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REVIEW

A comprehensive review on phytochemicals as potential therapeutic agents for stress-induced gastric ulcer

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Abstract

Gastric ulcers are the most common chronic gastrointestinal tract disorders, marked by an inflamed break of the mucus membrane covering the alimentary tract. According to recent research, stress-induced ulcers are widespread in our society. A stress ulcer is a mucosal defect that may become complicated due to upper gastrointestinal tract bleeding. The underlying cause of this condition is pH. Physiological stress leads to severe sickness by triggering the excessive secretion of peptic juices or gastric acid. There is a never-ending quest for safe and affordable medication for this disorder. Nature offers many medicinal plants that can be used to treat a wide range of human ailments. Due to their relatively harmless and comparatively free of harmful effects, health-promoting features, pharmacological practices, and affordability to common people to regulate various diseases, medicinal plants, and herbal preparations are gaining a lot of interest in scientific communities these days. Many studies have recently been performed to classify extracts and their constituents that may have a therapeutic effect on peptic ulcers. Therefore, this review aims to address the molecular mechanisms and pharmacological effects of various phytochemicals related to stress-induced gastric ulcers. Combining phytochemical constituents with modern drugs and treatment methods can lead to the development of therapeutic drugs for gastric ulcers. Gastric ulcers and other related diseases may be treated permanently with this approach.

Keywords Stress-induced gastric ulcer · Natural products · Phytochemicals · Peptic ulcer

Abbreviations

ACTH	Adrenocorticotropic hormone
CDC	Center for disease control and prevention
CRH	Corticotropin-releasing hormone
GFs	Growth factors
HSP	Heat shock proteins
H_2S	Hydrogen sulfide
NVSS	National vital statistics system
NCHS	National center for health statistics
NPG	Nature publishing group
NO	Nitric oxide
NF-κB	Nuclear factor-κB
PPARN	Peroxisome proliferation activated receptor neuropeptides
$PARP_2R$	Poly [ADP-ribose] polymerase 2
PGE	2Prostaglandin-E2
SDL	Saudi digital library
TNF-α	Tumor necrotic factor-α
uPA	Urokinase-type plasminogen activator

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1 Introduction

Ulcers represent a chronic and recurrent condition distinguished by the intermittent occurrence of sores within the mucosal membranes of the stomach [61]. Gastric ulcers, identified by the development of open sores in the stomach lining, have been acknowledged as a significant global health issue for a considerable period [71]. While ulcers can arise from diverse factors like *Helicobacter pylori* infection, nonsteroidal anti-inflammatory drug (NSAID) usage, and lifestyle choices such as excessive alcohol consumption, stress-induced gastric ulcers present a captivating focus for investigation. These ulcers are commonly attributed to chronic psychological stress and have garnered significant research attention due to the ongoing difficulties in effectively managing and treating them [61] [Figs. 1, 2].

Stress, as a complex phenomenon, exerts profound effects on the human body, influencing various physiological processes, including those of the gastrointestinal system. Stress can lead to changes in gastric physiology, such as heightened gastric acid secretion, diminished mucosal blood flow, and impaired mucosal defense mechanisms, all of which contribute to the formation of ulcers. This intricate interplay of factors underscores the complexity of addressing stress-induced gastric ulcers [26]. Phytochemicals, which are naturally occurring compounds found in plants, have emerged as promising candidates for managing stress-induced gastric ulcers. This thorough review explores a wide range of phytochemicals, including alkaloids, glycosides, flavonoids, tannins, terpenoids, polysaccharides, and saponins, emphasizing their potential therapeutic roles. Derived from various botanical sources, these bioactive compounds have demonstrated impressive anti-ulcerogenic properties in both

