R E V I E W

Plants with Anti-Ulcer Activity and Mechanism: A Review of Preclinical and Clinical Studies

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Abstract: Ulcer disorders including the oral mucosa, large intestine, and stomach mucosa, cause significant global health burdens. Conventional treatments such as non-steroid anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), histamine H_2 receptor antagonists (H_2RAs), and cytoprotective agents have drawbacks like mucosal injury, diminish gastric acid secretion, and interact with concurrent medications. Therefore, alternative therapeutic approaches are needed to tackle this health concern. Plants are rich in active metabolites in the bark, roots, leaves, fruits, and seeds, and have been utilized for medicinal purposes since ancient times. The use of herbal therapy is crucial, and regulations are necessary to ensure the quality of products, particularly in randomized studies, to assess their efficacy and safety in treating ulcer disorders. This study aims to explore the anti-ulcer activity of medicinal plants in treating peptic ulcer disease, ulcerative colitis, and aphthous ulcers. Articles were searched in Scopus and PubMed, and filtered for publication from 2013 to 2023, resulting in a total of 460 from Scopus and 239 from PubMed. The articles were further screened by title and abstract and resulted in 55 articles. Natural products, rich in active metabolites, were described to manage ulcer disease by protecting the mucosa, reducing ulcer effects, inhibiting pro-inflammatory factors, and reducing bacterial load, thus improving patients' quality of life. Natural extracts have proven effective in managing other health problems, including ulcers by reducing pain and decreasing lesions. This review provides an overview of preclinical and clinical studies on medicinal plants, focusing on their effectiveness in treating conditions like peptic ulcers, ulcerative colitis, and aphthous ulcers.

Keywords: anti-ulcers, aphthous ulcer, botanical drugs, peptic ulcer disease, ulcerative colitis

Introduction

The need to replace certain drugs due to their adverse effects exemplifies the universal role of plants in the treatment of disease and the maintenance of health. The utilization of medicinal plants for the treatment of various ailments has been practiced since ancient times and is commonly referred to as phytotherapy.[1] The healing effects of medicinal plants come from the fact that they accommodate a wide range of secondary metabolites, called phytochemicals, which can be synthesized again and again in nature. The richest sources of active metabolites are contained in seeds, bark, roots, leaves, and fruits of plants. Therefore, a multitude of plants have employed these phytochemicals as a defense mechanism against pathogens.

Phytochemicals have been used since ancient times for the treatment of various disorders and are generally considered safer as compared to synthetic medicines.[2–4] They are widely available in nature, and apart from therapeutic purposes, they are also consumed in the form of nutritional supplements.[5] Several plant-derived chemical constituents have been reported to possess anti-ulcerative properties in various preclinical studies. These constituents belong to the class of alkaloids, tannins, flavonoids, terpenoids, glycosides, carotenoids, and saponins.[6–8] Numerous botanical products have been confirmed to exhibit antiulcer activity although most studies focused on pharmacological action in animal models.

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Ulceration is a crater-shaped lesion or wound that can form on the oral mucosa, large intestine (colon), and stomach mucosa. The formation of an ulcer may cause the region to bleed or discharge unpleasant materials, creating a painful sore that is susceptible to infection. Ulceration can be characterized by flaws in the epithelium, underlying connective tissue, or both. The diagnosis of ulcerative lesions may be difficult due to the wide range of potential causes and presenting characteristics of every organ.[9] Despite the existence of various conventional and non-conventional treatment modalities for ulcer management, each approach is associated with certain limitations, including toxicity, low efficacy, and high cost.[10] It is crucial to highlight the fact that botanical products may contain a multitude of active constituents that possess both hazardous and advantageous effects. Thus, it is important to use herbal therapy and put in place regulations to ensure the quality of herbal products, especially when it comes to doing more randomized studies to find out how effective and safe different products are at treating ulcer disorders.[1]

Taking all into consideration, this review aims to provide an in-depth exploration of plants possessing anti-ulcer activity, elucidating their mechanisms of action through a combination of preclinical and clinical studies. By consolidating the current body of knowledge, this review aims to shed light on the potential of plant-based interventions as viable alternatives for the management of gastrointestinal ulcers. This review will encompass a thorough analysis of preclinical studies investigating various plant species and their active metabolites with demonstrated anti-ulcerative properties, as well as a critical evaluation of clinical trials investigating the efficacy and safety of plant-based interventions in ulcer management. Special emphasis will be placed on elucidating the underlying mechanisms, including their impact on gastric mucosal protection, modulation of acid secretion, anti-inflammatory effects, assessments of symptom relief, ulcer healing rates, and potential preventive effects on ulcer recurrence.

Methods

Initially, the search included references published from 2013 until 2023. Articles were searched in Scopus and PubMed, in addition to Google Scholar. Throughout the search process, synonyms and related terms were used interchangeably as keywords, and the Boolean operator "AND" was utilized to combine and exclude terms as follows: (1) in the Scopus database using the keywords Plants AND Anti-ulcerative Activity AND Clinical Studies, searched within Article title, Abstract, and Keywords, resulted in n = 6; using the keywords Plants AND Anti-ulcerative Activity searched within Article title, Abstract, and Keyword, resulted in n = 90; and using the keywords Plants AND Antiulcer AND Activity searched within Article title, Abstract, Keywords, resulted in n = 364, with a total of 460 articles from Scopus database; (2) in the PubMed database using the keywords Plants AND Anti-ulcerative Activity searched within Abstract, free full text, and in the last 10 years, resulted in n = 239.

All articles found through these searches were further screened and those that met the review's inclusion criteria (open access, written in English, related to antiulcer activity studied in animal models and humans, not studied in cells or computational simulation), were retrieved and evaluated by the authors. Finally, 55 articles were selected, as depicted in Figure 1. However, during the process, an additional search was conducted to obtain more articles to support the discussion.

Results

Of the 55 articles, 50 discussed in vivo (preclinical) methods (Table 1) and 5 discussed clinical (human) studies (Table 2). For example, 16 articles described the mechanisms for peptic ulcer disease, 33 articles described the mechanisms for ulcerative colitis, and 3 articles described the mechanisms for aphthous ulcer. Moreover, 33 articles discussed the active metabolites that demonstrated mechanisms for healing ulcers. Of these studies, 5 confirmed the importance or empirical history of the plants that had mechanisms for healing ulcers.

Most of the studies described Brazil (South America) and China as the origin locations of the plant collection, although other countries such as Iran, Egypt, Pakistan, Cameroon (Central Africa), Bangladesh, Poland, Malaysia, Korea, Nigeria (West Africa), and Indonesia were also mentioned.

