous extract of aerial parts and hentriacontane	1 g/kg; p. o. for extract and 5 mg/kg for compound	DSS/BALB/c mice	The extract attenuated body weight loss, reduction in colon length, serum and colonic IL-6 levels and COX-2 and NF-*κ*B expression in the colon. Hentriacontane reduced weight loss, colon shortening, and IL-6 in the colon.	Hentriacontane	[184]

continued

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▸ **Table 1** *Continued*

Family	Species	Extract and part of the plant	Dose and route	Model of colitis/ animal used	Summary of results	Bioactive compounds or classes of compounds found in the study	Reference
Solanaceae	*Solanum nigrum* L.	Hydroalcoholic extract of aerial parts	125, 250, and 500 mg/kg; p. o.	Acetic acid/ Wistar rats	All doses of the extract reduced the signs of colitis and levels of inflammatory mediators, although it was lower than the other extracts of plants tested.	None	[195]
	Withania somnifera	Aqueous extract of roots was used in a gel formulation	1 g/kg, i. r.	TNBS/Wistar rats	Treatment with the extract reduced histopathological parameters and MDA levels.	None	[221]
Valerianaceae	*Patrinia scabiosifolia* Link	Methanol extract of the root	10, 30, and 50 mg/kg; p. o.	DSS/ICR mice	Treatment with the extract reduced DAI, increased spleen size, and shortened the colon. It also decreased histological alterations, MPO activity, NO metabolites, expression of iNOS protein, and mRNA expression of TNF-α, IL-1β, and IL-6 in the colon.	None	[185]
Zingiberaceae	*Curcuma longa* L.	Powdered rhizome	1, 10, and 100 mg/kg; p. o.	Acetic acid/ Wistar rats	Treatment with the powdered rhizome reduced the macroscopic ulcer score, histological alterations, MPO activity, and IL-23 levels in colon tissue in animals treated before induction. In addition, an increase in the serum GSH level was observed in these animals.	None	[107]
	Zingiber officinale Roscoe	Hydroalcoholic extract of rhizomes	150, 350, and 700 mg/kg; p. o. and i. r.	Acetic acid/ Wistar rats	The highest dose of the extract (both p. o. and i. r.) reduced the macroscopic score, histopathological parameters, ulcer area and index, and weight/length ratio of the colon.	None	[99]
	Zingiber officinale Roscoe	Ethanol extract of rhizomes	100, 200, and 400 mg/kg; p. o.	Acetic acid/ Wistar rats	Macroscopic score and histological damage were both reduced by treatment with 400 mg/kg. All doses decreased MPO activity, TNF-α and PGE_2 concentrations, MDA, and protein carbonyl levels and increased GSH content and CAT and SOD activity.	None	[100]
	Zingiber officinale Roscoe	Volatile oil of rhizome	100, 200, and 400 mg/kg, p. o.	Acetic acid/ Wistar rats	Treatment with 200 and 400 mg/kg reduced ulcer severity, area, and index. Administration of 400 mg/kg reduced inflammation severity and extent.	Zingiberene	[106]

CAT: catalase; COX: cyclooxygenase; DAI: disease activity index; DNBS: dinitrobenzenesulfonic acid; DrG IB $sPLA_2$: dromedary group IB secretory phospholipase A_2; DSS: dextran sulfate sodium; GPx: glutathione peroxidase; GSH: glutathione; hG IIA $sPLA_2$: human group IIA secretory phospholipase A_2; i. p.: via intraperitoneal route; i. r.: intrarectally; IL: interleukin; iNOS: inducible nitric oxide synthase; JNK: c-Jun N-terminal kinase; LDH: lactate dehydrogenase; MDA: malondialdehyde; MPO: myeloperoxidase; mRNA: messenger ribonucleic acid; NF-κB: nuclear factor κB; NO: nitric oxide; p. o.: via oral route; PGE_2: prostaglandin E_2; p-JNK: phosphorylated c-Jun N-terminal kinase; p-p38: phosphorylated p38 kinase; SOD: superoxide dismutase; TNBS: 2,4,6-Trinitrobenzenesulfonic acid; TNF: tumoral necrosis factor

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▶ **Table 2** Models of colitis cited in the studies.

Model	Mechanism [1, 15, 16]	Number of studies
Acetic acid	Intrarectal administration of acetic acid induces non-transmural inflammation characterized by increased neutrophil infiltration in the colon tissue, massive necrosis of mucosal and submucosal layers, vascular dilation, edema, and submucosal ulceration.	39
TNBS	Intrarectal administration of TNBS induces transmural inflammation of the colon driven by a TH1-mediated mechanism that is characterized by infiltration of the lamina propria by $CD4^+$ T cells, neutrophils, and macrophages.	18
DSS	Oral administration of DSS causes loss of epithelium and entry of luminal organisms or their products into the lamina propria, resulting in stimulation of innate and adaptive lymphoid elements and secretion of proinflammatory cytokines and chemokines.	15
DNBS	Intrarectal administration of DNBS causes inflammation of the colon mucosa characterized by infiltration of neutrophils and ulceration.	2
Oxazolone	Intrarectal administration of oxazolone induces acute superficial inflammation of the mucosa in the distal colon characterized by infiltration of lymphocytes and neutrophils, edema of the lamina propria, and ulceration.	1
T cell transfer model	T cell transfer colitis is induced in lymphopenic naïve $CD45RB^{high}$ T cell mice, which are unable to generate regulatory T cells in a timely fashion to prevent the expansion of effector T cells that mediate inflammation.	1

They found that the ethyl acetate fraction is the main active fraction and arctigenin is the active compound in the fruit of this plant. A previous study has demonstrated that arctigenin exerts anti-inflammatory effects by inhibiting PI3K and polarizing M1 macrophages to M2-like macrophages [18]. Another study showed that the beneficial effect of arctigenin on colitis occurred through the downregulation of the differentiation of Th1 and Th17 cells via inhibition of the mammalian target of rapamycin complex 1 pathway, an important target for this differentiation [19]. Thus, this compound may have potential in the treatment of colitis in humans.

In addition, previous studies have reported the activity of this plant in experimental colitis. de Almeida et al. [20] demonstrated that an onopordopicrin-enriched fraction, obtained from *A. lappa* leaves, presented an anti-inflammatory effect on colitis induced by TNBS, most likely related to a decrease in neutrophil function, TNF-*α* production, and downregulation of COX-2 in addition to an increase in mucus production. In addition, Huang et al. [21] suggested that both inulins and chlorogenic acid play an important role in the prophylactic effect of *A. lappa* on DSS-induced colitis. In this study, the oral administration of *A. lappa* reduced body weight loss, the release of inflammatory mediators (IL-6 and TNF-*α*), and histological scores and maintained the colon architecture of mice that received DSS.

Different extracts obtained from *B. dracunculifolia* DC were shown to reduce gastric ulcers in rats, possess anti-inflammatory and antinociceptive effects [22], and protect liver mitochondria against oxidative damage [23]. Cestari et al. [24] evaluated the intestinal anti-inflammatory activity of the ethyl acetate extract from the aerial parts of *B. dracunculifolia* in colitis induced by TNBS in rats. The administration of doses of 5 and 50 mg/kg of this extract reduced the macroscopic colonic damage score and lesion extension, mainly due to the inhibition of MPO activity, reduction of lipid peroxidation, and increase in endogenous antioxidant defenses in the inflamed colon, such as the GSH level. Through HPLC analysis of the ethyl acetate extract of *B. dracunculifolia,* those authors identified some acid derivatives, such as caffeic acid, *p*-coumaric acid, 3-prenyl-*p*-coumaric acid (drupanin), 3,5-diprenyl-*p*-coumaric acid (artepillin C), and 3-prenyl-4-dihydrocinnamoiloxy-cinnamic acid (baccharin). Other studies have identified a flavonoid called artepillin C as the major component of both this plant and the green propolis [25, 26]. Hence, the effect of *B. dracunculifolia* on colitis can be linked to some of these compounds, and attention should be given to artepillin C, a *p*-coumaric acid derivative. This compound decreases the number of neutrophils during peritonitis and reduces PGE_2 levels *in vivo* at a dose of 10 mg/kg, which is orally available with a peak plasma concentration of 22 µg/mL after 1 h of administration. In addition, it decreases NO production and NF-*κ*B activity in human embryonic kidney 293 cells [25]. This compound, which is also a transient receptor potential ankyrin 1 activator, is an important target for colitis, mainly because it mediates visceral hypersensitivity [27–29].

