





Mechanistic Insights into the Therapeutic Potential of Phytochemicals Against Stress-Induced Gastric Ulcer

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Abstract: Gastric ulcers remain a prevalent gastrointestinal disorder aggravated by physical and psychological stress, which disrupts the balance between mucosal defense and aggressive factors. Conventional treatments, though effective, often produce adverse effects and recurrence. This review consolidates the mechanistic insights into phytochemicals, particularly flavonoids, terpenoids, alkaloids, and saponins that exert anti-ulcer effects through antioxidant, anti-inflammatory, and cytoprotective pathways. Emphasis is placed on their roles in modulating prostaglandin synthesis, nitric oxide signaling, cytokine expression, and H⁺/K⁺-ATPase inhibition. Furthermore, recent experimental evidence from stress-induced gastric ulcer models (WIRS, CRS, HRS) is summarized to correlate specific phytochemical classes with protective outcomes. The review underscores phytomedicines as promising, safer alternatives for managing stress-induced gastric ulcers and encourages future standardization and molecular validation studies.

Keywords: antioxidant, cytoprotection, gastric ulcer, IBD, phytochemical, stress

Introduction

Ulcers are inflammatory disruptions in the mucous membrane lining of the alimentary tract, caused either by increased aggressive factors or reduced mucosal resilience.^{1,2} Although the incidence of gastric ulcers (GU) has declined in industrialized nations, they remain the most prevalent upper digestive tract disorder and a major contributor to morbidity and mortality in developing countries.^{3,4} GU is a widespread global health problem, difficult to treat, and prone to recurrence. Triggers include *Helicobacter pylori* infection, alcohol consumption, smoking, NSAID use, poor dietary habits, and stress.^{5,6} An imbalance between aggressive factors (such as pepsin, gastric acid, and *H. pylori*) and protective mechanisms (including mucin, prostaglandins, bicarbonate, nitric oxide, and growth factors) disrupts normal gastric mucosal homeostasis. This leads to increased gastric acid and pepsin secretion, inhibition of prostaglandin synthesis and cell proliferation, reduced gastric blood flow, and altered motility, all of which contribute to GU pathogenesis.⁷⁻⁹

Globally, the age-standardized incidence rate of GU declined from 63.84 to 44.26 per 100,000 between 1990 and 2019, reflecting an annual reduction of 1.42%. The age-standardized death rate also decreased by 3.47% annually, while the age-standardized mortality rate dropped by nearly half (from 7.39 to 3.0 per 100,000). Moreover, inequalities associated with the sociodemographic index¹⁰ narrowed substantially during the same period, with the DALY gap between the richest and poorest countries reducing from 190.43 to 62.85 per 100,000.¹¹ Despite these improvements, men and the elderly remain at higher risk and require continued preventive and therapeutic interventions. Epidemiological studies across countries and demographic groups highlight persistent geographic and gender-based disparities in peptic ulcer disease (PUD). While the overall burden has declined, recent reports show that incident cases, DALYs, and ulcer-related deaths have again increased since 2019, suggesting that new lifestyle stressors and

comorbidities are influencing ulcer pathophysiology.^{12,13} This underscores the need to explore multifactorial etiologies especially the contribution of stress-related mechanisms.

Stress plays a critical role in gastric ulceration by inducing oxidative stress, disrupting gastric microcirculation, and weakening mucosal defenses.¹⁴ Both psychological and physical stressors markedly influence the onset and progression of gastrointestinal disorders.¹⁵ Psychological stress may act as a co-factor for *Helicobacter pylori*, either by stimulating gastric acid secretion or by promoting risk-related behaviors.¹⁶ Stress ulceration was first reported in 1969 during post-mortem examinations of critically ill patients, where it was characterized by focal lesions in the gastric mucosa.¹⁷ Endoscopic studies show that 74–100% of critically ill patients develop stress-related mucosal erosions and subepithelial hemorrhage within 24 h of admission.¹⁸ Stress ulcer bleeding is a frequent complication in such patients, with reported incidence rates ranging from 0.17% to 14%.¹⁹ Stress induces ulceration through multiple mechanisms, including increased histamine release, excessive gastric acid secretion, and reduced mucus production. It also slows gastric motility, allowing acid accumulation, which exacerbates or triggers ulcers. Moreover, stress alters appetite—causing either overeating or anorexia—both of which raise gastric acidity. These effects can result in serious gastrointestinal complications, such as gastritis, erosions, and ulcers, potentially progressing to severe bleeding and increased health risks.^{20–22}