In the preclinical studies, various types of ulcer inducers were used, eg, ethanol (9 articles), dextran sulfate sodium (8 articles), bethanechol (6 articles), acetic acid (6 articles), indomethacin (3 articles), histamine (2 articles), trinitrobenzene sulfonic acid (2 articles), and other inducers (pentagastrin, piroxicam, *Helicobacter pylori*, and a burnisher). Of those,
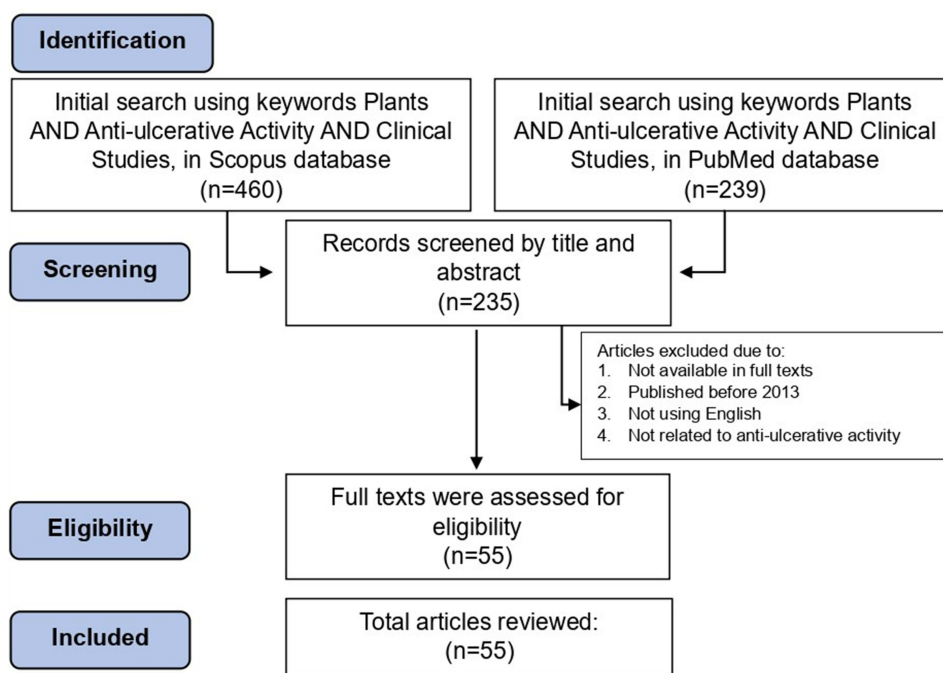
Figure 1 The study design of the review.

rats (*Rattus norvegicus*) were more selected (54.54%) as the animal model than mice (*Mus musculus*) (45.45%). The description of the diseases is presented below.

Nine plants were confirmed for their strong anti-peptic ulcer disease activity in animal models, twenty plants have shown strong anti-ulcerative colitis activity, and no plant exhibited strong anti-aphthous ulcer activity. Studies in humans indicated that *Nicotiana tabacum* (Solanaceae), *Glycyrrhiza glabra* (Fabaceae), and *Zingiber officinale* (Zingiberaceae) possessed strong antiulcer activity.

Peptic Ulcer Disease (PUD)

Peptic ulcer disease (PUD) is characterized by the presence of damage or ulcers in the mucosal lining of the gastro-intestinal tract (GI), which leads to the excessive secretion of gastric acid or pepsin. Typically, these symptoms appear within the gastric region and the proximal segment of the duodenum.[50] Peptic ulcer disease (PUD) is a global problem with a lifetime risk of development ranging from 5–10%.[51] In general, there has been a global decline in the prevalence of peptic ulcer disease (PUD) as a result of enhanced hygienic and sanitary practices, as well as the implementation of effective treatment strategies and the cautious utilization of non-steroidal anti-inflammatory drugs (NSAIDs). Therefore, epidemiological studies have demonstrated a reduction in peptic ulcer incidence, hospital admissions, and death but the case fatality rate has stabilized at 5–10%.[52]

PUD has various multiple factors. Traditionally, mucosal disruption in patients with peptic disease is considered to be a result of a hypersecretory of acid together with dietary factors or stress. The primary risk factors associated with gastric or peptic ulcers are infection with *H. pylori* and the utilization of nonsteroidal anti-inflammatory drugs (NSAIDs).[53,54] Nevertheless, the incidence of PUD is relatively low among individuals affected by *H. pylori* or those who use NSAIDs. This suggests that individual susceptibility affects the initial onset of mucosal damage.

The primary goal of presently antiulcer medications is not only limited to controlling the progression of the disease. It also aims to induce remission as quickly as possible and to maintain it for a long time The management of PUD currently uses a variety of conventional treatment modalities, but it's crucial to remember that each of these treatments has one or more negative side effects. The primary goal of currently used anti-ulcerative medications is not simply to manage the advancement of the ailment. It also aims to promptly initiate and sustain a state of remission over an extended period.[55,56] The primary

Table 1 The Anti-Ulcerative Properties of Various Plants in Preclinical Studies

Medicinal Plants Authority (family), Collected In, Year	Plant Part, and Extraction Method (Solvent Used)	Animal Used in the Preclinical study (n)	Inducement Method and Dose	Control (Negative and Positive)	Duration (Days)	Results	Interpretation	Ref
Peptic Ulcer Disease (PUD)								
Annona muricata L. (Annonaceae); Ceara, Brazil; 2015	Leaves; Maceration (Ethanol)	In vivo on male and female albino mice (*Mus musculus*), weight 20–30g (n=48).	Absolute ethanol and indomethacin (NSAID)	Vehicle (saline, 0.1 mL/kg p.o) as a negative control and Omeprazole (30 mg/kg p.o) as a positive control.	1	The extract at doses of 50, 100, 200, and 400 mg/kg produced a significant reduction in lesion area of 92.89%, 94.13%, 97.79%, and 96.55%, respectively. The dose of 200 mg/kg is the most effective in reducing the incidence of ulcers by 94.13%, and at 400 mg/kg decreased the incidence of ulcers significantly by 91.67% ($p < 0.05$). The extract at a dose of 200 and 400 mg/kg was more effective than the standard drug (omeprazole).	Strong activity	[11]
Arctium lappa L. (Asteraceae); Parana, Brazil; 2013	Roots; Percolation (Ethanol 96%)	In vivo on female Wistar rats (*Rattus norvegicus*) weight 180–200g (n=N/A)	Bethanechol, Pentagastrin (NSAID), and Histamine	Vehicle (water 1 mL/kg i.d.) as a negative control and Ranitidine (50 mg/kg i.d.) as a positive control.	1	The extract at a dose of 1000 µg/kg prevented the increase of gastric secretion in pylorus-ligated rats stimulated by bethanechol, histamine, or pentagastrin. The extract at a dose of 10 mg/kg i.d decreased the acidity of gastric secretion stimulated by bethanechol, histamine, or pentagastrin.	Strong activity	[12]
Artemisia absinthium L. (Asteraceae); Santa Catarina, Brazil; 2019	Aerial parts; Maceration (Water)	In vivo on female Wistar rats (*R. norvegicus*) weight 280–300g, age 3–4 months old (n=48).	Ethanol	Vehicle (water 10 mL/kg) as a negative control and Omeprazole (20 mg/kg) as a positive control.	1	The extract at doses of 3%; 10% and 30% presented a gastroprotective effect in the submucosa layer reducing the lesion area by 64.68%, 53.71%, and 90.04%, respectively.	Strong activity	[13]