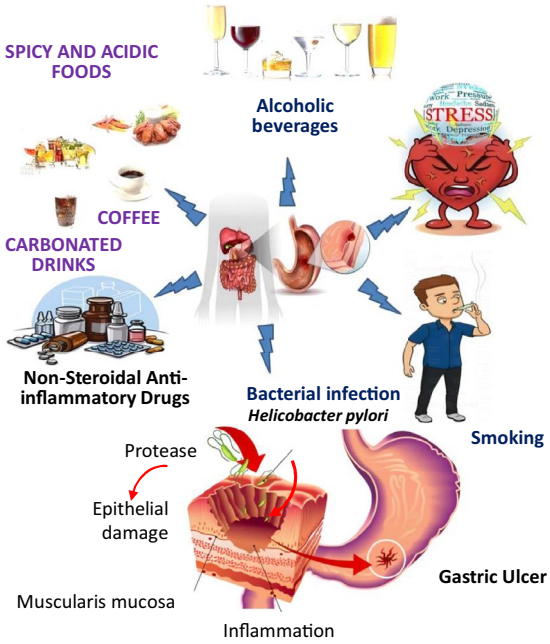

Fig. 2 Common causative factors for peptic ulcers

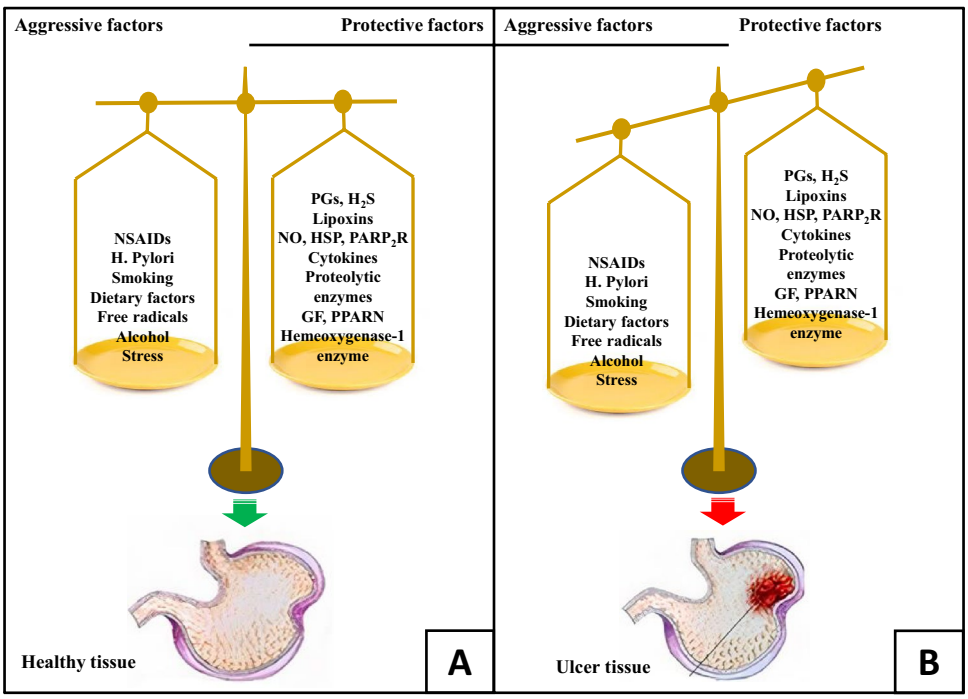

Fig. 1 Figure showing role of factors contributing to gastric ulcer (**A**). Balance in protective (prostaglandins (PGs), hydrogen sulfide (H_2S), lipoxins, nitric oxide (NO), heat shock proteins (HSP), $PARP_2R$, cytokines, proteolytic enzymes, growth factors (GFs), peroxisome proliferation activated receptor neuropeptides (PPARN), and hemoxygenase-1 enzymes) and aggressive factors (NSAIDs, *H. pylori,* smoking, dietary factors, free radicals, alcohol, and stress) in healthy mucosa and B. Imbalance leading to formation of gastric ulcer

preclinical and clinical studies, underscoring their significance in ulcer management [50, 108, 112].

Alkaloids have emerged as promising agents for countering stress-induced gastric ulcers due to their anti-ulcerogenic properties. *Berberine*, a compound naturally occurring in various plants such as those belonging to the Berberis species, showcases substantial ulcer-protective effects. These effects primarily involve the reduction of gastric acid secretion and the reinforcement of the mucosal barrier [43]. Glycosides encompassing a wide range of molecules with diverse biological activities have shown anti-ulcerogenic potential. Research has indicated that certain glycosides, like saponins, possess anti-ulcerogenic potential by modulating the secretion of gastric acid, promoting mucin production, and enhancing antioxidant defenses [8]. Flavonoids have gained recognition for their anti-ulcerogenic properties, often attributed to their antioxidant and anti-inflammatory activities. Compounds like quercetin and catechins, found in various fruits and vegetables, have shown the ability to mitigate oxidative stress and inflammation in the gastric mucosa [86]. Tannins found in various plant sources such as tea and grapes, have been investigated for their anti-ulcerogenic effects. Tannins can form stable complexes with proteins, offering a potential protective barrier on the gastric mucosa and reducing mucosal damage caused by stress-induced factors [24]. Terpenoids modulate gastric acid secretion, enhancing mucosal defense mechanisms, and reducing oxidative stress. Compounds like limonene and pinene have demonstrated promise in protecting against stress-induced gastric ulcers [75]. Polysaccharides have been shown to bolster mucosal defense, promote mucus production, and regulate immune responses within the gastric mucosa, thereby amplifying their anti-ulcerogenic effects [99]. Similarly, saponins exhibit anti-ulcerogenic properties through diverse mechanisms, such as diminishing gastric acid secretion, boosting mucin production, and mitigating inflammatory reactions in the stomach lining [88].

This review aims to offer a comprehensive insight into the latest research discoveries regarding the effectiveness of phytochemicals in alleviating stress-induced gastric ulcers. By exploring the mechanisms behind their therapeutic effects, we aim to illuminate the potential of natural compounds as complementary or alternative approaches for managing this challenging condition. The use of phytochemicals as therapeutic agents for stress-induced gastric ulcers presents a promising avenue for future research, potentially yielding novel treatments with reduced side effects and enhanced patient satisfaction. In the subsequent sections of this review, we will delve into specific phytochemicals, their natural sources, mechanisms of action, and the most recent evidence from both preclinical and clinical studies. Through this exploration, we endeavor to provide a comprehensive and current reference for researchers and healthcare professionals interested in the potential application of phytochemicals in the treatment of stress-induced gastric ulcers.

2 Methods of data collection

2.1 Literature search and article selection

By examining papers in indexed journals, extensive e-searches of literatures were undertaken during the years 2020–21, and electronic searches were conducted across multiple databases. Saudi Digital Library (SDL) provided access to PubMed, BioMed Central, Nature Publishing Group (NPG), Scopus, SciVerse, ScienceDirect, MEDLINE, Wiley Online Library, PubChem, SAGE, and Springer. 'Plant metabolites,' 'bioactive constituents and peptic ulcer disease,' 'anti-ulcer activity of plants,' and 'medicinal plants and gastric ulcer' were used as keywords. In vitro and in vivo epidemiological, clinical, and experimental investigations were chosen. The publications were found and chosen based on their keywords, titles, abstracts, and reported outcomes.