Proper gastrointestinal function is essential for survival, but disorders affecting the mucosa, musculature, or neural innervation may cause ulceration, inflammation, obstruction, diarrhea, constipation, or abdominal pain. Increasing evidence indicates that impaired intestinal barrier function contributes to many gastrointestinal diseases. Stress and negative emotions further aggravate common gastrointestinal conditions. Chronic stress in adults and early-life stress have both been linked to altered pain responses, abnormal gastrointestinal motility, and increased intestinal permeability. Early adverse experiences such as maternal deprivation, loss of caregivers, abuse, or immunologic stressors significantly increase the risk of gastrointestinal disorders later in life.^{23–25}

Although conventional therapies such as proton pump inhibitors and H₂-receptor antagonists are effective, their long-term use is often limited by adverse effects, recurrence, and drug resistance. In contrast, phytoconstituents from medicinal plants, especially flavonoids, terpenoids, alkaloids, saponins, and phenolic acids, have emerged as less toxic and mechanistically potent alternatives for preventing and treating gastric ulcers. These bioactive compounds exhibit multifaceted actions, including antioxidative, anti-inflammatory, cytoprotective, and mucosal-regenerative effects. They also modulate signaling pathways such as COX, NF- κ B, and nitric oxide synthase, which play central roles in ulcer healing. Hence, phytochemical-based therapeutics offer a promising integrative approach to managing stress-induced gastric ulcers by targeting multiple molecular mechanisms.^{26–28} This review highlights Ayurvedic and other medicinal plants with experimentally validated gastroprotective and ulcer-healing properties, compiling modern evidence of their therapeutic potential and underlying biological mechanisms.

Anatomy and Physiology of the Stomach

Contrary to common belief, the stomach plays little to no role in nutrient absorption. It is the most dilated portion of the digestive system, located between the esophagus above and the small intestine below. The stomach is a large, muscular, hollow organ with a capacity of approximately two to three liters, serving both as a reservoir and a mixer of food. Its primary functions include producing chyme, synthesizing proteins necessary for vitamin absorption, defending against microbial invasion, and initiating the peristaltic reflex. The stomach lining contains specialized cells that secrete gastric acid for digestion and others that release bicarbonate and mucus to neutralize excess acidity. When the stomach lining is damaged by external factors, its ability to neutralize acid diminishes, which can injure the gastric or intestinal tissues. Patients with gastric ulcers often present with symptoms such as pain, bloating, and nausea.^{29,30}

Physiological processes of the stomach, including gastric acid secretion and peristalsis, are regulated by the parasympathetic and enteric nervous systems, in conjunction with various neurohormones. The stomach also communicates closely with the brain, influencing sensations of hunger and satiety. Signals from the digestive tract convey information about stomach contents to the central nervous system (CNS). This interaction is bidirectional, as CNS input enhances gastric secretory activity and hormone release in response to food.^{31–33} By detecting its contents, signals send to the CNS, and this bidirectional communication influences gastric secretions and hormone release. The hypothalamic-pituitary-adrenal (HPA) axis is a key component of the stress response, releasing hormones that affect cognitive, physical, emotional, and behavioral

functions. Experimental studies demonstrate that gastric bleeding in stressed rats is associated with decreased gastric pH and elevated adrenocorticotrophic hormone levels, underscoring the HPA axis's involvement in stress-related ulcers.^{33–35}

Psychological and physical stressors, including inflammation, activate the HPA axis and stimulate the release of corticotropin-releasing factor and ACTH. This, in turn, triggers glucocorticoid release from the adrenal glands, enabling the body to adapt to environmental challenges. Historically, glucocorticoids have been implicated in the pathogenesis of GU. Chronic stress disrupts the brain–gut communication pathway and may activate both the HPA axis and the autonomic nervous system. This dysregulation contributes to the pathophysiology of functional gastrointestinal disorders such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), peptic ulcer disease (PUD), and gastroesophageal reflux (GER) (Figure 1).^{36–40}

Natural Endogenous Gastroprotective Mediators

The gut lumen is lined by a single layer of intestinal epithelial cells, which serve two essential functions. First, they act as a barrier to prevent harmful intraluminal substances such as bacteria, toxins, and foreign antigens from entering the body. Second, they function as a selective filter, allowing the absorption of water, electrolytes, and vital nutrients from the intestinal lumen into the bloodstream.⁴¹ Several endogenous mediators play critical roles in protecting the gastrointestinal tract. These mediators help prevent the early stages of gastric inflammation by limiting damage caused by external irritants through cytoprotective mechanisms.⁴² Gastrointestinal injury often occurs when these endogenous protective pathways are suppressed, leading to the development of gastric ulcers. Importantly, modulation of these endogenous mediators has therapeutic potential, enhancing gastric protection and reducing the risk of ulceration.⁴³