I. dentata (Thunb. ex Thunb.) Nakai is a traditional herbal medicine used in Asian countries to treat many conditions, including intestinal inflammation [30]. The aqueous extract of this plant, at 100 mg/kg, reduced epithelial injury, inflammatory cell infiltration into colon tissue, and microscopic injury in DSS-induced colitis in mice. Moreover, it prevented the increase of COX-2 expression, activated hypoxia-inducible factor-1*α*, and decreased IL-6 and TNF-*α* production caused by DSS administration. It has been previously reported that this plant contains triterpenoids, sesquiterpene lactones, and flavonoids, which appear to be important in light of their described anti-inflammatory effects [31]. A study by Kim et al. [30] found caffeic acid (3,4-dihydroxycinnamic acid) in the aqueous extract of *I. dentata*. Some studies have shown that caffeic acid can ameliorate colitis induced by DSS in mice [32, 33] through mechanisms that generally involve the reduction of cytokine production in colonic tissue. Ye et al. [32] showed that caffeic acid (1 mmol/L) administered in the diet of mice inhibited the colonic production of IL-6, TNF-*α*, and IFN-*γ* and the infiltration of T cells, neutrophils, and macrophages through the inhibition of the NF-*κ*B signaling pathway in the DSS model. Zhang et al. [33] dem-

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onstrated that caffeic acid (1.0 mmol/kg in diet) prevented body weight loss, colon length shortening, and colonic and cecal histopathology alterations caused by DSS. These effects were paralleled by a decrease in colonic MPO activity and mRNA expression of IL-17 and iNOS as well as an increase in IL-4 and CYP4B1 mRNA [32]. Interestingly, CYP4B1 oxygenates fatty acids and forms some eicosanoids in addition to playing a role in the metabolism of certain xenobiotics [34]. These studies suggest the likely participation of caffeic acid in the protective effect of *I. dentata* on colitis.

Family Lamiaceae

Numerous members of the family Lamiaceae possess traditional and medicinal uses and have been utilized in folk medicine for many years. Most species in this family are rich sources of terpenoids and contain a considerable amount of iridoid glycosides, flavonoids, and phenolic acids, such as rosmarinic acid and other phenolic compounds [35]. Lamiaceae herbs were also shown to have higher amounts of phenolic and antioxidants compounds than do other families [36].

Approximately 80 % of species in the family Lamiaceae are used for medical purposes. Lamiaceae species are mainly used for diseases related to the digestive system, especially flatulence and dyspepsia. Regarding the pharmacological evidence in the literature for treating UC, the studies selected in this review cited the species *Phlomis lychnitis* L., *Phlomis purpurea* L., *Origanum syriacum* L., *Origanum onites* L. and *Salvia lanigera* Poir.

Algieri et al. [37] investigated the effects of the hydroalcoholic extracts of the aerial parts of *P. lychnitis* L. and *P. purpurea* L. (at the doses of 10 and 25 mg/kg; p. o.) in the experimental model of rat colitis induced by TNBS. The macroscopic and microscopic analysis of colonic samples showed that both extracts, in all doses tested, caused an anti-inflammatory effect, which was confirmed biochemically by decreased colonic MPO activity, increased colonic GSH content, and downregulated iNOS expression. However, only the extract of *P. purpurea* at a dose of 25 mg/kg reduced the mRNA expression of IL-1β, IL-17, cytokine-induced neutrophil chemoattractant, monocyte chemotactic protein-1, and intercellular adhesion molecule-1 in colonic tissue. *P. lychnitis* and *P. purpurea* extracts were able to increase the mRNA expression of markers of epithelial integrity such as mucins (MUC-2, MUC-3) and villin, which are important to colonic permeability.

Overall, different compounds have been identified as chemical components of the genus *Phlomis*, including sesquiterpenoids, diterpenoids, triterpenoids, triterpene saponins, and flavonoids. However, for the species studied, the chemical constituents reported in *P. lychnitis* include flavonoids, apigenin, apigenin-7-glucoside, apigenin-7-p-coumaroylglucoside, chrysoeriol, chrysoeriol-7-glucoside, chrysoeriol-7-p-coumaroylglucoside, luteolin, luteolin-7-p-coumaroylglucoside, and phenylpropanoids [38]. In *P. purpurea*, the presence of flavonoids such as chrysoeriol-7-p-coumaroylglucoside, isorhamnetin-3-p-coumaroyl glucoside, kaempferol-3-p-coumaroylglucoside, and luteolin-7-glucoside was described [39, 40]. This diversity of metabolites may explain the effectiveness of these different species in TNBS-induced colitis.

Among these metabolites, apigenin and luteolin have been described as protective in colitis. Mascaraque et al. [41] found that a soluble form of apigenin (named apigenin K) reduced morphological signs and biochemical markers of colitis induced by both TNBS and DSS in rats. Additionally, Marquez-Flores et al. [42] demonstrated that apigenin decreased colitis induced by DSS in mice through the inhibition of the inflammasome NLR family pyrin domain-containing 3 signaling. In addition, Nishitani et al. [43] demonstrated that luteolin diminished macroscopic and histological colon damage, infiltration of macrophages, and IFN-γ-producing $CD4^+$ T cells as well as IFN-γ mRNA expression in the colon of mice that received DSS. Additionally, in this study, the authors described an *in vitro* effect of luteolin in a coculture of intestinal epithelial Caco-2 and macrophage RAW 264.7 cells under stimulation with lipopolysaccharide. This effect was characterized by reduced IL-8 mRNA expression in Caco-2 cells and decreased expression of TNF-α and mRNA expression of TNF-α, IL-6, and IL-1β in RAW 264.7 cells. These studies highlight a potential use for apigenin and luteolin in the treatment of colitis and suggest that these compounds may be responsible for the effects of *P. lychnitis* and *P. purpurea*.

Rosmarinus officinalis L. (rosemary) is a medicinal plant that originated from the Mediterranean region and is traditionally used as an herbal medicine for gastrointestinal problems. Minaiyan et al. [44] demonstrated that administration of the hydroalcoholic extract or essential oil of leaves of *R. officinalis* inhibited the alterations caused by TNBS in rats. Weight/length ratio, ulcer area and severity, inflammation severity and extension, and crypt damage were reduced by treatment with doses of 400 mg/kg of extract and 400 µL/kg of essential oil.

Despite the effectiveness of the extract and essential oil, their components are different. It was shown that the most important constituents of the hydroalcoholic extract of *R. officinalis* leaves are caffeic acid and its derivatives, such as rosmarinic acid [45]. These compounds are well absorbed from the gastrointestinal tract; they also alleviate cell or tissue damage in some inflammatory diseases, most likely by inhibiting NF-κB activation [46–48]. Interestingly, in the model of colitis induced by TNBS in rats, a lipophilic rosmarinic acid derivative (rosmarinic acid methyl ester) decreased the levels of proinflammatory mediators in the colon and upregulated the expression of hypoxia-inducible factor-1 and vascular endothelial growth factor (VEGF), which can account for an ulcer-healing effect [47].

On the other hand, α-pinene and 1,8-cineole were the major chemical constituents found in the oil of this plant [44]. Pretreatment with the terpene 1,8-cineole (also known as eucalyptol) decreased gross damage, wet weight, and MPO activity of the colon of rats rectally instilled with TNBS. These effects were accompanied by the repletion of colonic contents of GSH [49].