Bryophyllum pinnatum L. (Crassulaceae); Dschang, Cameroon; 2015	Leaves; Maceration (Methanol)	In vivo on Swiss mice *(M. musculus)* weight 17–23 g (n= 60)	Inoculation of *H. pylori* bacteria	Vehicle (200 µL of a sterile solution of 0.25% Tween 80) and inoculation of *H. pylori* bacteria as a negative control group and Ciprofloxacin (500 mg/kg) as a positive control group	7	The extract showed significant anti-Helicobacter activity (p < 0.05) with MIC and MBC values of 32 and 256 lg/mL, respectively. A combination of extract and ciprofloxacin reduced *H. pylori* colonization of gastric tissue from 100% to 17%. The extract (85.91 ± 52.91 CFU) and standard (25.74 ± 16.15 CFU) also significantly reduced (p < 0.05) the bacterial load of gastric mucosa as compared to untreated infected mice (11,883 ± 1831 CFU).	Strong activity	[14]
Casearia sylvestris Sw. (Salicaceae); Brazil; 2019	Leaves; Infusion (Distilled Water)	In vivo on female Wistar rats *(R. norvegicus)* weight 200–250 g, age 80 days old (n=56).	Piroxicam (NSAID) ethanol, and acetic acid	Vehicle (water 1 mL/kg P.O.) as a negative control and Omeprazole (40 mg/kg P.O.) as a positive control.	14	The extract at doses of 30 or 300 mg/kg prevented ulcers in the ethanol and piroxicam-induced acute. At a dose of 300 mg/kg, the extract also sped up the healing of acetic acid-induced ulcers in rats' stomachs by 48%. Ultrasonography records show that the extract reduced the thickness of the ulcerous lesions' walls and the amount of swelling around them. *C. sylvestris* extract helped rat stomachs heal faster by lowering MPO and NAG activities at ulcers caused by acetic acid. It also lowered nitrate and LOOH levels, raised mucin and SOD activity, and partially restored GSH levels.	Strong activity	[15]
Ceiba speciosa A. St.-Hil. (Malvaceae); Lajeado, Brazil; 2014	Stem bark; Maceration (Solution of 90% Ethanol)	In vivo on Wistar rats *(R. norvegicus)* weight 150–380 g (n=63).	Ethanol	Vehicle (1 mL saline p.o) as a negative control and Omeprazole (40 mg/kg) as a positive control.	7	*C. speciosa* A. St.-Hil. extract at dose (20, 40, 80, 400 mg/Kg) reduced the release of TNF-α in human blood and inhibited the activity of p38α, JAK3, and JNK3. Moreover, it reduced the leukocyte recruitment on the pouch exudate and the formation of edema. The extract presented a significant prevention of ulcer formation and a higher reduction than the control drug. In this case reported p-values below the conventional threshold of 0.05, ie 0.01 which indicates a statistically significant result, compared to vehicle and control group.	Strong activity	[16]

(Continued)

Table 1 (Continued).

Medicinal Plants Authority (family), Collected In, Year	Plant Part, and Extraction Method (Solvent Used)	Animal Used in the Preclinical study (n)	Inducement Method and Dose	Control (Negative and Positive)	Duration (Days)	Results	Interpretation	Ref
Cinnamomum glanduliferum Wall. (Lauraceae); Cairo, Egypt, 2014.	Leaves; Hydro distillation (Water)	In vivo on male Wistar albino rats (*R. norvegicus*) weight 150–170 g (n=60)	Ethanol	Vehicle (1 mL normal saline p.o) as a negative control and Indomethacin (10 mg/kg) as a positive control.	4 hours	Leaves extract at doses of 250, 500 and 1000 mg/kg significantly (p < 0.05) reduced paw volume to 94, 82 and 69%, respectively, significantly reduced COX-2 activity to 73.8, 50.7 and 21.4 nmol/min/mL, respectively. C. *glanduliferum* oil exhibited a significant (p < 0.05) modulatory effect on ethanol-induced gastritis in rats as the level of NO reduced to 32, 37 and 41 IM nitrate/g, a significant (p < 0.05) inhibition of lipid peroxidation via reduction of MDA concentration (1.15, 1.11, and 1.04 nmol/g).	Strong activity	[17]
Emex spinosa (L.) Campd. (Polygonaceae); Mirpur, Pakistan; 2022	Leaves; Maceration; Methanol	In vivo on white albino rats (*R. norvegicus*) weight 150–250 g (n=50)	Ethanol	Vehicle (10 mL/kg distilled water) as a negative control and Omeprazole (20 mg/kg) as a positive control.	14	The leaf extract at 250 mg/kg and 500 mg/kg reduced acidity and protected the stomach mucosa wall.	Strong activity	[18]
Melissa officinalis L. (Lamiaceae); Kerman, Iran; 2013	Leaves; Maceration (Methanol)	In vivo on male Wistar rats (*R. norvegicus*) weight 200–250g (n=8)	Indomethacin (NSAID)	Vehicle (1 mL saline P.O.) as a negative control and Ranitidine (25 mg/kg) as a positive control.	2	The ulcer index was lower in the indomethacin (1.3±0.09 and 1.5±0.19, respectively) compared to the control rats (2.5±0.28). The extract at a dose of 450 mg/kg did not prevent indomethacin-induced gastric ulceration (2.4 ± 0.26). There was no significant difference in the ulcer index for MO extract (150 and 300 mg/kg) and ranitidine-treated rats.	Weak activity	[19]
Phyllanthus niruri L. (Phyllanthaceae); Dhaka, Bangladesh; 2015	Leaves; Maceration (Methanol)	In vivo on female Swiss albino rats (*R. norvegicus*) weight 120–150 g (n=36)	Ethanol	Vehicle (5 mL/kg distilled water, P.O. + 25 mL/kg of 0.3 M HCl in 60% ethanol) as a negative control and Omeprazole (20 mg/kg) as a positive control.	1	The extract at doses (100, 200 and 400 mg/kg) significantly (p < 0.05) exhibited a reduction of 69.59, 74.32 and 80.40%, respectively in the ethanol- acid induced gastric erosion in all the experimental groups when compared to the control.	Strong activity	[20]