Cyclooxygenase

The gastric mucosa is protected by several endogenous factors, including prostaglandins (PGs), nitric oxide, adequate blood flow, and epidermal growth factors. In contrast, irritant factors include *Helicobacter pylori*, reactive oxygen species

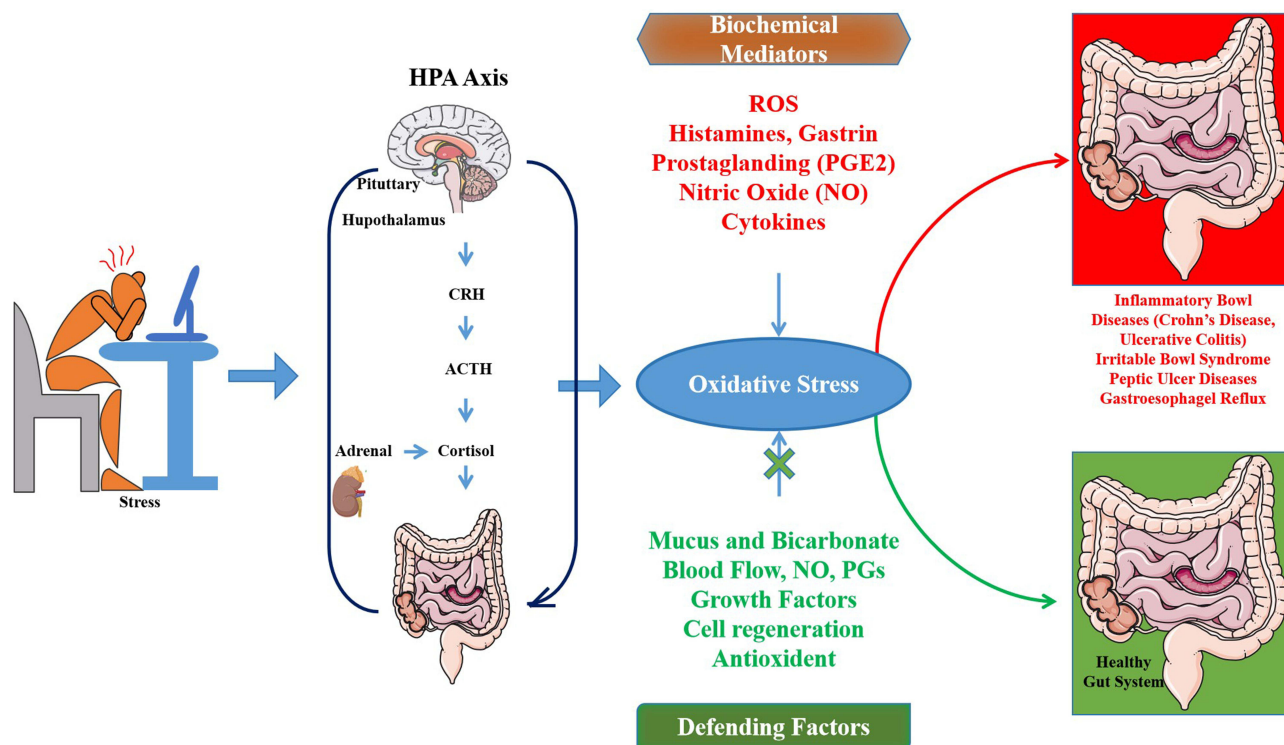


Figure 1 The pathophysiology of stress-induced brain-gut-microbiota disruption. Image(s) provided by Servier Medical Art (<https://smart.servier.com>), licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0/>).

(ROS), gastric acid, pepsin, alcohol, and other injurious agents. PGs play a central role in mucosal defense by stimulating mucus and bicarbonate secretion, promoting mucosal blood flow, strengthening epithelial resistance to cytotoxin-induced injury, and inhibiting leukocyte recruitment into the gastric mucosa.^{43,44} Additionally, PGs suppress gastric acid secretion both directly—by acting on parietal cells—and indirectly by inhibiting histamine release from enterochromaffin-like cells in the gastric mucosa. However, nonsteroidal anti-inflammatory drugs (NSAIDs), commonly used in clinical practice, inhibit the cyclooxygenase (COX) pathway, leading to reduced PG synthesis. This suppression compromises mucosal defenses and substantially increases the risk of gastric injury and ulcer formation.^{44–47}