3 Pathophysiology of gastric ulcer

3.1 Physiology of the stomach

The stomach is composed of different cell types that play crucial roles in producing gastric acid for protein digestion, enzyme breakdown, bicarbonate production, and acid neutralization. Individuals with gastric ulcers may experience symptoms such as burning or aching pain, bloating, and nausea [73]. Emerging research proposes a link between intestinal barrier function deficiencies and gastrointestinal tract ailments. Symptoms of gastrointestinal disorders frequently intensify during periods marked by stress and negative emotions [34].

3.2 Gastrointestinal barriers

The intestinal epithelium is a single layer of cells lined the gut lumen that acts as a barrier to prevent injurious, intraluminal entities as well as microorganisms, toxins, foreign antigens, and allowing the translocation of essential electrolytes, dietary nutrients, and water from lumen into the circulation [16, 51, 72]. Mucus secretion includes bicarbonate, which helps maintain a neutral pH at the epithelial surface, while surfactant phospholipids serve as a physical barrier alongside luminal digestive enzymes [6]. The surface mucosal epithelium releases elements of the mucus barrier along with intrinsic protective agents like cathelicidins, heat shock proteins, and prostaglandins. These substances aid in fortifying the physical barrier and inhibit

the retrograde diffusion of digestive enzymes and gastric acid [65, 101]. Mucosal blood flow plays a crucial role in providing adequate vascular perfusion to the gastric lining, thus safeguarding against epithelial damage, and preventing necrosis in the deeper layers of the mucosa. Thromboxane A2, leukotriene C4, and endothelin, which are vasoconstrictors, are neutralized by nitric oxide and prostaglandin I2 created by endothelial cells to protect gastric mucosa from injury [23]. In response to *H. pylori* infection, neutrophils and macrophages infiltrate the gastric mucosa within the mucosal immune system. During the immunopathogenic development of ulcers, these cells release leukocytes and lysosomal enzymes, which compromise mucosal protection but also contribute to mucosal damage [62, 79].

3.3 Mechanisms of gastric barrier function

The gastric barrier is regulated with coordination of corresponding structure and function to minimize the potential damage and maximize the protective effects [52, 97]. Bicarbonate secretion is stimulated in the gastric and duodenum by the presence of acid in the lumen with the help of mucosa sensing pCO_2 generates at the surface through the response between luminal H^+ with secreted bicarbonate [37]. The renewal of cells from progenitor mucosal cells is crucial for maintaining the structural integrity of the mucosa. In cases of superficial damage, the epithelial surface undergoes rapid reconstruction, typically within minutes, facilitated by the migration of preserved epithelial cells located in the neck region of gastric glands [115]. The vascular system beneath the gastric mucosa promptly reacts to a significant surge in mucosal blood flow when exposed to aggressive luminal factors, a process mediated by sensory afferent nerves [77].

3.4 Endogenous gastro-protective mediators

The endogenous mediators might be reserved by contributing risk factors important to gastric ulceration [44]. Prostaglandins contribute significantly to mucosal defense by increasing mucosal blood flow, strengthening epithelial cell resistance to cytotoxin-induced injury, and dampening the release of multiple inflammatory mediators [17, 63, 98].

Lipoxin-A4 places an important role in mucosal defense by contributing to the resolution of inflammation and regulates trans-epithelial electrical resistance and protects the stomach since damage induced by aspirin via inhibiting leukocyte adherence within gastric micro-circulation [58, 109]. Nitric oxide plays a role in regulating inflammation. It interacts with prostaglandins to modulate the activities of mucosal immunocytes and reduce epithelial permeability and bicarbonate secretion. This results in enhanced mucosal resistance to ulceration.

The gastric mucosa is more susceptible to injury when nitric oxide is inhibited. Conversely, prolonged release of nitric oxide significantly reduces inflammation and promotes ulcerative healing [53, 60]. Another gaseous mediator is hydrogen sulfide generated endogenously in the gastric mucosa with the help of cystathionine synthase and cystathionine lyase that inhibits adhesion of leukocytes to the vascular endothelium, vasodilatation, tumor necrotic factor (TNF)-α expression and NSAID-induced gastric mucosal injury [101]. TNF-α promotes the repair of mucosa after damage linked with *H. pylori* α factor-infection and NSAID usage by stimulation of cell proliferation [10, 11]. The activation of proteinase-activated-2 receptors in the stomach stimulates mucus secretion. This action also reduces endothelial damage during NSAID induction. To accomplish this, it modulates sensory afferent nerves and regulates platelet VEGF release. Angiogenesis facilitates ulcer healing through this process [76]. Angiogenesis is mediated by urokinase-type plasminogen activator (uPA) and its inhibitor, uPAI type-1. Additionally, they play a significant role in inflammation and contribute to ulcer healing [18, 58]. Repair of injured gastric mucosal epithelium is regulated by various types of growth factors. Particularly, transforming, and epidermal growth factors, which are present in gastric progenitor cells, play a role. They are transactivated by prostaglandin (PG)-E2 and gastrin, which in turn activate the repair of gastric mucosa and cell proliferation [59, 64]. The peroxisome proliferation-activated receptor is a nuclear transcription factor acting as a vital task in the mechanism of NSAID action, controlling nuclear factor (NF)-κB, vascular cell adhesion molecule-1, endothelin-1, in endothelial cells, matrix metalloproteinase-3, TNF-α and other transcription factors [31, 74, 83]. The neuropeptide ghrelin is associated with gastro-protective effects on gastrointestinal motility and energy homeostasis. It controls the gastric ulcer induced by ethanol on COX-1-derived PGE2 action [35, 94]. Antioxidant induced hemeoxygenase-1 upregulation in apoptotic resistant cells were proven to have gastroprotective effects against non-steroidal drugs induced ulcer [103, 118].