Ulcerative Colitis (UC)								
Spondias mombin L. (Anacardiaceae); Paraíba, Brazil, 2014.	Leaves; Percolation (Absolute Ethanol)	In vivo on male Wistar rats (*R. norvegicus*) weight 180–250 g (n=35)	Indomethacin (NSAID) and ethanol	Injured control (0.9% NaCl solution) as a negative control and Lansoprazole (30 mg/kg) as a positive control.	14	The extract reduced the area of ulcerative lesions induced by ethanol in 23.8, 90.3, and 90.2%, respectively. In NSAID model, the extract induced protection of 36.8, 49.4, and 49.9%, respectively. GA (10 mg/kg) or EA (7 mg/kg) or the association of GA+ EA (10 + 7 mg/kg) inhibited the ethanol-induced lesions in 71.8, 70.9, and 94.9%., respectively, indicating synergistic action. The extract (100 mg/kg) decreased acid secretion and H+ concentration in the gastric contents, increased levels of mucus, and showed to be dependent of −SH groups and NO on the protection of the gastric mucosa.	Strong activity	[21]
Tagetes erecta L. (Asteraceae); Campinas, Brazil; 2019	Flowers; Hydroalcoholic (Methanol-Water)	In vivo on male Swiss mice (*M. musculus*) weight 20–30 g (n=36)	DSS (Dextran Sulfate Sodium)	Vehicle (10 mL/kg distilled water, P.O. + 1% Tween 80) as a negative control and 5-ASA (100 mg/kg p.o) as a positive control.	9	The colitis group treated with *T. erecta* L. (300 mg/kg, once a day for 9 days) presented a weight loss of 11%. The extract reduced the colon shortening by 16% in relation to the vehicle-treated colitis group, reduced IL-6 levels by 26%, increased the GSH availability by 22%.	Strong activity	[22]
Terminalia catappa L. (Combretaceae); Brazil; 2010	Leaves; Percolation (Absolute Ethanol)	In vivo on male Wistar rats (*R. norvegicus*) weight 180–250 g (n=35).	Ethanol	Vehicle (10 mL/kg saline) as a negative control and Lansoprazole (30 mg/kg) as a positive control.	14	The extract at a dose of 25 mg/kg greatly reduced the number of ulcerative sores caused by ethanol, activated protective factors for the mucosa, such as the nitric oxide (NO) pathway and endogenous prostaglandins. Oral treatment with extracts for seven and 14 days significantly (p < 0.05) reduced the lesion area (80% and 37%, respectively) compared to the negative control group	Strong activity	[23]

(Continued)

Table 1 (Continued).

Medicinal Plants Authority (family), Collected In, Year	Plant Part, and Extraction Method (Solvent Used)	Animal Used in the Preclinical study (n)	Inducement Method and Dose	Control (Negative and Positive)	Duration (Days)	Results	Interpretation	Ref
Amphiterygium adstringens (Schltdl.) (Anacardiaceae); San Rafael, United States; 2013	Bark; Maceration (Ethanol)	In vivo on albino mice (*Bagg Albino*), age 6–8 weeks (n= 24).	DSS (Dextran sulfate sodium)	Untreated as the negative control.	10	The extract at dose 200 mg/kg lowered the levels of TNF-α (321.5 ± 24.75 pg/mL), IFN-γ (183.3 ± 12.02 pg/mL) and IL-1β (227.6 ± 8.66 pg/mL) compared to control group. The extract also decreased the infiltration of inflammatory cells as well as the damage to the colon's mucosa. The extract showed induce a wide range of activities like reducing oxidative stress, suppressing inflammation, modulating multiple signal transduction pathways, and inducing apoptosis.	Strong activity	[24]
Anneslea fragrans Wall. (Pentaphylacaceae); Yunan, China; 2020	Leave; Ultrasonic-assisted extraction (Methanol)	In vivo on Kunming mice (*M. musculus* Km.) weight 21–23 g (n=20).	Bethanechol	Vehicle (distilled water + DSS 2.5%, w/v) as a negative control and Sulfasalazine (450 mg/kg) as a control positive	14	*A. fragrans* Wall. extract at doses of 1000 mg/kg; 2000 mg/kg; 5000 mg/kg enhanced the levels of IL4 and IL10 and decreased the levels of IL6, IL1β, and TNF-α. Furthermore, in colon tissue, the extract significantly blocked the phosphorylation of the target protein of the NF-κB and MAPK signaling pathways.	Strong activity	[25]
Belamcanda chinensis L. (Iridaceae); Poland; 2014	Rhizome; Maceration; Methanol	In vivo on Wistar rats (*R. norvegicus*) weight 160–220 g (n= 79)	TNBS (Trinitrobenzene Sulfonic Acid)	Vehicle (Distilled water and TNBS solution 0.3 mL/kg) as a negative control and for the positive control is not applicable.	16	*B. chinensis* L. exerted a protective effect, lowering the intensity of damage produced by TNBS acid. The extract at the doses of 30 and 100 mg/kg reduced the macro- and microscopic damage score and the MDA level in colon tissues, and at the dose of 100 mg/kg showed a lower TNF-a and IL-17 concentrations, and SOD activity in colon tissues.	Strong activity	[26]

Berberis lycium Royle (Berberidaceae)	Fruits; Percolation (Water)	In vivo on albino mice (Bagg Albino) weight 10–23 g and age 6–8 weeks old (n= 30)	Bethanechol	Vehicle (Distilled water and DSS solution 3.5%) as a negative control and 5-aminosalicylic acid (ASA) (250 mg/kg) as a positive control	14	B. lycium Royle extract treatment significantly improved survival rates, DAI score, colon length, and structural damage in DSS-exposed mice. It decreased oxi-inflammatory markers and Th1/Th2/Th17 cytokines expression, while enhancing tight junction proteins, IgA levels, and anti-inflammatory cytokines. It modulated intestinal epithelial cell proliferation and apoptosis, inhibiting inflammatory signaling pathways and increasing Treg cell proliferation.	Strong activity	[27]
Brucea javanica L. (Simaroubaceae); Guangdong, China; 2018	Fruits	In vivo on male Sprague Dawley (R. norvegicus) weight 210–230 g, Age 7 weeks old (n= 12).	TNBS (Trinitrobenzene Sulfonic Acid)	Vehicle (distilled water and TNBS solution 25 mg/kg) as a negative control and Azathioprine (9 mg/kg) for the positive control.	7	The extract significantly (p < 0.050) reduced the mucosal damage to the colon, including edema, hyperemia, thickening of the bowel wall, erosions of the mucosa, and ulcers, significantly restored the colon length and body weight, reduced disease activity index (DAI) and colon pathology, decreased histological scores, diminished oxidative stress, and suppressed TLR4, MyD88, TRAF6, NF-kB p65 protein expressions in TNBS-induced UC.	Strong activity	[28]
Canna x generalis (Cannaceae); Giza, Egypt; 2018	Rhizome; Sonication (Methanol)	In vivo on Swiss albino mice (B. albino) weight 20–25 g (n= 30).	DSS	Vehicle (distilled water and 0.5% CMC_Na) as a negative control and Sulphasalazine (200 mg/kg) as a positive control.	7	The extract restored intestinal mucosal barrier, reduced oxidative stress, the inflammatory cascade, and the activation of the NF-PB/TLR4 and NLRP3 pathways in colonic tissues.	Medium activity	[29]
Centella asiatica L. (Apiaceae); Guangdong, China; 2018	Leaves; Reflux; Ethanol	In vivo on albino mice (B. albino) weight 22–24 g and age 8 weeks old (n= 48)	Bethanechol	Vehicle (Distilled water 3%) as a negative control and 5-aminosalicylic acid (ASA) (400 mg/kg) as a positive control.	7	The extract at dose 100, 200, 400 mg/kg improved intestinal motility, was able to modify the gut microbiome of the mice that were in pain, by reducing the abundance of colitis-associated genera like Helicobacter, Jeotgalicoccus, and Staphylococcus, altered the community and enhanced α-diversity.	Strong activity	[30]