There is no study testing the effect of α-pinene in colitis models, but this compound decreased the production of IL-6, TNF-α, and NO and the expression of iNOS and COX-2 in bacterial lipopolysaccharide-stimulated macrophages [50]. In addition, it inhibited the translocation of NF-κB induced by LPS in human monocyte THP-1 cells [51]. These findings suggest that the substances present in both the extract and the essential oil from *R. officinalis* may be useful in the treatment of colitis.

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Scutrellaria baicalensis Georgi is a very popular herb traditionally used in China for the treatment of many inflammatory conditions. Chung et al. [52] investigated the effect of the extract of the root of *S. baicalensis* (100 mg/kg) on UC induced by DSS in rats. This extract reversed body weight reduction, colon shortening, and ulceration and reduced colon histological damage and MPO activity. Baicalein, oroxylin A, and wogonin are some of the components of *S. baicalensis* [53]. The combination of these substances produced a higher inhibition of TNF-α-induced COX-2 expression in HT-29 cells than the individual components; it also reduced histopathological severity and suppressed the expression of COX-2 and the production of TNF-α and interleukin-1β in TNBS-induced colitis in mice [54].

Ziziphora clinopodioides Lam. was used by Amini-Shirazi et al. [55] in the DSS-induced colitis model. The authors showed that the methanol extract of the aerial parts of *Z. clinopodioides* Lam. at 75, 150, and 300 mg/kg, administered in the drinking water of mice, prevented DSS-induced colitis by inhibiting the synthesis or release of nitric oxide and TNF-α and by reducing oxidative stress through an increase in SOD, CAT, total thiol contents, and total antioxidant capacity, besides decreased lipid peroxidation. According to Li et al. [56], four compounds were identified in the methanol extract of this plant: pinocembrin-7-O-rutinoside, acacetin-7-O-rutinoside, picein, and protocatechuic acid, which are compounds with antioxidant and chelating properties [57]. Among these compounds, protocatechuic acid at 10 mg/kg reduced body weight loss, diarrhea, bleeding, colon shortening, and markers of colon inflammation in rats subjected to DSS administration [58].

Family Fabaceae

Fabaceae is the third largest family of plants in the world, comprising 727 genera and 19 325 species [59], and contain a large number of genera and species of economic importance. Regarding the treatment of colitis, five species and their effects were highlighted: *Abarema cochliocarpos* (Gomes) Barneby & J. W. Grimes, *Bauhinia tomentosa* L., *Copaifera langsdorffii* Desf., *Hymenaea stigonocarpa* Hayne, and *Retama monosperma* (L.) Boiss.

A. cochliocarpos (Gomes) Barneby & J. W. Grimes was first investigated in the TNBS-induced model of colitis in rats by da Silva et al. [60]. The butanolic fraction of the extract of the bark of this plant at doses of 100 and 150 mg/kg decreased macroscopic and histological alterations, MPO activity, TNF-α concentration and COX-2, and iNOS expression in the colon. These effects, along with increased IL-10 concentrations in tissue, were related to the activation of the JNK signaling pathway.

This study identified (+)-catechins and tannins in *A. cochliocarpos* extract. A previous study from the same group had shown the presence of catechins and tannins [60] in this extract, although they noted that the major constituent was (+)-catechins. Some studies have demonstrated that catechin intake is associated with beneficial effects on experimental UC [61, 62], although the mechanism of action is still unknown.

Later, da Silva et al. [60] also showed that chronic administration (14 days) of the butanolic fraction of the extract of the bark of *A. cochliocarpos* (150 mg/kg) protected rats from TNBS-induced colitis. This effect was mediated by the reduction of expression of phosphorylated mitogen-activated protein kinases (JNK and p38) in addition to the blockage of IκB degradation, which led to the downregulation of COX-2 and iNOS protein expression, diminished TNF-α, and increased IL-10 levels in colonic tissue.

Treatment with the methanol extract of *B. tomentosa* L. (5, 10. and 20 mg/kg) reduced the colon wet weight and macroscopic lesion score in UC induced by acetic acid in rats [63]. This extract also inhibited lipid peroxidation and increased colonic GSH content and SOD activity. Additionally, MPO activity, NO production, iNOS expression, TNF-α production, and lactate dehydrogenase activity were decreased by treatment with this extract. According to Kannan and Guruvayoorappan [63] and Aderogba et al. [64], the extract of *B. tomentosa* possesses phytochemical constituents such as kaempferol-3-O-rhamnoside, kaempferol-3-O-rutinoside, quercetin 3-O-glucoside, and quercetin 3-O-rutinoside (rutin). Others have shown that rutin (25 and 100 mg/kg) decreased microscopic injury and reverted GSH depletion without affecting MPO activity or leukotriene B_4 synthesis in the acetic acid-induced model of colitis in rats [65]. Kwon et al. [66] demonstrated that the administration of rutin in the diet (0.1 %) of mice for two weeks reduced DSS-induced colitis; it decreased body weight loss, histological scores, colonic production of IL-1β, and mRNA expression of IL-1β and IL-6 in the colon. Another study showed that the administration of rutin (57 mg/kg/day) decreased macroscopic and microscopic scores of colitis, reduced colonic MPO activity and mRNA expression of IFN-γ, TNF-α, chemokine (C–X-C motif) ligand 1 (CXCL1), and IL-1β, and prevented the activation of splenic CD4+ cells and plasma cytokine levels in the model of colitis induced by CD4+ CD62 L+ T cell transfer [67]. Thus, the presence of rutin in the extract may account for the beneficial effect observed in rats.

Paiva et al. [68] evaluated the effect of the oleoresin from the bark of *C. langsdorffii* Desf. (copaiba) at doses of 200 and 400 mg/kg on acetic acid-induced colitis in rats. The rectal administration of copaiba oleoresin reduced the macroscopic damage at both doses. Additionally, it effectively reduced the intensity of inflammatory cell infiltration into the colonic tissue. Both oral and rectal administration of copaiba oleoresin decreased MPO activity and MDA levels in the colon. The beneficial effect of the oleoresin of *C. langsdorffii* can be attributed to the presence of kaurenoic acid, a diterpene from this plant. Paiva et al. [68] previously demonstrated that this compound reduced colitis induced by acetic acid in rats.

Other compounds can also contribute to the effect of *C. langsdorffii* on colitis. According to Gelmini et al. [69], the constituents of *C. langsdorffii* oleoresin are α-bergamotene, α-himachalene, β-selinene, and β-caryophyllene. Among these compounds, β-caryophyllene is considered a cannabinoid receptor 2 activator that was shown to decrease colitis induced by DSS in mice [70], an effect reversed by a cannabinoid receptor 2 antagonist or a peroxisome proliferator-activated receptor antagonist, implying that the activation of these receptors is involved in the effects of β-caryophyllene [71].

Gonzalez-Mauraza et al. [72] showed that the aqueous extract of the aerial parts of *R. monosperma* (L.) Boiss. at doses of 9 or 18 mg/kg reduced the clinical parameters of damage to the colonic mucosa induced by TNBS in rats (body weight changes, diar-

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rhea, and colon weight/colon length) and increased the amount of mucus in the colon mucosa. These effects were related to a reduction of iNOS and COX-2 expression, inhibition of phosphorylation of p38 and JNK, and inhibition of the NF-*κ*B pathway by preventing the inhibitory protein I*κ*B-*α* from being degraded. These beneficial effects might be attributed, at least in part, to its high content of flavonoids, such as genistein, genistin, daidzein, rutin, apigenin, and luteolin. As explained above, luteolin, rutin, and apigenin have potential for the treatment of colitis [41–43]. Genistein was present at a higher concentration in this extract (57.2 mg/100 g of extract) than other flavonoids. Oral treatment with this flavonoid at 100 mg/kg reduced the expression of COX-2 mRNA and protein, and decreased MPO activity in TNBS-induced UC in rats [73]. In addition, it was shown that a new genistein derivative named genistein-27 exerted antiproliferative effects and inhibited colitis-associated colorectal cancer induced by azoxymethane plus DSS in mice [74]. In this way, the presence of the flavonoids genistein, rutin, luteolin, and apigenin may account for the beneficial effect of the extract of *R. monosperma* on TNBS-induced colitis, as demonstrated by Gonzalez-Mauraza et al. [72]. However, other minor bioactive compounds present in the extract or a combination of them may also contribute synergistically to this effect, such as quinolizidine alkaloids [75].