Nitric Oxide

Nitric oxide (NO), is a volatile gas with several physiological characteristics, including the ability to regulate inflammation, is produced when NO synthase oxidises arginine. It plays an important role in control the defence mechanisms of the gastrointestinal mucosa. Since NO decreases leukocytic endothelial adhesion and modifies mucosal immune cell activity, some of its effects are similar to those of PGs. Furthermore, it decreases epithelial permeability and modifies mucosal blood flow, which increases mucosal resistance to ulceration. Additionally, NO stops leukocytes from adhering to the vascular endothelium. This gaseous mediator also affects the release of bicarbonate and gastric mucus.⁴⁸

Hydrogen Sulphide

Another endogenous gaseous mediator that causes vasodilatation, reduces leukocyte adhesion to vascular endothelium, prevents mucosal damage from NSAIDs, and suppresses the expression of tumour necrosis factor is hydrogen sulphide (H₂S).⁴⁹ The enzymes cystathionine synthase and lyase are in charge of producing H₂S in the stomach mucosa. Although this gas protects against damage to the mucosa, it is hypothesised that H₂S plays a part in the pro-inflammatory effects of *H. pylori* infection.⁵⁰ However, when combined with NSAIDs, H₂S protects the stomach by causing the up-regulation of cyto-protective and anti-inflammatory genes, such as insulin-like growth factor (IGF) receptor, vascular endothelial growth factor (VEGF), HMOG-1, and a number of genes linked to the transforming growth factor (TGF) receptor signaling pathways.^{51,52}

Cytokines

Cytokines play a vital role in regulating the mucosal immune system and maintaining mucosal defenses.⁵³ The early systemic inflammatory response to infection or injury involves the production of interleukin-1 (IL-1) and tumor necrosis factor (TNF). IL-1 is synthesized by various cells, including fibroblasts, neutrophils, endothelial cells, monocytes, and macrophages. IL-1 reduces the severity of ulcerative damage and enhances the resilience of the gastric mucosa. It exerts these effects by strongly suppressing gastric acid secretion, promoting the production of prostaglandins (PGs) and nitric oxide (NO), and inhibiting ulcer-promoting mediators such as platelet-activating factor (PAF) released from mast cells. TNF is another important cytokine involved in gastric mucosal injury.^{54,55} However, it also contributes to mucosal regeneration following damage caused by *H. pylori* infection or NSAID exposure, primarily by promoting epithelial cell proliferation. Thus, TNF can help restore gastric mucosal integrity.^{53,56}

Proteinase-Activated Receptors

Protease-activated receptor-2 (PAR-2) is widely expressed throughout the gastrointestinal tract, particularly in epithelial cells and sensory afferent neurons. Activation of these receptors reduces NSAID-induced damage to the gastric endothelium. This protective effect is achieved by regulating the release of VEGF from platelets and modulating sensory afferent neurons, thereby promoting angiogenesis and facilitating ulcer healing.⁵⁷

Proteolytic Enzymes

Proteolytic enzymes play an essential role in both the prevention and treatment of gastric ulcers. Alterations in these enzymes, particularly within the tissue-type plasminogen activator–inhibitor (PAI) system, can impair fibrinolysis and delay healing. Cathepsins, expressed in the gastric epithelium, possess antimicrobial properties that aid in ulcer healing and help prevent bacterial infection. Urokinase-type plasminogen activator and PAI-1 are also key mediators in

angiogenesis, inflammation, ulcer repair, and cell proliferation. In addition, matrix metalloproteinases (MMPs) contribute to gastric ulcer healing through tissue remodeling. Heat shock proteins (HSPs), produced by gastric epithelial cells in response to stress, further support mucosal recovery. They promote cell survival by modulating enzymes involved in inflammation and ulcer repair, assist in the stabilization and refolding of damaged proteins, and facilitate the transport of precursor proteins to essential organelles.^{58–61}

Growth Factors

Cell proliferation, division, migration, and re-epithelialization are significantly regulated by growth factors (GFs). Following tissue injury, numerous GFs are activated to promote cell proliferation and facilitate the repair of the damaged gastric mucosal epithelium. Key GFs—including basic fibroblast growth factor (FGF), hepatocyte growth factor (HGF), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF)—bind to their respective cell surface receptors and initiate intracellular signaling cascades that accelerate ulcer healing and stimulate epithelial proliferation and migration. Among them, EGF is particularly critical for epithelial proliferation, migration, re-epithelialization, and regeneration of gastric glands, as well as for inducing a mitogenic response in gastric tissue.⁶² VEGF is essential for angiogenesis, vascular remodeling, and mucosal regeneration, while transforming growth factor (TGF) supports wound healing and protects the gastric mucosa from injury. Gastrin and PGE₂ can trans-activate epidermal growth factor receptors (EGFRs) and TGF receptors, which are expressed in gastric progenitor cells, thereby promoting cell division and mucosal healing. Platelets, macrophages, and damaged tissues are the primary sources of these GFs.⁶³ Moreover, ulceration induces the expression of GF-encoding genes in epithelial cells at the ulcer margins. Acting through autocrine and paracrine pathways, these locally produced GFs enhance epithelial cell migration and proliferation, thereby facilitating gastric mucosal repair.^{64,65}