(*Continued*)

Table 1 (Continued).

Medicinal Plants Authority (family), Collected In, Year	Plant Part, and Extraction Method (Solvent Used)	Animal Used in the Preclinical study (n)	Inducement Method and Dose	Control (Negative and Positive)	Duration (Days)	Results	Interpretation	Ref
Eucheuma cottonii (Solieriaceae); Sabah, Malaysia; 2018	Seaweed; Maceration; Ethanol	In vivo on albino mice (*B. albino*) age 6 weeks old (n= 48)	Bethanechol	Vehicle (distilled water 3%) as a negative control and Curcumin (0.10 kg) as a positive control.	7	The extracts raised IL-10 levels, decreased colonic damage, and reduced the expression of pro-inflammatory cytokines. Consequently, the extract decreased DSS-induced intestinal inflammation, making it a viable option for the treatment of colitis.	Medium activity	[31]
Evodia rutaecarpa (Rutaceae) Juss.; Chengdu, China; 2018	Fruits	In vivo on C57BL/6 mice (*M. musculus*) weight 21–23 g (n=48).	Acetic acid	Vehicle (distilled water 2.5% and DSS 2.5% dissolved in water) as a negative control.	15	The extract restored the equilibrium of *Lactobacillus* and *Escherichia coli*, lowered the concentration of plasmatic lipopolysaccharide (LPS), prevented UC as well as having a possible protective impact on colitis caused by DSS.	Strong activity	[32]
Forsythia koreana (Oleaceae); Yong-In, Korea; 2015	Flowers	In vivo on mice (*M. musculus*) (n=12).	DSS	Vehicle (distilled water Contained DSS 4% dissolved in water) as a negative control and 5-aminosalicylic acid (ASA) (75 mg/kg) as a positive control.	7	At dose of 20 mg/kg the extract reduced the infiltration of inflammatory cells such prostaglandin E2 (PGE2), cyclooxygenase-2 (COX-2), nitric oxide (NO), and inducible nitric oxide synthase (iNOS). The extract also reduced the symptoms of colitis in mice with DSS-induced colitis, inhibited inflammatory responses by downregulating JAK/STAT, NF-κB, and AP-1 signaling.	Strong activity	[33]
Garcinia kola (Clusiaceae); Ibadan, Nigeria; 2013	Seeds; Soxhlet; Petroleum ether	In vivo on Wistar rats (*R. norvegicus*) weight 180–200 g and age 10–12 weeks old (n= 36).	DSS	Corn oil (2 mL/kg) as a negative control and Sulfasalazine (500mg/kg) as a positive control.	5	*G. kola* extract significantly prevented the increase in these inflammatory mediators in the colon of DSS-treated rats, also significantly modulated DSS-induced decrease in body weight gain as well as prevented incidence of diarrhea and bleeding. There was a significant (p < 0.05) elevation in the levels of TNF-α and IL-1β in rats exposed to DSS alone when compared with the control group.	Strong activity	[34]

Vitis vinifera (Vitaceae); Xinjiang; China.	Seeds; Water-Ethanol	In vivo on female C57BL/6 mice (*M. musculus*) weight 18–20 g and age 8 weeks old (n= 4)	DSS	Vehicle (distilled water Contained DSS 200μL dissolved in 0.01 mol/L phosphate-buffered saline) as a negative control and for the positive control is not applicable.	6	The extract treated mucosal injury, inflammatory infiltration, bloody stools, diarrhea, and weight loss, may lessen IEC apoptosis by downregulating the mRNA expression of the inflammatory cytokines IL-6, IL-1β, and TNF-α as well as the phosphorylation of STAT3. There was a significant ($p < 0.05$) elevation in the levels of cytokines IL-6, IL-1β, and TNF-α also ($p < 0.05$) treated the effects of UC when compared with the control group.	Medium activity	[35]
Gymnema sylvestre R. Br. (Apocynaceae); Egypt; 2014	Leaves; Ethanol	In vivo on Wistar albino rats (*R. novergicus*) weight 250–280g, age 12 weeks old (n= 42).	Acetic acid	Vehicle (distilled water contained acetic acid solution 200μL 4%) as a negative control and Mesalazamine (300 mg/kg) for the positive control.	7	The extract significantly ($p < 0.05$) preserved the mucosal content and inhibited the oxidative and inflammatory response, increased colonic weights compared to control group, showed antioxidant activities, and inhibited acetic acid in colons and showed marked increase in SOD activity compared to control group. The extract significantly ($p < 0.05$) lower levels of IL-1b, TNF-α, and IL-6 compared to the animals in vehicle group.	Strong activity	[36]
Ilex kudingcha C.J. Tseng (Aquifoliaceae); Chongqing, China; 2012	Leaves; Maceration; Methanol	In vivo on male C57BL/6 mice (*M. musculus*) age 6 weeks (n=24)	DSS	Vehicle (normal saline 0.9%) as a negative control and for the positive control is not applicable.	7	The extract at dose 50 and 200 mg/kg, respectively, decreased the colonic MDA levels of 0.79±0.07 and 0.63±0.07 nmol/mg protein, reduced the expression of the iNOS and COX-2 genes. Furthermore, the extract significantly ($p < 0.05$) and dose-dependently decreased the levels of COX-2 and iNOS mRNA.	Strong activity	[37]
Morinda citrifolia L. (Rubiaceae); State of Ceara, Brazil; 2019	Fruits; Distiled water	In vivo on male Swiss mice (*M. musculus*) weight 25–30 g (n= 36)	Acetic acid	Vehicle (normal saline 0.9%) as a negative control and Dexamethasone (2 mg/kg) for the positive control.	18 hours	The extract decreased the macroscopic lesions compared to vehicle group, the extract also reduction wet weight of the colon as well. Furthermore, pro-inflammatory cytokines, MPO activity, GSH, MDA, NO3/NO2, and COX-2 expression levels decreased.	Strong activity	[38]

(Continued)

Table 1 (Continued).