3.5 Risk factors

The common risk factors for gastritis and peptic ulcer causes include infection with *H. pylori* and NSAIDs (Chronic administration for pain, inflammation, fever, cardiovascular disease, and rheumatic cause adverse effects like gastric or duodenal ulceration, gastric erosions and hemorrhage [91]. Less common risk factors like alcohol, stress, cocaine, smoking, illness, radiation therapy, autoimmune problems, and Crohn's disease. Recent studies state that modulation of lifestyle factors such as reducing smoking and alcohol intake, proper dieting, and controlling stress may directly prevent the beginning of gastric ulcers [21].

3.6 Hypothalamic Pituitary axis and Stress

Stress has a reflective effect on the gastrointestinal tract through early-life stress and chronic adult stress, is capable of altering pain circuitry, causing a change in permeability and motility [78]. The early-life stress like psychosocial (maternal deprivation, physical and emotional abuse, and loss of caregiver) and immunological (allergy, infection, metabolic/nutritional), have occupied as risk factors of later in life. Both physical and psychological stressors, in conjunction with inflammation within the central nervous system, initiate a cascade of both positive and negative feedback responses. These responses are regulated by the release of stress hormones from the hypothalamus and pituitary gland, namely corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), respectively. ACTH then stimulates the adrenal gland to release glucocorticoids, which possess various downstream physiological properties. These properties aid the host in rapidly adapting to environmental changes, primarily by modulating the release of corticotropin-releasing hormone from the hypothalamus [19, 20]. A commonly noted disturbance in the mutual communication between the brain and the gut arises in reaction to chronic stress. This disturbance prompts the activation of both the hypothalamic-pituitary axis and the autonomic nervous system, consequently influencing the manifestation of symptoms in functional gastrointestinal disorders. These disorders encompass inflammatory bowel diseases, irritable bowel syndrome, gastroesophageal reflux, and peptic ulcer [4, 12, 28, 38] [Fig. 3].

3.7 Stress and ulcers

Stress-related gastrointestinal bleeding is estimated to occur in around 25% of untreated seriously ill patients. but it is largely prevented with proper prophylaxis. Because stress bleeding treatment is often ineffective and has a high death rate, systematic prophylaxis for susceptible patients should be implemented. Mucosal ischemia and the inability to manage back-diffused hydrogen appear to be the most critical factors that contribute to the establishment of stress ulcers. Antacids and histamine-2-blocking agents are currently the cornerstones of effective prophylaxis, but because they have been linked to nosocomial pneumonias caused by bacterial overgrowth in the stomach, research into alternative prophylactic agents like sucralfate and prostaglandins that do not alter gastric acidity is ongoing.