Peroxisome Proliferation-Activated Receptor

The nuclear receptor transcription factor family includes peroxisome proliferator-activated receptors (PPARs), which are closely involved in the mechanism of action of NSAIDs. PPARs inhibit transcription factors such as NF-κB and regulate genes associated with cell differentiation, glucose homeostasis, and lipid metabolism. Activation of PPARs by NSAIDs suppresses the production of inflammatory mediators in macrophages and endothelial cells, thereby attenuating pro-inflammatory pathways and enhancing anti-inflammatory effects.^{66–70}

Neuropeptides

Several neuropeptides contribute to gastroprotection, with particular emphasis on ghrelin and orexin-A. Ghrelin enhances gastrointestinal motility, prevents ethanol-induced gastric ulcers by stimulating PGE₂ production, and improves mucosal blood flow. Orexin-A also supports mucosal defense by increasing gastric blood flow and reducing mucosal injury. In addition, heme oxygenase-1 an enzyme involved in drug detoxification provides cytoprotective effects through its antioxidant and anti-apoptotic properties. HO-1 plays a key role in shielding gastric mucosal cells from NSAID-induced injury.^{14,71–74}

Ulcer Inducing Agents

GU are caused by a combination of lifestyle choices and medical conditions, influenced by factors such as excessive NSAID use, *H. pylori* infection, diet, smoking, alcohol consumption, and stress.^{75–78} NSAIDs are commonly used for pain and inflammation but can harm the gastrointestinal tract with prolonged use, increasing the risk of ulcers and related complications, particularly with aspirin.^{79–82} *Helicobacter pylori* is a significant contributor to gastrointestinal disorders, responsible for many ulcers and gastric cancer cases globally.^{83–86} Smoking exacerbates the risk and healing of ulcers by increasing acid production and impairing protective mechanisms.^{87–90} Dietary factors, such as caffeine, high salt, and alcohol consumption, also play a role in ulcer development and severity. The interplay of medication, infection, lifestyle, and diet emphasizes the need for comprehensive prevention and treatment strategies for GU.^{78,90–94}

Among the multiple risk factors for gastric ulcer—such as NSAID use, *H. pylori* infection, diet, smoking, and alcohol consumption - stress exerts a particularly multifaceted and influential role in disease onset and progression. Its effects on

gastric acid secretion, mucosal integrity, and inflammatory responses make stress a critical and often underappreciated contributor to ulcer development. Accordingly, this review focuses on stress-induced gastric ulcers and highlights the promising therapeutic potential of phytochemicals in mitigating stress-related gastric injury and promoting mucosal healing.

Stress

Hans Selye was a clinical endocrinologist and experimental biologist who pioneered the study of stress, introducing key concepts such as stress, stressors, eustress, distress, and General Adaptation Syndrome (GAS). He defined stress as the body's failed response to emotional or physical threats, emphasizing the harmful effects of chronic stress on health. Common disorders related to stress include stress ulcers and psychiatric conditions like depression and anxiety, often triggered by factors like surgery, trauma, and emotional stress. The HPA axis plays a crucial role in the stress response by releasing hormones that affect cognitive, physical, emotional, and behavioral functions. Research has shown that stress can lead to gastric bleeding in rodents, linking the HPA axis to stress-related gastrointestinal issues. Despite ongoing studies, many aspects of the neuroendocrine mechanisms behind stress ulcers and depression remain unclear^{34,35,95–102} suggesting the role of the HPA axis in stress ulcer formation and development. While multiple studies have been devoted to understand the neuroendocrine components of stress ulcers and depression, much remains unknown.