Family Rosaceae

Rosaceae is among the six most economically important families, including many crops of economic and nutritional importance, such as almond, apple, apricot, blackberry, cherry, peach, pear, plum, raspberry, rose, and strawberry. Recently, much attention has been directed to naturally derived products from fruits or vegetables, which may beneficially affect a number of pathologic conditions of the gastrointestinal tract, such as UC. In this review, we highlighted three species from the Rosaceae family: Cydonia oblonga Mill., *Malus domestica* Borkh., and *Rosa × damascena* Herrm.

C. oblonga Mill. is recognized as an important dietary source and is traditionally used as a gastric tonic, antidiarrheal, antiulcer, anti-inflammatory, antiemetic, and astringent as well as for uterine and hemorrhoid bleeding. Minaiyan et al. [76] investigated the effect of quince (the fruit of *C. oblonga*) juice and quince hydroalcoholic extract on UC induced by TNBS in rats. When administered via the oral route, both quince juice (400 and 800 mg/kg) and quince extract (200–800 mg/kg) reduced ulcer lesions, colon weight/length ratio, and histopathological parameters. The same results were also observed with the intraperitoneal administration of quince extract (500 mg/kg), but not quince juice. These effects seem to be related to the presence of phenolic constituents in quince. Previous studies identified chlorogenic acid (as the main phenolic component) as well as rutin, quercetin, and kaempferol in quince fruit [77, 78]. Chlorogenic acid at 1 mM in the drinking water (~ 354 mg/L) reduced body weight loss, diarrhea, fecal blood, shortening of the colon, histological scores, and mRNA expression of colonic macrophage inflammatory protein-2 and IL-1*β* in DSS-induced colitis in mice [79]. In addition, kaempferol decreased DSS-induced colitis in mice. This effect was observed following administration of 0.3 % (~ 10.5 mM) kaempferol, which reduced colon MPO activity and upregulated colonic mRNA expression of trefoil tracker-3 (a marker for goblet cell function). In addition, it diminished plasma concentrations of NO, PGE_2, and leukotriene B_4 [80]. Other substances described in quince, such as tannins and pectin, could also contribute to its protective effect on colitis [81–83]. Tannins preserve intestinal mucosal layers and protect the layers against proteolytic enzymes and chemical injuries [84]. In a similar way, pectins are suggested to possess a protective role in colitis [83] and are used in pharmaceutical preparations to release drugs for the treatment of colonic diseases [85].

D'Argenio et al. [86] demonstrated that the methanol extract of apple (*M. domestica* Borkh.) rectally administered at a concentration of 100 µM (of catechin equivalent, according to D'Argenio et al. [87]) in rats submitted to TNBS injection decreased the extent of inflammatory infiltration and damage to the surface area of the colon. These authors also found diminished expression of COX-2 and TNF-*α*. In addition, they described an inhibition of the expression of calpain, an enzyme involved in the cleavage of proteins such as tissue transglutaminase, which, in turn, is linked to colonic tissue remodeling [87, 88]. Interestingly, tissue transglutaminase expression was decreased in animals with colitis, and the methanol extract of apple of *M. domestica* counteracted this change, reinforcing an important role for tissue transglutaminase as a mediator of the protective action of this extract of apple. This extract is rich in polyphenols such as flavonoids, catechins, and epicatechins, which may play a role in its protective effect against ulcerative colitis induced by TNBS.

Latifi et al. [89] evaluated the effect of the hydroalcoholic extract of flowers of *R. × damascena* Herrm. at 250, 500, and 1000 mg/kg (p. o.) or 125, 250, and 500 mg/kg (i. p.) and the volatile oil of flowers at 100, 200, and 400 µL/kg on acetic acid-induced colitis in rats. In relation to the volatile oil, only the treatment with 100 or 200 µL/kg p. o. was effective to reduce all macroscopic parameters, such as ulcer area, severity and index, and weight/length ratio. Similar results were also observed when considering all histological parameters of colon inflammation and edema, except for MPO activity, which was reduced by all doses used. According to Verma et al. [90] and Sadraei et al. [91], the major components of the volatile oil of *R. damascena* are citronellol and geraniol.

Interestingly, treatment with geraniol reduced clinical signals, oxidative stress, and inflammation associated with colitis induced by TNBS in rats. It also modulated the expression of caspase-3, intercellular adhesion molecule-1, and glycogen synthase kinase-3*β* as well as the *β*-catenin, p38 MAPK, NF-*κ*B, and peroxisome proliferator-activated receptor *γ* signaling pathways in the same way as did sulfasalazine [92]. In addition, treatment with geraniol reversed DSS-induced inflammation and oxidative alterations [93]. However, no study has investigated the effect of citronellal on colitis.

Regarding the hydroalcoholic extract of *R. damascena*, Latifi et al. [89] showed that all doses administered via oral route reduced the weight/length ratio, ulcer index, histological alterations, and MPO activity in colon tissue. Via the intraperitoneal route, only the smallest dose was effective in the parameters observed, which was rather expected since the intraperitoneal administration of crude extracts is not ideal due to interference of the effects of the great variety of compounds present in the extract, some of

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which cannot be absorbed by the gastrointestinal tract. The hydroalcoholic extract of *R. damascena* contained 15.7 ± 0.2 g of gallic acid/100 g of the plant [89]. Gallic acid decreased colonic damage, disease activity index, colon shortening, lipid peroxidation, and MPO activity as well as the expression of iNOS, COX-2, and mRNA expression for IL-21 and 23 induced by DSS in mice. These effects were mediated by the suppression of p65-NF-κB, activation of the IL-6/signal transducer and activator of transcription 3 (STAT3), and activation of nuclear erythroid 2-related factor 2 [94].

Other families

Studies involving the effects of plants from several other families on colitis were found in the literature, as summarized in ▸ **Table 1**. Among the families with two or three studies each, we have detailed below the evidence brought by some of the studies.

The species *Panax quinquefolius* L. (known as American ginseng) belongs to the family Araliaceae, and three studies have addressed the effectiveness of this plant against UC. The first study was published by Jin et al. [95] and investigated the ethanol extract of the root of *P. quinquefolius* mixed in the chow at a quantity consistent with that currently consumed by humans as a supplement (75 ppm, equivalent to 11.9 mg/kg daily). These authors demonstrated the beneficial effect of this extract on colitis induced by DSS not only in a prophylactic but also in a therapeutic way, likely due to the inhibition of NO synthesis, COX-2, and NF-κB. Furthermore, in a coculture of HT29 colon cancer and ANA-1 murine macrophages, the authors demonstrated that American ginseng attenuated the activation of macrophages and reduced DNA damage in these cells.