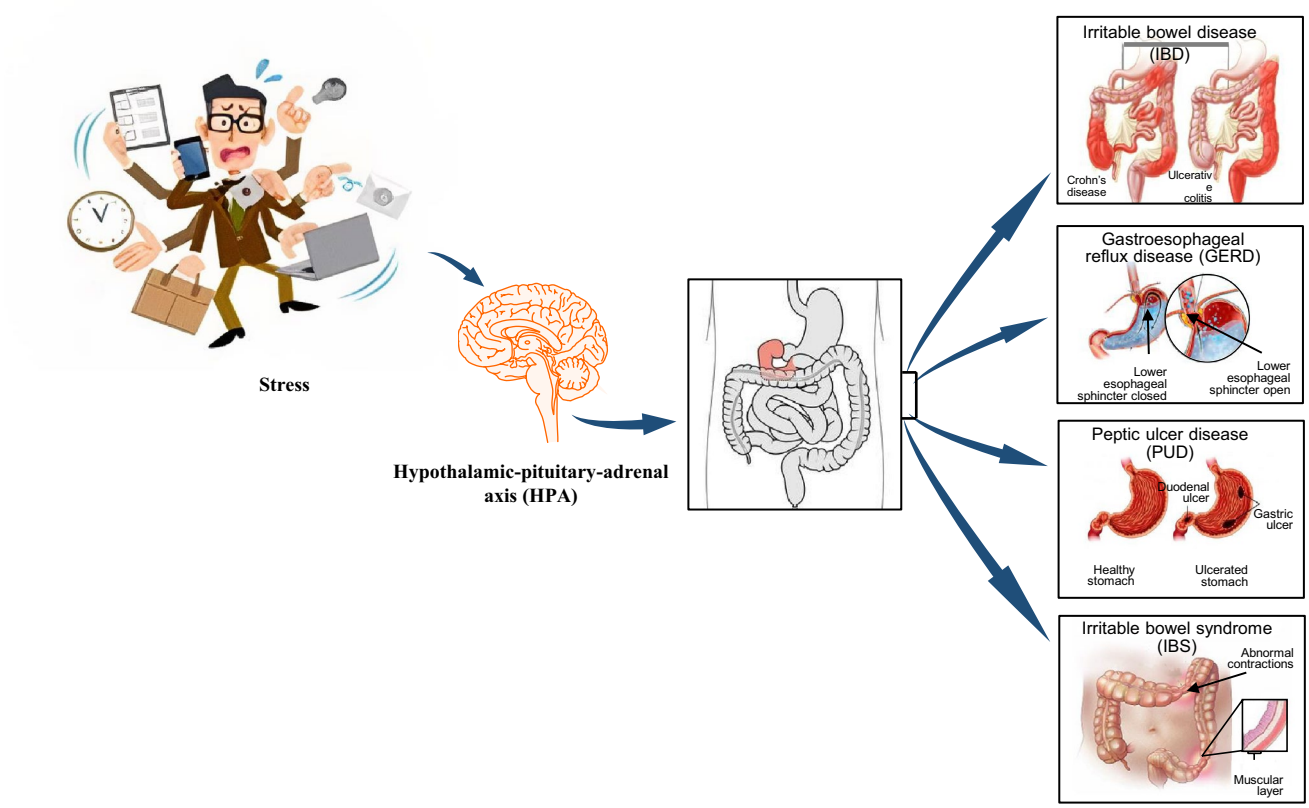

Fig. 3 The consequences of pathophysiological disruption of brain-gut-microbiota axis by stress

3.8 Stress

Stress plays a significant role in gastroduodenal ulceration etiopathology. It causes decreased gastric mucosal blood flow, gastric motility, prostaglandin synthesis, increased vagal activity, and mast cell degranulation. There is a considerable suggestion that physical and psychological stressors play a central part in the beginning as well as infection of gastrointestinal disorders to affect potential intermediaries like cytokines corticotropin-releasing hormone, and thyrotropin-releasing hormone. Stress induces ulceration through the release of histamine by increased acid secretion and decreased mucus production. Unless there is an ulcer, increased acidity may affect or help ulcer healing, as well as induce changes in appetite such as hunger or overeating. More consumption of food leads to increased acid production and loss of appetite subjected to acid secretion in the empty stomach [29].

Gastrointestinal lesions by stress induction including erosion, gastritis, duodenal, and gastric ulcers cause upper gastrointestinal hemorrhage, increased mortality, and morbidity [22]. Conventional treatments are effective and fewer side effects are frequently inevitable and limit clinical utility. Both experimental and clinical studies have established that herbal medicines show beneficial effects for gastric ulcer with lesser side effects.

4 Therapeutic intervention of phytochemicals in gastric ulcer

Nemours are beneficial, protective, endogenous, physical, and physiological factors, mediations are able to aid in the prevention and formation of gastric ulcer. Traditional approaches for preventing gastric ulcers are also utilized, particularly among individuals predisposed to such conditions. Researchers have explored certain drugs that are not commonly prescribed for gastric ulcer treatment due to their potential protective effects against ulcer formation. Therefore, currently the phytochemicals play a foremost role in the management of various human health problems [7, 44, 115].

Phytochemicals are a natural, biologically energetic, active compounds present in plants, which offer health benefits for humans when there is a significant intake. These phytochemicals are different secondary metabolites that can be used for drug development in human and veterinary medicine. The major constituents of secondary metabolites are terpenes, alkaloids, and flavonoids derived from leaves, bark, flowers, fruits or seeds, roots [7][Fig. 4]. In the current, exploration for natural bioactive products from herbal sources that have anti-ulcer activities of plant-derived active compounds and plant crude extracts are tried in various experimental models for stress-induced gastric ulcer. List of favorable phytocompounds and plant extracts with therapeutic potential for stress-induced gastric ulcer is given in Table 1.

4.1 Flavonoids

The flavonoids, constituting the largest and most significant class of polyphenols found in plants, are prominent secondary metabolites. These compounds demonstrate gastroprotective, anti-secretory, antioxidant, and cytoprotective properties [68]. Among the natives of the region, *Mouriri pusa*, also known as Manapuca and Jaboticaba do mato, is frequently used to prevent gastric ulcers [105].

The polyphenol compound quercetin is a flavonoid, which is found in vegetables, leaves, and fruits. Adult male Wistar rats received treatments of quercetin or omeprazole at doses of 25, 50, 100, or 200 mg/kg (*p.o.*) and 20 mg/kg (*s.c.*),

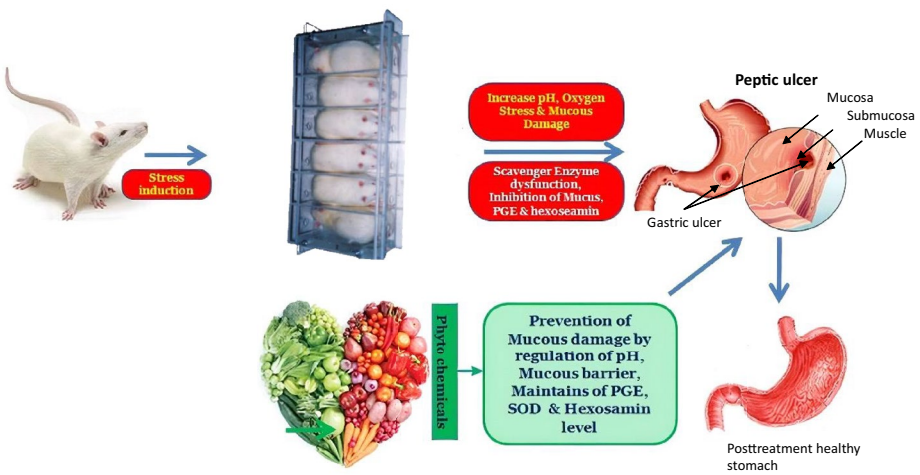

Fig. 4 Therapeutic interventions phytochemicals on prevention of gastric ulcer

Table 1 Plant extracts and bioactive compounds with therapeutic potential for gastric ulcer