Stress is a factor that contributes to various diseases and disorders, including depression and peptic ulcers. An major factor in the etiopathology of GU is stress. It results in decreased stomach mucosal blood flow, mast cell degranulation, increased gastric motility, vagal hyperactivity, and prostaglandin synthesis. Physical and psychological stressors significantly affect mediators such as cytokines, corticotropin-releasing hormone, and thyrotropin-releasing hormone as well as playing a significant role in the development and regulation of GI diseases (Figure 2). Stress impacts stomach motility

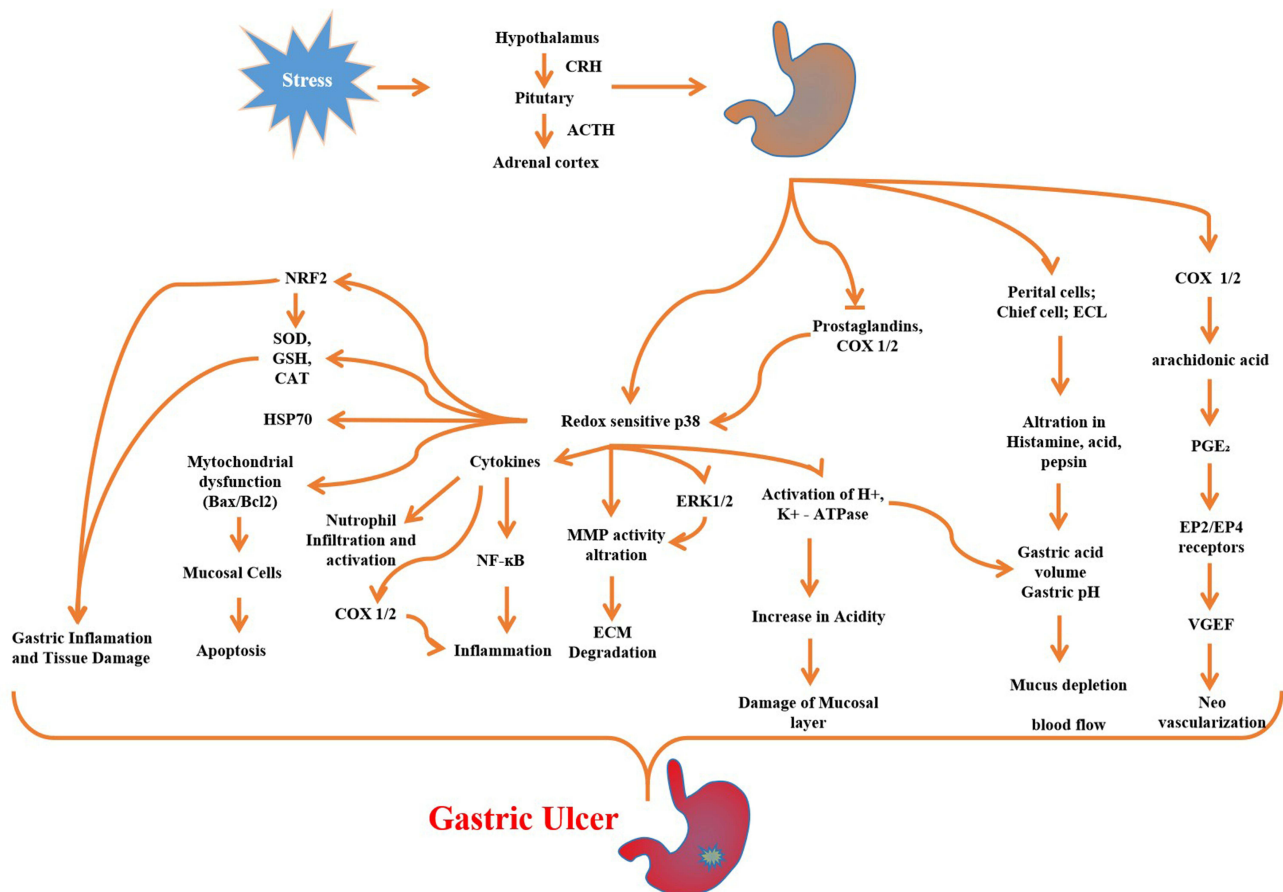


Figure 2 Mechanism of action of gastric ulcers induced by stress.

in different ways, with faster emptying potentially increasing the risk of duodenal ulcers and delayed emptying raising the risk of GU.¹⁰³

When post-mortem exams revealed focal lesions in the gastric fundus's mucosa in 7 (out of 150) severely ill patients, stress ulceration was first identified in 1969.¹⁷ Stress causes ulcers, most likely by the release of histamine, increased secretion of acid, and decreased production of mucus. When under stress, the digestive system slows down and allows more stomach acid to build up. An ulcer that currently exists may be exacerbated or predisposed to by increased stomach acidity. Additionally, it may alter appetite, resulting in either overeating or a lack of appetite. While a lack of appetite exposes the stomach mucosa to the acid produced in an empty stomach, overeating stimulates the stomach to create more acid.²⁰ Stress-induced gastrointestinal lesions, including gastritis, erosion's, and ulcers, can lead to significant upper gastrointestinal bleeding and increased morbidity and mortality. A Danish cohort study found that psychological stress raises the incidence of peptic ulcers by affecting health risk behaviors, impacting ulcers related to both *H. pylori* infection and those unrelated to *H. pylori* or NSAID use.^{104,105}

Mechanisms of Action of Phytochemicals as Therapeutic Interventions to Prevent Stress-Induced Gastric Ulcers

Stress is a complex, phenomena that has a significant impact on the human body, affecting many physiological functions, including the digestive system. Ulcers can develop as a result of altered stomach physiology brought on by stress, including increased secretion of gastric acid, decreased blood supply to the mucosa, and compromised defensive mechanisms. This complicated interaction of variables highlights how difficult it is to treat stomach ulcers brought on by stress. Phytochemicals, natural compounds in plants, show potential in managing stress-induced GU.