Medicinal Plants Authority (family), Collected In, Year	Plant Part, and Extraction Method (Solvent Used)	Animal Used in the Preclinical study (n)	Inducement Method and Dose	Control (Negative and Positive)	Duration (Days)	Results	Interpretation	Ref
Olea europaea Hoffmannsegg (Oleaceae); 2021	Leaves	In vivo on male albino rats (*R. norvegicus*) age 6–8 weeks old (n=35).	Histamine	Untreated (No induced by AA) as negative control and for the positive control is not applicable.	7	The extract demonstrated efficacy in lowering the disease activity index (DAI) and death rate, reduced oxidative stress and inflammation in colon tissue was also demonstrated by the extract, which resulted in a significant (p < 0.05) downregulation of pro-inflammatory cytokines as well as a significant reduction in colon MDA, MPO, and NO levels as well as an elevation in SOD, CAT, and GPX levels.	Strong activity	[39]
Polygonum cuspidatum Siebold & Zucc. (Polygonaceae); Pakistan; 2013	Whole plant	In vivo on Sprague-Dawley rats (*R. norvegicus*) weight 150–200 g (n=36)	Acetic acid	Vehicle (sodium carboxy methyl cellulose suspension 1%) as a negative control and Ranitidine (50 mg/kg) for the positive control Ranitidine.	4	The extract decreased the pH of the gastric juice when compared to the vehicle-treated controls, exhibited a marked gastroprotective effect in the aspirin-induced pyloric ligation ulcerogenesis model. The extract at doses of 100 mg/kg, 200 mg/kg, and 400 mg/kg afforded significant anti-ulcerogenic proclivity (P < 0.05) evidenced by non-significant changes in the ulcerative biochemical parameters.	Medium activity	[40]
Tagetes erecta (Asteraceae); Campinas, Brazil; 2019	Flowers Hydroalcoholic; Methanol-Water (9:1)	In vivo on male Swiss mice weight 20–30 gr (n=36).	DSS	Vehicle (10 mL/kg water + 1% Tween 80) contained DSS as a negative control and 5-aminosalicylic acid (ASA) (100 mg/kg) for the positive control Ranitidine	9	The extract reduced the ulcerated area by 66%, expedited the healing of stomach ulcers, increased GST activity and mucin quantity, decreased LOOH levels, SOD, CAT, and MPO activities, and decreased the lesion area in the recurrence model by 94%, decreased the thickness of the stomach wall and TNF levels, and raised the amount of IL-10.	Strong activity	[41]

Taraxacum officinale (Asteraceae); 2018	Root; Water	In vivo on C57BL/6 mice (*M. musculus*) aged 6–8 weeks old (n= 40)	Bethanechol	Vehicle (water 2% w/v contained DSS) as a negative control and for the positive control is not applicable.	10	The extract effectively reduces progressive acute injury as evidenced by decreased body weight loss, reduced disease index severity scores, and shorter colon length during DSS treatment. It also lessens oxidative stress and inflammatory conditions in the colon of DSS-induced mice. The extract has the potential to be an effective anti-colitis complex mixture.	Strong activity	[42]
Terminalia chebula (Combretaceae); Varnasi; 2012	Fruits; Maceration Ethanol	In vivo on Inbred Charles-Foster (CF) strain albino rats (*R. norvegicus*) weight 150–170 g (n= N/A)	Acetic acid	Vehicle (carboxy methyl cellulose 1.0% in distilled water) contained DSS as a negative control and Sulfasalazine (100 mg/kg) for the positive control Ranitidine	14	The extract shown antibacterial activity and increased antioxidant levels while lowering free radicals and myeloperoxidase activity in colitis caused by acetic acid.	Strong activity	[43]
Aphthous Ulcer								
Morinda citrifolia L. (Rubiaceae); Indonesia; 2017	Leaves; Maceration: Ethanol 96%	In vivo on Wistar rats (*R. norvegicus*)	Using a 3 mm diameter burnisher touched on the labial mucosa below the rate for one second.	Vehicle (distilled water) as a negative control and triamcinolone acetonide (0.1%) for the positive control.	10	The extract has no significant effect on healing percentage compared to control groups with p = 0.138 and 0.694 (p > 0.05), recovery day for treat group was eighth day and for each control groups were tenth day.	Weak activity	[44]

Table 2 The Anti-Ulcerative Properties of Various Plants in Clinical Studies

Medicinal plant (Family), Collected In, Year	Plant Part,	Class of Metabolites	Type of Study	Control (Negative and Positive)	Duration (Days)	Results	Interpretation	Ref
Punica granatum (Punicaceae); Iran; 2013	Flower; Percolation; Ethanol	Phenol	Double blind RCT in 210 patients with active or ever had Aphthous ulcers.	N/A	10	*P. granatum* var. extracts have a significant therapeutic impact on mild RAS.	Medium activity	[45]
Nicotiana tabacum (Solanaceae); Kermanshah, Iran; 2015	Leaves	Alkaloid	RCT in 60 patients with active or ever had aphthous ulcers for the past 1–5 years.	Using placebo as a control group	5	The extract decreased ulcer pain by 79.2% and 93.8% and ulcer size was reduced by 69.1% and 92.2% (days 3 and 5, respectively), In various established mechanisms, such as the antibody-forming cell response, the suppression of neutrophil-mediated inflammation, the inhibition of endothelial cell release of interleukin (IL)-8, the inhibition of IL-1β, IL-2, IL-10, the release of tumor necrosis factor (TNF)-α and interferon (IFN)-γ, and the decrease in immune globulin levels in circulation, nicotine and its metabolites have been shown to exhibit immunosuppressive activity and reduce inflammatory condition.	Strong activity	[46]
Glycyrrhiza glabra (Fabaceae)	Roots	Glycyrrhizin acid	Randomized control trials (RCT) in 120 patients caused by PUD	Negative control is not applicable. Clarithromycin (500 mg), Amoxycillin (1 g), 20 mg of Omeprazole as the positive control.	210	Thirty percent in both groups had peptic ulcers, and the surrogate for *H. pylori* eradication and positive therapeutic response *G. glabra* showed was 83.3% in the LR group compared to 62.5% in the control group (p = 0.018). Response rate based on endoscopic findings was significantly higher for the extract group to treat PUD.	Strong activity	[47]
Zingiber officinale (Zingiberaceae); Atlanta, Georgia; 2015	Roots	Gingerol and Shogaols	Double-blind RCT in 44 patients with active UC	Standard treatment combination with placebo capsules as a control group	84	Gingerol and shogaols administered orally increased the survival and proliferation of IECs and reduced the pro-inflammatory cytokines (TNF-a, IL-6, and IL-1b) and increased the anti-inflammatory cytokines (IL-10 and IL-22) in colitis models. Ginger-derived nanoparticles, offer a novel, natural delivery system that can enhance the prevention and treatment of IBD.	Strong activity	[48]
Trigonella foenum graecum L. (Fabaceae); Iran; 2020	Seeds; Sonication; Water	Flavonoid	RCT in 60 patients with active or ever had Aphthous ulcers for the past 1–5 years	Negative control is not applicable and Dexamethasone mouthwash was the positive control.	10	Patients receiving the extract showed a significant improvement in the size of the lesion and level of pain starting on the fourth day of treatment. After six days of the intervention, there was a substantial decrease (p < 0.05) in both the ulcer's size and erythema level.	Medium activity	[49]