Poudyal et al. [96] demonstrated a proapoptotic action in inflammatory cells in an *in vitro* setup for the hexane fraction of the aqueous extract of American ginseng. This fraction suppressed colitis induced by DSS at a dose of 11.9 mg/kg by oral gavage. The hexane fraction had potent antioxidant and proapoptotic properties paralleled by the suppression of iNOS and COX-2 transcription. Another finding from this study was that this fraction mitigated azoxymethane/DSS-induced colon cancer in mice. Thus, this extract offered protection against colitis and colitis-associated colon cancer. Poudyal et al. [97] suggested that the protective effects of the hexane fraction of American ginseng was independent of NF-κB, because DSS-induced colitis was decreased by the administration of this fraction to both C57BL/6 $p53^{-/-}$ and C57BL/6 $p53^{+/+}$ mice. These results weakened the hypothesis that the suppression of colitis by American ginseng extract is p53-dependent [98], but raised the possibility that American ginseng also acts through a p53-independent pathway in order to suppress colitis. The protective effect of American ginseng against colitis can be associated with the presence of different components in the extract, such as fatty acids comprising 43% w/w, polyacetylenes comprising 26.52% w/w, and less than 0.1% w/w ginsenosides [97]. This suggests that specific fatty acid ingredients, specific polyacetylenes, or both are responsible for the proapoptotic property of the extract through p53-dependent and p53-independent mechanisms.

Minaiyan et al. [99] evaluated the hydroalcoholic extract of rhizomes of *Zingiber officinale* Roscoe (Zingiberaceae; ginger) at doses of 150, 350, and 700 mg/kg orally and 350 and 700 mg/kg rectally, prior to colon inflammation induced by acetic acid in rats. The administration of the highest dose of extract via both oral and rectal routes reduced the macroscopic score, histopathological parameters, ulcer area and index, and weight/length ratio of the colon. Lower doses of the ethanol extract of ginger rhizomes (100, 200, and 400 mg/kg; p. o.) were evaluated in the study by El-Abhar et al. [100]. These authors observed the reduction of macroscopic score, histological alterations, MPO activity, and TNF-α, and PGE_2 concentrations in tissue by treatment with ginger. This extract also induced an antioxidant effect characterized by a decrease in malondialdehyde (a marker for lipid peroxidation) and protein carbonyl paralleled by an increase in GSH content and CAT and SOD activity.

The anti-inflammatory action of ginger extract may be related to the presence of compounds such as gingerols, which are the major pungent compounds present in the rhizomes of ginger [101] and show anti-inflammatory and antioxidant effects [102, 103]. In addition, the protective effects of 6-gingerol against DSS-induced colitis in mice were recently described. Treatment with this compound reduced the disease activity index, colonic shrinkage, NO concentration, MPO activity and oxidative stress, and concentrations of IL-1β and TNF-α in serum [104]. In addition, Chang and Kuo [105] correlated the anti-inflammatory effect of 6-gingerol on DSS-induced colitis with the activation of adenosine monophosphate-activated protein kinase.

Additionally, a study by Rashidian et al. [106] evaluated the effects of the volatile oil of ginger at the doses of 100, 200, and 400 mg/kg for 5 days in Wistar rats subjected to colon inflammation induced by acetic acid. This study demonstrated that the volatile oil reduced the colon weight/length ratio and ulcer severity, area, and index. The evaluation of microscopic scores showed that a dose of 400 mg/kg of volatile oil was effective to reduce inflammation severity and extent similar to prednisolone. Eighteen constituents of the volatile oil were characterized by this study, accounting for 97.67% of the total oil components detected. The main constituent of ginger oil was zingiberene, a sesquiterpene hydrocarbon, followed by ar-curcumene and α-sesquiphellandrene.

Curcuma longa L. belongs to the family Zingiberaceae and is commonly known as turmeric. Bastaki et al. [107] investigated the protective effects of the powdered rhizome of *C. longa* at doses of 1, 10, or 100 mg/kg/day (p. o.) administered for both 3 days before or 7 days after on acetic acid-induced colitis in rats. The macroscopic ulcer score, histological alterations, MPO activity, and IL-23 levels in the colon tissue were reduced when the animals were treated before induction. These effects were paralleled by an increase in the serum GSH level. These beneficial effects can be clearly associated with the presence of curcumin, a flavonoid with well-described activity against ulcerative colitis [108].

Curcumin suppressed the activation of dendritic cells by modulating the Janus kinase/STAT/suppressor of the cytokine signaling proteins signaling pathway to restore immunologic balance in TNBS-induced colitis [109]. Furthermore, curcumin induced the repression of IκB phosphorylation and NF-κB activation, consistent with the reduction of mRNA levels of iNOS, TNFα, IL-1β, and IL-6 [110]. In addition, an open-label clinical study reported

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that curcumin treatment improved the condition of a small number of patients with proctitis or Crohn's disease [111]. Another randomized, double-blind, multicenter trial showed that the administration of curcumin improved the clinical activity index and endoscopic index of patients and decreased the percentage of patients who relapsed [112].

Yang et al. [113] found that the methanol extract of the leaves of *Polygonum hydropiper* L. (Polygonaceae) at a dose of 100 mg/kg partially reverted the reduction of colon length induced by DSS in mice. The focus of this study was on the mechanisms involved in the anti-inflammatory effect of *P. hydropiper* extract on RAW 264.7 cells *in vitro*. These authors found that the extract decreased the production of NO, TNF-α, and PGE_2 by these cells during the activation of Toll-like receptor 4 through the inhibition of NF-κB, activator protein-1 (AP-1), cAMP-responsive element binding protein, and their upstream signaling cascades. This species contains many flavonoids, sesquiterpenoids, and coumarins, including 7,4-dimethylquercetin, 3-methylquercetin, quercetin, isoquercitrin, polygodial, warburganal, hydropiperoside, rhamnazin, and persicarin [114, 115]. Of these compounds, quercetin is known to exert anti-inflammatory effects through suppression of NF-*k*B and activator protein-1 [116]. In models of colitis, some studies have noted a protective effect of quercetin. In TNBS-induced colitis, quercetin (50 or 100 mg/kg, oral route) for 10 days following TNBS ameliorated clinical, histological, and biochemical alterations in rats [117]. In acetic acid-induced colitis in rodents, quercetin (50 or 100 mg/kg, oral route) decreased biochemical and morphological alterations in the colon of rats [118], and quercetin-loaded microcapsules (100 mg/kg, oral route) reduced neutrophil migration, microscopic and macroscopic damage, edema, and IL-1β and IL-33 production in the colon [119]. However, in DSS-induced colitis, the administration of quercetin in the diet (0.1%) of mice did not induce any effect [66]. Thus, although there seems to be a potential for quercetin to treat colitis, the different results found in these studies still require clarification, but we can suggest that the route of administration was a decisive factor in such discrepancies.

Aleisa et al. [120] evaluated the preventive properties of the ethanol extract of the leaves of *Gymnema sylvestre* (Retz.) R. Br. ex Sm. (Apocynaceae) (50, 100, and 200 mg/kg; p. o.) against colitis induced by acetic acid in rats. Pretreatment with this extract mitigated the damage to the cytoarchitecture of the colon in a dose-dependent manner. Mucus content was increased after treatment with the higher dose of extract (200 mg/kg). The antioxidant effect of *G. sylvestre* extract may account for these effects, since this extract diminished lipid peroxidation and sulfhydryl content and increased SOD and CAT activity. The concentration of IL-1β, IL-6, TNF-α, PGE_2, and NO in colon tissues was also reduced by treatment with the extract of *G. sylvestre*. A number of oleanane-type triterpenoid saponins known as gymnemic acids were found as constituents of this extract, but no description of the beneficial effect of these compounds on colitis was described [121–123].