Biologically active, naturally occurring chemical substances known as phytochemicals are present in plants and offer additional health benefits to humans than macro and micronutrients. It is now well established that they play an essential role in safeguarding human health when consumed regularly as part of the diet. Phytochemicals comprise a wide range of secondary metabolites that can serve as valuable precursors for drug development. The major categories of these secondary metabolites include terpenes, flavonoids, alkaloids, phenolics, and glycosides. Since ancient times, plant products made from roots, barks, leaves, flowers, fruits, or seeds have been used as phytomedicines.¹⁰⁶

Phytochemicals have long been used to treat a variety of ailments and are generally considered safer and less toxic than synthetic drugs. They are abundant in nature and are often consumed as nutritional supplements. Several plant-derived compounds, including alkaloids, tannins, flavonoids, terpenoids, glycosides, carotenoids, and saponins, have demonstrated potent anti-ulcer activities in preclinical models.^{28,107–109}

H. pylori infection or prolonged use of NSAIDs are the most common factors linked to GU.^{110,111} This gastrointestinal ailment has shown promising responses to treatment with phyto medicines. Flavonoids, tannins, and terpenoids are plant-derived compounds known to inhibit *H. pylori* growth, enhance the gastric mucosal barrier, and regulate gastric acid secretion. Their gastroprotective effects arises through multiple mechanisms, including antibacterial action against *H. pylori*, stimulation of mucus and bicarbonate secretion, inhibition H⁺/K⁺-ATPase activity, antioxidative and anti-inflammatory effects, and modulation of leukotriene and prostaglandin pathways that favor mucosal protection.^{112–115}

According to evidence from both human and experimental animal studies, herbal remedies exert multi-targeted therapeutic effects against gastric ulcers. These include stimulation of mucus production, suppression of inflammation and acid secretion, enhancement of mucosal proliferation, reinforcement of the epithelial barrier, and restoration of antioxidant defenses.^{116,117} Collectively, these mechanisms underscore the therapeutic promise of phytochemicals as safer, effective, and sustainable alternatives for preventing and treating stress-induced gastric ulcers (Figure 3).

The Effects of Phytochemicals in Representative Animal Stress Models

Stress is a common factor contributing to mental disorders, as both acute and chronic distress can lead to conditions like depression. Creating animal models of stress in the laboratory can help researchers understand the causes and mechanisms of stress-related mental disorders. Anxiety and stress-related disorders are significant psychiatric conditions that hinder daily performance and impose a high public health cost. Charles Darwin's observation of shared emotional