negative consequences encompass gastrointestinal disruptions such as feelings of nausea, vomiting, constipation, and diarrhea, as well as impacts on the cardiovascular system.[10]

Based on the findings, it has been reported by the World Health Organization (WHO) that approximately 80–85% of the global population relies on natural products for disease management and nutritional supplementation. Botanical products are being utilized as alternative medicines for the treatment of various diseases due to their perceived safety in comparison to synthetic medicines.[57] An in vivo or preclinical study of the active metabolites in a plant showed that the metabolites treat peptic ulcer disease by protecting the gastrointestinal mucosa wall, reducing the effects of ulcers, decreasing or reducing the lesion area caused by ulcers, inhibiting cytokine pro-inflammatory factors such as TNF-α, IL-1β, and IL-6, an ulcerative agent, and reducing the bacterial load on the gastric mucosa caused by *Helicobacter pylori* in the test animal, and clinical studies of the active metabolites showed that the combination of metabolites as a supplement makes a better treatment for PUD.

Ulcerative Colitis (UC)

Ulcerative colitis is a long-lasting inflammatory condition of the colon that causes the wall of the colon to become easily detached and wear away at the surface, often with bleeding. Typically, this condition is characterized by inflammation that is localized to the mucosal and submucosal layers of the colon. In general, the onset of the disease occurs within the rectum and progresses in a contiguous manner towards more proximal regions. Ulcerative has no cure and is a lifelong disorder with a significant impact on both physical and mental health.[58] The etiology of inflammatory bowel disease remains uncertain. The prominent independent risk factor of familial disease history, which is present in about 8% to 14% of affected people, suggests that a primary genetic component plays a significant role. Individuals who have a family diagnosed with ulcerative colitis are at a significantly elevated risk, approximately four times higher, of developing the same disease.[59]

There is a growing emphasis in treatment strategies on achieving intestinal healing rather than solely focusing on symptomatic relief, to mitigate the likelihood of long-term complications and the need for surgical interventions.[60,61] Treatments can be broadly categorized as those employed to initiate remission, either at the time of diagnosis or during a subsequent flare-up.[62] Currently, the dietary management is to improve symptoms while offering support. In recent years, there has been a notable shift in dogma toward the utilization of dietary therapies that target specific mechanisms to induce disease remission.[63–65] Most research has focused on how the immune system changes in the early stages, but over the past 20 years, a lot of evidence has shown that ulcerative colitis (UC) is mostly a disease of the epithelial tissue.[66] The pathogenesis of the colonic epithelium is mostly caused by metabolic defects, which play a key role and may contribute to the breakdown of the mucosal barrier. Consequently, the epithelium may experience additional harmful effects due to the presence of microbial metabolites, such as hydrogen sulfide (H_2S) and nitric oxide (NO), which can be toxic when present in excessive amounts.[67]

People with UC can get relief from their symptoms through a variety of pharmacological interventions. However, a large number of these therapeutic medications are linked to serious side effects.[68] Therefore, researchers are currently placing increased emphasis on natural compounds,[69] as they have the potential to mitigate adverse effects. A clinical study of gingerol and shogaol, which are the active metabolites in the *Zingiber officinal* plants, found that they were more likely to cause a clinical response and significantly improve a patient's quality of life.[70] Recent research has shown that using natural lipid nanoparticles (nLNP) loaded with 6-shogaol (6S/nLNP) can effectively change the types of bacteria in the gut, cause metabolic changes in feces, and reduce inflammation in a model of acute colitis caused by DSS.[71] An in vivo or preclinical study of the active metabolites in a plant showed that the active metabolites inhibited cytokine pro-inflammatory factors such as TNF-α, IL-1β, and IL-6, an ulcerative agent, in the test animal, also the metabolites protected colon mucosa from ulceration through their strength aspect, such as antioxidant, or anti-inflammatory. According to preclinical and clinical studies.

Aphthous Ulcer (Mouth Ulcer)

Aphthous ulcers, also known as mouth ulcers, show inflamed spots with a white-reddish appearance that develop on the mucous membrane that lines the oral cavity. Despite being painful, these injuries generally undergo spontaneous healing and do not result in any complications. There is variation in the recurrence of canker sores, with certain individuals experiencing a reoccurrence within a few weeks, while others may encounter them after months or even years.[72]

Aphthous stomatitis is estimated to impact around 20% of the overall population. The prevalence of this phenomenon is slightly higher among females and individuals from affluent socioeconomic backgrounds and countries. Most people get them for the first time when they are a teenager or young adult. The age of onset may be during childhood, but more commonly in the second and third decades of life, becoming less common with advancing age. This disease is more common in women than in men. The cause of aphthous stomatitis is idiopathic and multifactorial but likely involves activation of the cell-mediated immune system. Since acute infections are not the cause of aphthous ulcers, they are not contagious. Local trauma, emotional or physiological stress, allergy or sensitivity, menstruation, or changes in the oral microbiome can all cause aphthous stomatitis. Aphthous ulcers are more prevalent in nonsmokers and smokers who quit and less common in individuals with good oral hygiene practices.[73–75]

The present treatment plan for this disease primarily focuses on managing symptoms, aiming to alleviate pain, facilitate lesion resolution, and extend the duration between episodes.[76] The primary strategy for the treatment is to control the inflammation, suppress the inflammation-associated cells' activity, reduce the pain of the lesion, and accelerate the healing process.[77] The most commonly used anti-inflammatory agents to treat oral cavity inflammations are topical corticosteroids.[78]