Cordia dichotoma G. Forst. (Boraginaceae) is an important plant for indigenous systems of medicine, and many medicinal properties have been attributed to this species. Various parts of this plant are used as an antipyretic, an antianemic, a remedy for impotency, and treatments for gastric pain, asthma, mouth ulcers, bronchitis, diarrhea, rheumatism, and dental caries [124, 125]. Traditionally, the bark of the plant is reported for the treatment of colitis. Ganjare et al. [126] observed mild pathological change scores in animals treated with the methanol fraction of methanol extract of the bark of *C. dichotoma* (50 mg/kg, p. o.) as well crude methanol extract (500 mg/kg, p. o.). These extracts reduced MPO activity and malondialdehyde in tissue and blood. One interesting finding of this study is the increased presence of phenolic compounds in the methanol fraction. Ganjare et al. [127] identified apigenin in the methanol fraction of the methanol extract of the bark of *C. dichotoma* and showed that apigenin isolated from this plant (5 mg/kg, p. o.) diminished histopathological damage in the colon as well as MPO activity and malondialdehyde levels in the blood and tissue of mice subjected to acetic acid-induced colon inflammation. It is known that apigenin exerts an anti-inflammatory effect by inhibiting TNF-α production and NF-κB transcriptional activation [128] and that it decreases colitis induced by DSS in mice [42]. This evidence strongly reinforces the role of apigenin as a promising compound in the treatment of colitis.

A study by Deshmukh et al. [129] evaluated the effects of the methanol extract of *Emblica officinalis* (Euphorbiaceae) fruit at 100 and 200 mg/kg for 7 days of oral administration on the acetic acid model. This study demonstrated that the extract reduced lactate dehydrogenase, the ratio of colon weight/length, macroscopic score, and the histopathological alterations caused by acetic acid. Some studies have shown the presence of phytochemicals such as quercetin, gallic acid, corilagin, and ellagic acid in this plant [130]. All these compounds have been described as beneficial for colitis, based on experimental studies. As previously mentioned, quercetin [117] and gallic acid caused beneficial effects on animals with colitis, with the key participation of the NF-κB pathway [94]. Ellagic acid was studied in models of colitis. Ogawa et al. [131] have demonstrated that the administration of microspheres containing ellagic acid decreased DSS-induced colitis in rats in a dose-dependent manner with an effective dose $(ED)_{50}$ of 2.3 mg/kg. Rosillo et al. [132] showed that diet supplementation with both ellagic acid (10 mg/kg/day) and ellagic acid-enriched pomegranate extract reduced MPO activity, TNF-α levels, COX-2 and iNOS expression, MAPK phosphorylation, and NF-κB translocation in TNBS-induced colitis in rats. Marin et al. [133] demonstrated that supplementation with ellagic acid inhibited both acute and chronic colitis induced by DSS. In the acute set of experiments, supplementation with 2% ellagic acid for 7 days in female Balb/C mice reduced the effect of concomitant administration of DSS on macroscopic parameters and IL-6, TNF-α, and IFN-γ production in colonic tissue. In female C57BL/6 mice subjected to chronic DSS administration, ellagic acid (0.5%) reduced intestinal inflammation and histological scores, downregulated the expression of COX-2 and iNOS, and reduced the activity of the p38 MAPK, NF-κB, and STAT3 signaling pathways. Regarding corilagin, Xiao et al. [134] demonstrated that this compound reduced colon damage and cytokine production in DSS-induced colitis in mice by downregulating the expression of caspase 3 and 9 and NF-κB signaling. These studies evidence the potential of ellagic acid and corilagin in the treatment of colitis and reinforce the possibility of their involvement in the protective effect of *E. officinalis*.

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A study by Patel et al. [135] evaluated the effects of the aqueous extract of the bark of *Ficus bengalensis* Linn. (Moraceae) at doses of 250 and 500 mg/kg for 21 days on a TNBS model in rats. Patel et al. [136] also evaluated the ethanol extract of the bark of this plant. Treatment with both extracts decreased the colonic mucosal damage index, disease activity index, MPO activity, malondialdehyde concentrations, and NO levels in tissue; in addition, it increased SOD activity. As the polarity of the extracts is close, Patel et al. [135] argued that the effectiveness of the extracts may occur due to the presence of flavonoids and terpenoids. However, data from the literature indicate that the bark contains ketones, β-sitosterol-α-D-glucose, and meso-inositol [137]. It is possible that β-sitosterol-α-D-glucose may contribute to the protective action to some extent. Phytosterols are potential nutraceutical compounds for gastrointestinal inflammatory diseases since pretreatment with phytosterols reduces the clinical symptoms and exerts a protective effect on DSS-induced colonic inflammation [138]. In addition, a protective role was suggested for β-sitosterol in TNBS-induced colitis in mice since the administration of this compound decreased colon shortening, macroscopic damage, MPO activity, expression of TNF-α, IL-1β, IL-6, and COX-2, and activation of the NF-κB pathway [139].

Gholap et al. [140] demonstrated that both the ethanol extract and the aqueous extract of the roots of *Moringa oleifera* Lam. were effective in the treatment of colitis induced by acetic acid in Swiss mice. These authors tested two doses (100 and 200 mg/kg; oral route). However, only the higher dose reduced MPO activity and MDA levels in tissue and blood. Interestingly, based on traditional knowledge, these authors utilized in the same study a combination of *M. oleifera* root extracts and *Citrus sinensis* fruit rind extract. Animals treated with this combination showed less ulceration and hyperemia in the histopathological analysis, which was paralleled by a decrease in MPO activity and MDA levels in the colon after challenge with acetic acid. Another study also demonstrated the effect of hydroalcoholic extract of *M. oleifera* Lam. seeds and its chloroform fraction on acetic acid-induced colitis in rats [141]. The hydroalcoholic extract (50, 100, and 200 mg/kg) decreased ulcer severity, area, and index, mucosal inflammation severity and extent, crypt damage, total colitis index, and MPO activity in the colon. However, a beneficial action was observed for the fraction only at 100 mg/kg and 200 mg/kg. Several bioactive compounds were recognized in the leaves, seeds, flowers, pods, stems, and roots of *M. oleifera* Lam., such as vitamins, carotenoids, polyphenol, phenolic acids, flavonoids, alkaloids, glucosinolates, isothiocyanates, tannins, saponins and oxalates, and phytates [142, 143]. In relation to the seeds, Guevara et al. [144] isolated niazimicin and niazirin as well as O-ethyl-4-(alpha-L-rhamnosyloxy)benzyl carbamate, 4(alpha-L-rhamnosyloxy)-benzyl isothiocyanate and various derivatives of β-sitosterol from the seeds of *M. oleifera*. Additionally, Choudhary et al. [145] found the presence of moringine and moringinine in the root-bark extract. Some of these compounds, such as steroids, should contribute to the effectiveness of extracts.

The search strategy in the present study enabled us to find only one study for some families of plants (▸ **Table 1**). The details of some of these studies are presented.

For example, *Andrographis paniculata* (Burm.f.) Nees (Acanthaceae) is a plant used for inflammatory and infectious diseases in Asian countries, Sweden, and Chile [146]. A proprietary *A. paniculata* extract named HMPL-004 prevented the development of UC in a model consisting of CD4+CD45RB^{high} T cells transferred into Rag1$^{-/-}$ mice [147]. Mice treated with HMPL-004 (300 mg/kg) did not lose weight and displayed only very mild intestinal inflammation in comparison to non-treated mice. In addition, TNF-α, IL-1β, INF-γ, and IL-22 expression were decreased in HMPL-004-treated mice, which also presented higher percentages of naive CD4$^+$ T cells in the colonic lamina propria. Splenic cell counts and CD4$^+$, IL-17$^+$, and IFN-γ^+ T cells were decreased by HMPL-004 treatment, and it also mitigated the proliferation of CD4$^+$ T cells and their differentiation into Th1/Th17 cells *in vitro*. These results reinforced previous data regarding a clinical trial with HMPL-004 [146], which showed that this preparation reduced the remission and response of patients with UC to the same extent as the slow release of mesalazine granules. Among the many compounds identified in *A. paniculata*, andrographolide is a diterpenoid lactone and considered to be one of the main bioactive components. This compound induces anti-inflammatory action by inhibiting NF-κB signaling and suppressing iNOS and reactive oxygen species [148–151]. In addition, andrographolide sulfonate was shown to inhibit TNBS-induced colitis in mice through negative modulation of the Th1/Th17 response [152]. These results strongly indicate a great value for *A. paniculata* extract and andrographolide in the treatment of colitis.