Substance	Animal	Weight	Models	Treatment	Standard Drug	Route of administration	Effect	Reference
VX765 (Caspase-1 inhibitor)	C57BL/6 J mice	4 weeks	Cold restrain	12.5 µmol/kg (10 mg VX765)	40 mg/kg Rabeprazole	i.p	Significant reduction of inflammatory marker and caspase-1 expression	[117]
Fluoxetine	Male albino rats	175–225 g	Wire mesh restrainer	20 mg/kg b.w	–	i.p	Increased weight and organ somatic index, decreased reactive oxygen species generation	[49]
Monohydroxybenzoic acids	Male Swiss mice and wistar rats	20 ± 5 g and 150 ± 50 g	Foot shock	20 mg/kg for 11 days	–	Oral	Suppression of Inflammatory Markers	[46]
Withania somnifera	Wistar Albino male mice	25 ± 5 g	Foot Shock Stress Induced Hyperthermia	10, or 20 or 40 mg/kg daily for 10 days	–	Oral	Decreased basal core temperature, hyperthermic response	[25]
Methanolic *Piper longum* fruit extract and piperlongumine	Male Swiss albino mice	25 ± 5 g	Foot Shock	1, 4, 16, 64 and 256 mg/kg for 11 days	Doxycycline and aspirin	Oral	Their no significant adverse effect on body weight, Suppressed foot shock stress induced hyperthermia	[113]
Curcuma longa extract (CLE), Curcumin and Turmeric oil (TO)	Male mice	20 ± 5 g	Hyperthermia	Curcumin (5 mg) or CLE (5, 20, and 80 mg) or TO (1, 3, 10, 30 and 100 mg) kg/day	–	Oral	Body weight is recovered after 7 days of CLE treatment, hyperthermic response was decreased after 5 days	[106, 107]
Cinnamomum tamala (CT) leaves (aqueous extract)	Wistar albino rats	180 ± 20 g	Water immersion-restraint	100, 200, 400 mg/kg/day for 7 days	*W. somnifera* 100 mg/kg	Oral	Significantly decreased the ulcer index, weight of the adrenal gland	[104]

Table 1 (continued)

Substance	Animal	Weight	Models	Treatment	Standard Drug	Route of administration	Effect	Reference
Monomethyl Fumarate and a *Fumaria indica* Extract	Male adult Charles Foster albino rats	150 ± 10 g	Chronic Foot-Shock Stress-Induced Ulcer	MFI 60, 120, 240 mg/kg/day; MMF 1.25, 2.5, 5 mg/kg/day; for 21 days	–	Oral	Dose dependent effect were observed in the body weight treated with MFI and MMF, decreased ulcer index, level plasma corticosterone, IL-1b, increased level of 5-HT in HYP	[87]
Quercetin and triethylene glycol	male albino mice	20 ± 5 g	Foot shock	5, 20, 100 and 400 mg/kg/day for 10 days	Fumaric acid (10 mg/kg/day)	Oral	Suppression of transient hyperthermia and Weigh loss	[93]
Phloroglucinol and its trimethyl ether	Charles foster rats and Wistar rats	150 ± 50 g and 20 ± 5 g	Foot shock and cold restraint	3, 10, 30, 100, or 300 mg/kg/day for 7 days	–	Oral	Reduction of ulcer index, increased glandular	[80]
Mono-hydroxybenzoic acids	male Wistar rats/male Swiss mice	150 ± 50 g/20 ± 5 g	Stress induced hyperthermia/Forced swimming	3, 10, 30, 100 and 300 mg/kg for 11 days	Fluoxetine (10 mg/kg)	Oral	Dose dependently beneficial effect was observed	[46]
Phloroglucinol	Charles Foster albino rats and Wistar Rat	150 ± 10 g and 20 ± 5 g	Foot-Shock and cold restraint stress	1, 4, 16 mg/kg/day for days	–	Oral	Suppressed hyperthermia, decreased ulcer index, Improved behavior	[80]
Curcumin	Male adult Sprague–Dawley rats	200–250 g	water immersion—restraint	20 mg/kg for 7 days	–	Oral	Significant change in the histopathological aspect and suppresses H^+, K^+-ATPase mRNA expression	[36]
Lactic acid	Swiss albino male mice	20 ± 5 g	Stress induced hyperthermia	5, 25, 125 and 625 mg/kg/day for 12 days	Diazepam 5 mg/kg	Oral	Decreased body weight, Hyperthermia on 5th day, equal to normal rectal temperature, in the lactic acid treated groups	[92]

Table 1 (continued)

Substance	Animal	Weight	Models	Treatment	Standard Drug	Route of administration	Effect	Reference
Aqueous and Methanolic Seed Extracts of Ladies Finger (*Abelmoschus esculentus* L)	Male Swiss albino mice	22 ± 2 g	Acute Restraint	200 mg/kg for 7 days	Diazepam (2 mg/kg, i.p)	Oral	Decreased level of serum glucose, corticosterone, cholesterol, and triglycerides	[27]
Sodium hydrosulfide	Male Sprague–Dawley rats	150–200 g	Cold Restraint	60 µmol/kg	BCA (50 mg/kg)	i.p	Decreased ulcer index, serum TNF-α and MPO levels, increase in juice volume and pH, free and total acid concentrations were reduced	[1]
Crude ethanolic extract *Zanthoxylum rhoifolium* Lam	Wistar rats	180–240 g	Hypothermic restraint	125, 250 and 500 mg/kg) for 4 h	Cimetidine 100 mg	Oral	Inhibition of gastric lesions, release of the nitric oxide, opening of K channels, the participation of the non-protein sulfhydryl groups (NP-SH), catalase and the increases mucous secretion	[30]
UlGen (Polyherbal product)	Wistar albino rats	180–220 g	Cold Restraint	0.8 g kg for 10 days	Aspirin (0.2 g/kg for 3 days)	Oral	Acid inhibition and cytoprotection	[70]
Tinospora malabarica (Lamk.)	Swiss albino mice and Wistar rats	20–25 g and 160–200 g	Water immersion	Aqueous, alcoholic, and petroleum ether extract (500 mg/kg) for 3 days	Ranitidine 20 mg/kg)	Oral	Reduced ulcer index, possessing antisecretory, cytoprotective and H2 blocking/proton pump inhibition	[47]