Biological and laser therapies have emerged as novel therapeutic modalities for the treatment of mucosal diseases, garnering considerable anticipation in the medical community. Changes in oral microbiota have been linked to the development,[79] which paves the way for probiotic treatments that can be put directly in the mouth. However, long-term exposure to these medications may cause drug resistance, oral flora imbalance, and secondary fungal infections.[80]

Natural extracts have already been proven effective for managing other oral health problems, apart from ulcers. Several clinical studies have shown the positive effects of natural extracts in reducing the pain and duration of mouth ulcers.[45,79,80] A clinical study revealed that patients with aphthous ulcers treated with *Nicotiana tabacum* E. metabolites were likely to show reduced ulcer lesions compared to placebo, which was the control of the randomized control trial. The metabolites contributed to the suppression of pro-inflammatory cytokines and decreased the size of lesions on oral mucosa.[46]

Discussion

The investigation of anti-ulcerative activity has also encompassed the study of isolated metabolites derived from plants. The phytochemical constituents in plants have a variety of functions in anti-ulcerative activity, for example, alkaloids were reported for their anti-ulcerative effects by modulating the gastric acid secretion and cytoprotective properties.[81] Flavonoids exhibit potent anti-inflammatory and antioxidant activity, contributing to ulcer healing and mucosal protection.[82] Saponin has been found to inhibit gastric mucosal injuries induced by factors such as ethanol or indomethacin.[83] Tannins, a type of phytochemical can form protective barriers on the mucosal surface,[84] and polyphenols, which are also found in plants have multifaceted actions, such as anti-secretory and anti-inflammatory effects.[82] Hence, plants are paving the way for the development of targeted and efficacious treatments for ulcerative disorders. The assessment of potential anti-ulcerative activities in plants that are often used to treat ulcers is a very important step in proving that these plants work as medicines. Various plant materials may exhibit multiple types of anti-ulcer effects, including safeguarding the mucosa against ulcers and impeding pro-inflammatory cytokine activity. This is attributed to the fact that individuals with chronic wounds, such as ulcers, tend to have elevated systemic and local levels of TNF-α.

The mitogen-activated protein kinase (MAPK) pathway plays a crucial role in the regulation of pro-inflammatory cytokine production, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). This substance is classified as a proinflammatory cytokine that is rapidly secreted in response to an inflammatory stimulus. It plays a critical role in initiating various intracellular processes and is involved in the development of both acute and chronic inflammatory responses. This leads to the activation of nuclear factor kappa B (NF-kappaB), as well as the promotion of the release of additional pro-inflammatory cytokines, chemokines, and proteases.[85] The overproduction of TNF-α has a direct correlation with various inflammatory disorders, including arthritis and inflammatory bowel disease. Consequently, regulating TNF-α levels can serve as an effective therapeutic approach for managing these diseases.[86]

Cytokine proinflammatory factors, such as IL-1, TNF-α, IL-6, and IFN-γ, were found to be upregulated.[87] These factors are known to be involved in gastric inflammation caused by *H. pylori*. The involvement of the acute phase response pathway and NF-kappaB signaling pathways was also suggested.[88] TNF-α plays a key role in mediating inflammatory events, involved in both acute and chronic responses.[89] IL-6 produces an acute phase response, promoting

the induction of intracellular signaling cascades, which give rise to the production of other inflammatory cytokines.[90] At first, proinflammatory cytokines help acute wounds heal by boosting the growth of keratinocytes and making them make more antimicrobial peptides. Nevertheless, excessive production of proinflammatory cytokines can result in the persistence of inflammation and impaired wound healing.[91,92] Hence, the therapeutic efficacy of chronic wound healing can be attributed to the inhibition of excessive proinflammatory cytokines.[93] The extract contained phenolic compounds that demonstrated antioxidant properties by inhibiting oxidative stress, reducing the production of nitric oxide (NO), and preventing the activation of p38. Consequently, this inhibition led to the suppression of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), thereby exhibiting anti-inflammatory and antiulcerogenic effects.[16]

The suggested mechanisms of action are explained through cytoprotective mechanism (causing an increase in gastric mucus), antioxidant activity (preventing depletion of sulfhydryl groups and reducing levels of lipid peroxidation and myeloperoxidase activity in the gastric mucosa), and finally healing ability.[94,95] The small size of metabolites facilitates their passage through the mucus layer, enabling them to interact with colonic cells and initiate immune responses.[91,93,96,97] Hence, metabolites derived from plants possess the potential to modulate the advancement of intestinal inflammation, thereby offering translational prospects.[71] Ulcer, being a chronic inflammatory disease, exhibits distinct characteristics during the progression of chronic inflammation in the colon.[98] Notably, the integrity of the mucus layer remains largely unaffected, and the permeability of the epithelial lining undergoes minimal alterations. In contrast, the acute colitis model demonstrates significant compromise to both the mucus layer and the permeability of the epithelial lining.[71]

In the present study, we found two plants with double anti-ulcerative activities, ie, *T. erecta* (strong anti-peptic ulcer disease and anti-ulcerative colitis) and *M. citrifolia* (strong anti-ulcerative colitis and weak anti-aphthous ulcer), thus presuming their potential to be further developed as anti-ulcer botanical drugs.

Conclusion

This review elaborates on an overview of the preclinical and clinical studies that have been done on medicinal plants. It focuses on how well they work to treat conditions such as peptic ulcer disease (PUD), ulcerative colitis (UC), and aphthous ulcers. The phytochemicals and pharmacological properties have also been elucidated. These active metabolites, derived from various plant sources such as alkaloids, flavonoids, tannins, saponins, and polyphenols, have a variety of functions in the treatment of ulcers and contribute synergistic interactions to the anti-ulcerative efficacy of plant extracts. For most of the plants that have been looked at, however, there is a clear lack of anti-*H. pylori* activity and clinical studies on metabolites derived from plant studies. The opportunity to conduct such studies is available to determine whether these plants possess both clinical and non-clinical properties. Also, there is a limitation of the study, we found that not all articles explain the controls used in preclinical and clinical studies, not all articles explain where and when the plants were collected, and not all articles explain the extraction method and solvent used which makes this article a constraint. More pharmacological activity assays are needed to figure out the mechanism of how each metabolite works, for example, by studying what proteins, pathways, or genes are altered by the plant extract or metabolite. These studies will be essential to validate the potential use of these metabolites in the treatment of ulcers. From a future perspective in the realm of plants, we can anticipate the isolation and synthesis of the active metabolites from plants for their capability as targeted therapies with enhanced efficacy and reduced potential for adverse effects. This review provides a piece of scientific evidence supporting the utilization of plant metabolites as a potential therapeutic approach for the treatment of ulcers.

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