Allium sativum L. (garlic, Amaryllidaceae) was tested by Harisa et al. [153] against colitis induced by acetic acid in rats. The administration of a garlic formulation (garlic bulbs initially extracted with water) at a dose of 250 mg/kg alone or coadministered with L-arginine attenuated the alterations induced by acetic acid in the colon tissue contents of malondialdehyde and GSH as well as activity of SOD and CAT. These effects could be caused by compounds like diallyl sulfides, which are known as antioxidants and positive modulators of antioxidant enzyme activity. This results in the inhibition of lipid peroxidation [154, 155]. Recently, a study by Balaha et al. [156] has shown that garlic oil (25–100 mg/kg) inhibited colitis induced by DSS in rats.

Many constituents of garlic have been described; among them are alliin, allicin (a compound formed from alliin), and other volatile organosulfur substances (e.g., diallyl sulfide, diallyl disulfide and diallyl trisulfide) as well as nonvolatile compounds such as S-allyl-L-cysteine and S-allylmercapto-L-cysteine, which are well studied regarding their biological properties [157]. Allicin (30 mg/kg) decreased the alterations induced by the administration of TNBS to rats due to the inhibition of the p38 and JNK signaling pathways and expression of NF-κB [158]. Likewise, allicin (10 mg/kg) inhibited colitis induced by DSS in mice through modulation of the IL-6/STAT3 and NF-κB pathways [159].

The protective action of allyl sulfides in colitis and/or associated colon cancer has also been described by some studies. Colitis induced by DSS in mice was reduced by treatment with diallyl trisulfide through mechanisms involving NF-κB and STAT3 signaling [160]. Other allyl sulfides (diallyl sulfide and diallyl disulfide) also inhibited colitis induced by intracolonic administration of dinitrobenzenesulfonic acid to mice [161], and diallyl disulfide (diet sup-

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plementation with 85 ppm) protected mice against colorectal cancer triggered by the administration of the carcinogen azoxymethane plus DSS by a mechanism associated with the inhibition of glycogen synthase kinase-3*β* and a resulting reduction in NF-*κ*B translocation [162]. Interestingly, a common finding about the effect of allicin or allyl sulfides is the involvement of NF-*κ*B in their beneficial effects on colon damage.

The oral administration of hydroalcoholic extract of the aerial parts of *Kelussia odoratissima* Mozaff. (Apiaceae) in rats decreased acetic acid-induced colitis at 125 and 250 mg/kg, but not 500 mg/kg [163]. Macroscopic score, ulcer area, ulcer index, histological alterations, and weight/length ratio in the colon were diminished by this extract. Accordingly, MPO activity in colon was decreased only in the lower doses. Interestingly, when the extract was given at a high dose, its efficacy declined. This can probably be attributed to some active harmful constituents also existing in the extract that are absorbed in the GI tract after higher dose administration and oppose the therapeutic actions of other beneficial active ingredients that have been identified in this extract, such as rutin, 3,4,7-trihydroxyflavonol, caffeic acid, and phthalide [164].

Minaiyan et al. [165] investigated the anti-inflammatory effect of *Berberis vulgaris* L. (Berberidaceae) fruit extract on colitis induced by acetic acid. This plant is a shrub from the family Berberi daceae with pharmacological potential. Hydroalcoholic extract of the fruit, at doses of 750 and 1500 mg/kg, reduced macroscopic parameters and the weight/length ratio in the colon of rats subjected to acetic acid administration. However, only the high dose affected the severity and extent of inflammation and crypt. damage Hemmati et al. [166] reported that *B. vulgaris* hydroalcoholic extract contains berberine, a compound with antioxidant and anti-inflammatory properties [167]. Zhou and Mineshita [168] showed the beneficial effect of berberine on the healing process of the colon mucosa, possibly due to the inhibition of IL-8 production, in TNBS-induced colitis in rats.

A study by Joshi et al. [169] demonstrated that the aqueous extract of the root bark of *Oroxylum indicum* (L.) Kurz (Bignoniaceae), at doses of 100, 200, and 400 mg/kg (oral route), decreased colitis induced by intracolonic instillation of dinitrobenzenesulfonic acid in rats. Gross damage area, body weight loss, and an increase in colonic and spleen weight were impaired by administration of the extract. These authors observed that the extract caused a reduction of colonic MPO activity, malondialdehyde levels, and NO concentrations and an increase in GSH levels, along with attenuation of inflammatory cell infiltration and submucosal edema in the colon. According to Joshi et al. [169], a qualitative phytochemical analysis of extract of the root bark of *O. indicum* (L.) Kurz confirmed the presence of saponins, phenolic compounds, and flavonoids. They also identified chrysin, baicalein, biochanin A, and ellagic acid in this extract. The efficacy of the extract on colitis may be attributed to the presence of these compounds. Chrysin (25 mg/kg) prevented colitis induced by DSS in mice, an effect characterized by a reduction in weight loss, colonic histological alterations, MPO activity, NO, PGE_2, and cytokines [170]. Recently, Dou et al. [171] showed that chrysin mitigated both DSS- and TNBS-induced colon inflammation, in part due to the pregnane X receptor and the NF-*κ*B pathway. Treatment with baicalein (20 mg/kg, oral route), a flavonoid known as an active component of *Scutellaria baicalensis* Georgi, reduced the symptoms of DSS-induced colitis in mice (body weight loss, blood hemoglobin content, rectal bleeding, and histological and biochemical parameters) [172]. Another study showed that baicalein (1–10 mg/kg incorporated into the diet) reduced the development of colon tumors, increased colon length, and decreased the histological inflammatory alterations associated with cancer development in the azoxymethane/DSS-induced model of colon cancer in mice [173]. These findings suggest that chrysin and baicalein may exert potentially clinically useful anti-inflammatory effects on colitis.

Somani et al. [174] demonstrated that the methanol extract of leaves of *Dillenia indica* L. (Dilleniaceae) at a dose of 800 mg/kg (oral route) decreased macroscopic damage, colon MPO activity, lipid peroxidation, and TNF-*α* levels in the model of colitis caused by acetic acid. These effects were paralleled by increases in GSH levels and SOD and CAT activity. These authors also showed that the chloroform fraction of this extract, at a dose of 200 mg/kg, decreased macroscopic damage associated with colitis and modulated other inflammatory/oxidative markers in the same ways as did the crude extract. Preliminary phytochemical screening showed the presence of steroids, terpenoids, glycosides, fatty acids, flavonoids, phenolic compounds, and carbohydrates [175]. A study by Kumar et al. [176] identified betulinic acid, *n*-heptacosan-7-one, *n*-nonatriacontan-18-one, quercetin, *β*-sitosterol, stigmasterol, and stigmasteryl palmitate in the leaves of *D. indica*. Among these compounds, previous reports have shown that betulinic acid suppresses the disease activity index and mRNA expression of IL-1*β*, IL-6, and TNF-*α* in the colon by a mechanism that involves the selective activation of the TGR5 receptor [177]. Interestingly, the TGR5 receptor is a Gs protein-coupled receptor specific for bile acids, expressed not only in enteroendocrine L cells located in the distal small and proximal large intestines but also in other tissues; once activated, it stimulates the release of glucagon-like peptide-1 release from L cells, a process that is relevant to intestinal motility and secretion [178]. In addition to betulinic acid, the presence of quercetin [117–119] and/or *β*-sitosterol [139] may contribute to the effect of this extract.