Table 1 (continued)

Substance	Animal	Weight	Models	Treatment	Standard Drug	Route of administration	Effect	Reference
Aqueous extracts of stem of *Tinospora malabarica* (Lamk.)	swiss albino mice and wistar rats	20–25 g and 160–200 g	Cold resistant	500 mg/kg for 7 days	*Withania somnifera*	Oral	Found to be non-toxic, increased anoxia, Tolerance and swimming endurance time, decreased glucose, cholesterol, triglycerides, BUN and cortisol, reduction of liver, adrenal gland weight, decreased RBC, WBC and DLC counts	[89]
Aloe arborescens Miller var. natalensis	Wistar rats	180–250 g	Water immersion	> 5,000 MW and < 50,000 MW	–	Oral	No significant alterations were observed in ulcer index, Haemorrhagic areas were diminished in the Aloe-treated rats	[100]
Ocimum sanctum Linn (OSE)	Wistar albino rats/ Mice	100–120 g/20–30 g	Cold Restrain/Swimming	100 mg/kg	–	–	Reduced ulcer index, Mice treated with increased swimming duration	[13]

respectively. Following a one-hour treatment period, except for the control group, all other animals were placed in plexiglass restrainers and submerged in water at 23 °C for 3.5 h. After an additional 3.5-h period, the rats were euthanized for further analysis. Analyzed results showed increased acid content, decreased pH, and ulcer index was observed in the quercetin treated groups [32].

The anti-ulcerogenic potential of hesperidin from *Citrus sinensis* (L.) dried peel treated with hypothermic restrained stress-induced rats by oral treatment of 150, 300 and 450 mg/kg showed a significant increase in pH, glutathione and mucin levels, and a decrease in acidity and ulcer index and display the histological evidence of cytoprotection [15].

4.2 Alkaloids

Alkaloids represent a group of low molecular weight secondary metabolites which contain a nitrogen group and are reported to possess gastroprotective activity [119]. Indomethacin induced gastric affronts by administration at a dose of 200 mg/kg b.w. of aqueous extract from the leaf of *S. mombin* or *F. exasperate*, indicating their tremendous antioxidative potential and gastroprotective action in rats [82]. Exerts on *Cortex phellodendri* a favorable neurohumoral regulation and involved in the gastroprotective effect [111].

The rutaecarpine (8, 13-dihydroindolo- [2′, 3′:3, 4]-pyrido [2, 1-b] quinazolin-5(7H)-one) is an indolopyridoquinazoline alkaloid [41] isolated from *Evodia rutaecarpa* by ketone extraction (Lee et al., 2008); found in other genera of the family Rutaceae, as Evodia, Horit, Zanthoxylum, Phellodendron among the others. The rats treated with rutaecarpine by intravenous in the doses of 100 or 300 mg/kg significantly showed a reduction in the pH value and ulcer index in the acetylsalicylic acid (ASA) and stress induced model [110].

The chromane alkaloid Rohitukine, extracted from plants belonging to the Meliaceae family such as *Amoora rohikuta* and *Dysoxylum binectariferum*, exhibits promising effects in reducing ulcerative lesions and gastric juice levels. It also decreases free/total pepsin levels, inhibits H^+/K^+ ATPase activity, normalizes gastrin levels, and diminishes Ca^{2+} levels in parietal cells. Moreover, Rohitukine enhances gastric mucosa defense mechanisms by boosting levels of PGE2 and mucin. These beneficial effects were observed in stressed animals orally administered doses of 10, 20, and 40 mg/kg [95].

4.3 Terpenoids

Terpenoids are the largest naturally occurring organic chemicals related to terpenes. The oral intake of herbal medicines up to 4 weeks achieved greater efficiency of cimetidine in the treating of gastritis as well as gastric and duodenal ulcers. Herbal medicine along with ranitidine revealed a synergistic outcome in targeting gastric ulcers. Treatment with herbal medicine and ranitidine achieved 62.4% and 50.7% curative rate, respectively. Likewise, oral administration of omeprazole and the phytocompound for a duration of 4 weeks notably reduced the gastric ulcer recurrence rate to 25%, in contrast to the 57.1% recurrence rate observed with omeprazole treatment alone during a follow-up six months later [14, 116]. Eugenol (clove oil), has protective activities in the establishment of gastric ulcer induced by indomethacin, regulated by its antioxidant activity, which increases mucus production and decreases acid-pepsin secretion [66, 85]. Lysophosphatidic acid, present in Antyu-san and soybean lecithin, demonstrates protective properties against experimentally induced gastric ulcers in animal models. This implies that regular consumption may offer a protective effect against gastric ulcers in humans [2]. Similarly, curcumin has the defensive effect on gastric ulcer via relieving oxidative stress, gastric acid secretion inhibition, and ameliorating apoptosis [102, 113]. Numerous study reported that naturally occurring Chinese plant phytochemicals have gastroprotective action against *H. pylori* [56]. Several medicinal plants that are widely used in India have been tested for their gastroprotective activities such as *Chamomilla recutita* aqueous extract [3], *Hedyotis puberula* methanol extract [42], and *Mukia maderaspatana* ethanol extract [33].