Different parts of *Punica granatum* L. (pomegranate, Lythraceae) are traditionally used in Europe, India, China, the Philippine Islands, and South Africa for many purposes, including the treatment of diarrhea, dysentery, colic, and ulcers. The extract of the flowers of *P. granatum* reduced macroscopic and histological alterations, MPO activity, histamine concentration, lipoperoxidation, and superoxide concentration in the colon [179]. Interestingly, the same study showed that a fraction of the extract enriched with ellagic acid seemed to induce better effects than did the crude extract. These authors suggested that the beneficial action of *P. granatum* in DSS-induced colitis might be attributed to mast cell-stabilizing, and anti-inflammatory and antioxidant activities. The beneficial effects of ellagic acid have been shown by others [131], as described above in the present study. Additionally, *P. granatum* juice (400 mg/kg, p. o.) and purified punicalagin (4 mg/kg, p. o.) reduced colitis induced by 2,4-dinitrobenzene sulfonic acid in rats, an effect that was accompanied by the reduction of TNF-*α*, IL-18, IL-1*β*, and NF-*κ*B mRNA expression in the colon [180].

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De Melo et al. [181], in their study, evaluated the effect of oral administration of the aqueous extract of the aerial parts (25, 100, and 200 mg/kg) of *Phyllanthus niruri* L. (Phyllanthaceae) in rats with colitis induced by acetic acid. They showed that this extract prevented GSH depletion and lipid peroxidation and that it reduced microscopic damage and MPO activity in colon tissue. In addition, decreased protein expression of TNF-*α*, IFN-*γ*, and the p53 subunit of NF-*κ*B was observed. Other studies have shown the presence of ellagic acid, catechin, chlorogenic acid, epicatechin, phyllanthin, and hypophyllanthin in *P. niruri* extract [182]. Additionally, corilagin is present in the leaves of *P. niruri* [183] and may contribute to the beneficial effects of this extract as previously noted by the work of Xiao et al. [134].

Oldenlandia diffusa (Willd.) Roxb. (Rubiaceae) is used as a traditional Asian medicine to treat inflammation. A study by Kim et al. [184] investigated the protective effect of the aqueous extract of *O. diffusa* (1 g/kg; p. o.) on DSS-induced colitis in mice. These authors showed that this extract reduced the weight loss, colon shortening, and disease activity index of the mice. They attributed these effects to a decrease in IL-6 levels and COX-2 expression as a result of the negative regulation of NF-*κ*B. Likewise, the same study showed that hentriacontane (5 mg/kg by oral route), an alkane hydrocarbon present in *O. diffusa*, decreased weight loss, colon shortening, and IL-6 levels induced by DSS. Thus, the effect of *O. diffusa* aqueous extract can be associated with the presence of hentriacontane.

Cho et al. [185] investigated the effects of the methanol extract of the root of *Patrinia scabiosifolia* Link (Valerianaceae) in the model of colitis induced by DSS in mice, because this plant is traditionally used in Korea to treat intestinal inflammation. These authors observed that 10, 30, and 50 mg/kg of the extract attenuated the disease activity index score, shortening of colon length, and increase in spleen size. Histological examinations indicated that treatment with this extract suppressed edema, mucosal damage, loss of crypts, and infiltration of neutrophils and macrophages induced by DSS in colons. In addition, it inhibited colon MPO activity, nitric oxide metabolites, and expression of iNOS. Furthermore, this extract decreased the abnormal mRNA and protein expression of TNF-*α*, IL-1*β*, and IL-6. These effects can be related to the anti-inflammatory action of certain chemical constituents, such as oleanolic acid and ursolic acid, that are present in *P. scabiosifolia* [186, 187].

Oleanolic acid ameliorated DSS-induced colitis by inhibiting Th17 cell differentiation and increasing Treg cell differentiation. Moreover, it inhibited expression of TNF-*α*, interleukin (IL)-1*β*, and IL-17 and activation of NF-*κ*B and mitogen-activated protein kinases, and it increased IL-10 expression [188]. The benefits of ursolic acid on colitis have also been described. Chun et al. [189] showed that ursolic acid inhibits the production of proinflammatory cytokines, I*κ*B*α* phosphorylation/degradation, and NF-*κ*B binding to DNA in COLO 205 cells, a lineage of human intestinal epithelial cells. Additionally, it reduced the severity of DSS-induced murine colitis, as assessed by the disease activity index, colon length, and histopathological alterations. Furthermore, it reversed I*κ*B*α* phosphorylation in the colonic tissue. Additionally, Liu et al. [190] demonstrated that ursolic acid reduced serum levels of IL-1*β* and TNF-*α*, decreased MDA content, increased SOD activity, and reduced the expression of the p65 subunit of NF-*κ*B in a DSS model of colitis.

Strengths and limitations

Data from studies in experimental animals have shown that many medicinal plants possess efficacy against UC. In the present review, we highlighted some of these plants, such as *A. lappa, A. paniculata, A. sativum, B. dracunculifolia, B. tomentosa, C. langsdorffii, C. oblonga, D. indica, E. officinalis, F. benghalensis, I. dentata, O. diffusa, O. indicum, P. scabiosifolia, P. granatum, R. damascena, R. monosperma, R. officinalis, S. baicalensis*, and *Z. officinale*. However, it is still a challenge to make decisions regarding advancement to clinical trials because of the limitations of the studies published. In our search, we encountered a great number of studies that are merely descriptive, and more attention should be given to aspects that are important to permit advancement from basic to translational studies, such as the ethnopharmacological connections, the toxicological findings for each plant, the identification of compounds in the plants under investigation, and the signaling pathways by which these compounds can ameliorate colitis.

In spite of these limitations, a few species have already drawn interest and have undergone clinical tests that found them to be effective against UC in humans. For example, patients treated with *A. paniculata* extract (HMPL-004) at a dose of 1800 mg daily were more likely to achieve a clinical response than were those receiving a placebo [191]. In the same way, another study suggested the effect of *P. granatum* peel extract (6 grams per day) on UC in patients [192].

The identification of chemical constituents in the plants discussed in the present review deserves special attention and is also an interesting outcome. Many of these substances are flavonoids (apigenin, artepillin C, baicalein, caffeic acid, chlorogenic acid, chrysin, corilagin, curcumin, ellagic acid, gallic acid, kaempferol, luteolin, *p*-coumaric acid, quercetin, rosmarinic acid, and rutin), which collectively possess many pharmacological properties, including antioxidant and anti-inflammatory activity that seems relevant to the treatment of UC [10, 193]. Other compounds include terpenoids (1,8-cineole, andrographolide, betulinic acid, geraniol, kaurenoic acid, oleanolic acid, ursolic acid, α-pinene, and *β*-caryophyllene), phytosterols (*β*-sitosterol and genistein), sulfide-containing compounds (allicin and diallyl sulfides) and other chemical classes (e.g., arctigenin, gingerols, gymnemic acid, and hentriacontane). Based on the present study, we can highlight the potential of these substances to treat colitis in experimental animals and present them as potential contributors to future approaches designed to treat UC.

Finally, regarding the intracellular pathways involved in the beneficial effects of compounds or crude extracts, we can state that the NF-*κ*B signaling was the most studied and implicated in the effects of plants or isolated compounds. However, other pathways have also attracted interest as mechanisms involved, mainly the MAPK (JNK, Erk and p38), STAT3, and Nrf-2 signaling pathways.

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Conclusions

The present review study indicates that some medicinal plants have shown promising results in experimental studies, mainly based on their anti-inflammatory and antioxidant effects, and therefore may possess efficacy in the treatment of UC. However, the majority of studies do not translate to human application. A possible explanation is that many studies in the literature are purely descriptive, which limits their findings and hinders their translation to clinical practice or validation of the popular uses of products.

Despite these limitations, the presence of flavonoids and terpenes in the plants selected from the literature certainly contributes to their pharmacological effects through a diversity of mechanisms. Particular attention should be paid to these compounds as possible drug candidates for the treatment of colitis in humans. As a final statement, we can reinforce the potential of medicinal plants as a source of alternative treatment approaches for UC.

Conflict of Interest

None.

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