4.4 Tannins

Tannins are water-soluble phenolic compounds which are widely found in plants and foods such as fruits and vegetables. They are a class of bioactive compounds known for their astringent taste in food products. Tannins are mostly used in traditional medications to treat various ailments. They are reported to possess gastroprotective activity against peptic ulcer [24]. *Rhizophora mangle* aqueous bark extract was able to inhibit gastric ulcer in an ethanol-hydrochloric acid induced gastric ulcer using rat model [84]. Tannin fractions of *Mouriri pusa* methanolic leaf extract were determined for protective effects on gastric ulcers in a mice model and were successful in reducing the lesion area along with promoting larger regeneration of mucosa [105]. The Indian Gooseberry, *Emblica officinalis* Gaertn is known for its enormous pharmacological activities. This plant is reported to possess gastroprotective activity due to the presence of bioactive compounds like tannins and alkaloids [24]. Several purified tannins from medicinal plants have been examined for their protective effects against peptic ulcer in preclinical studies. Tannins extracted from *Quercus suber* and *Quercus coccifera,* namely, castalagin, phillyraeoidin A, pedunculagin, and acutissimin B were tested for gastroprotective activity against ethanol-induced gastric lesions in mice. The results were positive with increased protection due to prevention of gastric acid secretion [48]. Scientific

reports of in vitro and in vivo preclinical studies confirmed that tannins from medicinal plants can prevent gastric ulcer formation and promote healing of the ulcers [24], [88].

4.5 Saponins

Saponins are phytocompounds with foamy nature which could also be found in marine organisms. Although the actual role of saponins in plants is not characterized, these compounds normally function as anti-microbials agents [67]. The bioactivity of saponins has been evaluated and reported to have anticancer properties against human cancer cell lines in an in vitro study. It has been reported also that these bioactive compounds have other therapeutic effects for numerous diseases [67, 96]. Several isolated saponins from plants have been reported with anti-ulcerogenic potential. Araloside, a saponin isolated from the root bark extract of *Aralia elata* (Miq.), showed gastroprotective and anti-ulcerative properties against ethanol-hydrochloric acid and pyloric ligation induced gastric ulcers in rats [54]. Glycyrrhizic acid was isolated from *Glycyrrhiza glabra* L., *Glycyrrhiza radix* Br., and *Glycyrrhiza uralensis*, to be tested against indomethacin induced gastric ulcers in a rat model which gave positive results [39, 57]. Another saponin isolate which showed anti-ulcerative properties against ethanol-hydrochloric acid induced gastric ulcers in mice and indomethacin induced gastric ulcers in rats is Ginsenoside Rb1, an isolated of *Panax ginseng* leaves and roots [9, 40]. Saponins mostly prevent gastric ulcer formation through an anti-secretory mechanism which inhibits excessive gastric juice secretion along with the total acid output, which leads to a pH value alteration in the gastrointestinal tract [54].

4.6 Polysaccharides

Polysaccharides are naturally occurring biopolymers that function to be one of the major macromolecules in cellular proliferation. Polysaccharides found in plants and other natural products are known as bioactive polysaccharides due to their biological effects that can be employed as therapeutic approaches for numerous diseases [5, 65]. Pharmacological properties of bioactive polysaccharides include anticancer, anti-inflammatory, anti-viral, antioxidant, immunomodulatory effects, and so on [55]. The gastroprotective effects of polysaccharides have been studied and reported that these compounds are able to modulate the gastric ulcer occurrence [9]. Pectins are polysaccharide bioactive compounds which are found as the primary cell wall component of fruits and vegetables. It was found that pectins are able to lower intestinal cholesterol levels and decrease gastric acid secretion in animals [69, 81]. Another polysaccharide known as Fucoidan isolated from an edible seaweed *Cladosiphon okamuranus*, which was able to prevent gastric ulcer formation induced by acetic acid in rats [90]. Polysaccharides from natural sources other than plants have been also tested to possess anti-ulcerative activities against chemically induced gastric ulcer in animal models [9, 45, 114].

5 Conclusion

In conclusion, this review underscores the potential of phytochemicals as therapeutic agents for stress-induced gastric ulcers, complementing conventional treatments. Emerging research highlights their protective abilities through diverse mechanisms, making them valuable candidates for ulcer management. Phytochemicals, secondary metabolites found in plants, offer diverse health benefits. Flavonoids show gastroprotective, anti-secretory, and antioxidant properties. Alkaloids and terpenoids also display gastroprotective qualities, influencing pH levels and ulcer indices. Tannins and saponins, present in numerous plants, exhibit anti-ulcerogenic potential by modulating acid secretion. Polysaccharides offer anti-inflammatory and antioxidant effects. The synergy of herbal medicines and conventional therapies shows promise in ulcer treatment and prevention. Phytochemicals' protective actions against stress-induced gastric ulcers emphasize their therapeutic potential. Further exploration is needed to understand their mechanisms and translate findings into clinical applications. Continued research should harness phytochemicals as adjunctive options in managing stress-induced gastric ulcers.

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Declarations

Conflict of interests All authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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