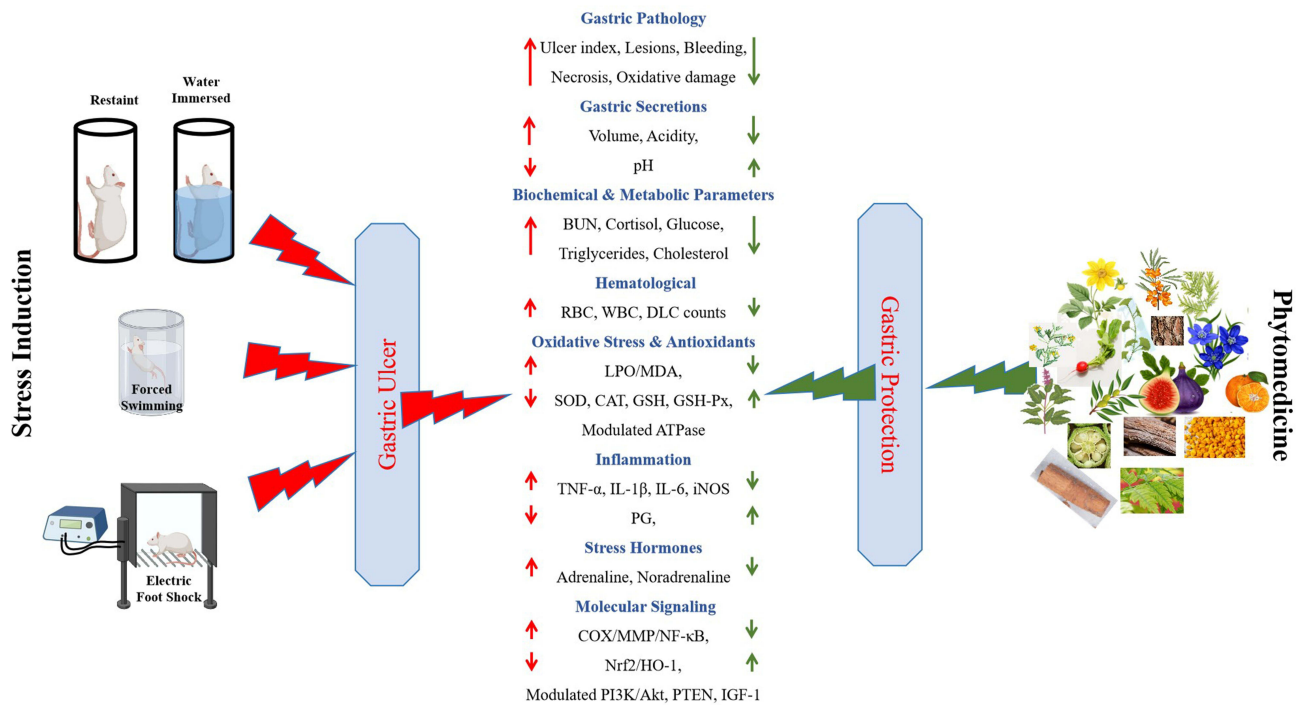


Figure 3 Protective Role of phytochemicals on stress induced gastric ulcer (Created in <https://BioRender.com> and “Designed by Freepik” www.freepik.com).

expressions between humans and animals enables the study of these disorders in mammals, particularly rodents. Animal models for anxiety and stress have been developed, aiding in the identification of pharmacological mechanisms and the evaluation of drug effects (Table 1). These models often involve conflict situations that create opposing motivations. The review discusses various rodent models used globally, categorizing them into acute and chronic stress types. For chronic stress, common models include restraint stress and chronic unpredictable mild stress (CUMS), while acute stress models include repeated social defeat stress (RSDS), forced swim test (FST), tail suspension test (TST), and acute electric foot-shock stress.^{118,119}

Hypothermic Restraint Stress (HRS) and Hypothermic Stress

In laboratory animals, various stressors lead to temporary increases in body temperature (T_c), known as stress-induced hyperthermia or stress-induced fever. Social defeat stress can raise T_c by 1.5–2.0°C within 25 minutes before returning to baseline levels. Other stressors, like inserting a thermometer probe, can cause similar transient hyperthermic responses. However, prolonged inescapable stress may result in hypothermia, as seen in restrained rabbits, where T_c decreases.¹⁷¹ In hypothermic stress models, *Artemisia annua*,¹²¹ *Raphanus sativus* (radish juice),¹³⁵ *Citrus sinensis* (hesperidin)¹⁵² and *Zanthoxylum rhoifolium*¹⁴³ extracts (Table 1) showed gastroprotective actions. These included increased mucosal adherent mucus and prostaglandin production, inhibition of ulcer index, and enhanced antioxidant enzyme activities. Hesperidin and related flavonoids also lowered total acidity and raised gastric pH while boosting tissue GSH and enzyme defenses—supporting an antioxidative and prostaglandin-mediated cytoprotective mechanism.

Restraint / Immobilization Stress (Acute and Chronic)

Restraint stress is a simple and mostly painless model that causes no lasting effects. Immobilization is a variation that restricts locomotion without limiting specific limb movement, typically involving 1–6 hrs of restraining an animal daily in a device for 14–21 days.^{172,173} Restraint-type models (immobilization or cold immobilization) tested extracts such as *Hippophae rhamnoides*,¹²⁰ *Tinospora malabarica*,¹²⁹ *Solanum torvum*,¹³⁶ *Eugenia jambolana*,¹³⁴ and *Ginkgo biloba*.¹³¹ Outcomes commonly reported are reduced ulcer area/index, less intraluminal bleeding, and improved mucosal histology (Table 1). Mechanistic findings included suppression of lipid peroxidation, elevation of mucin content, stimulation of NO

Table 1 The Effects of Phytochemicals on Various Stress Induced Gastric Ulcer Models

Plants	Phytochemicals	Stress Models	Animals and Treatment Conditions Along with Std Drug	Key Results	[Ref.]
<i>Hippophae rhamnoides</i>	Fruits hexane extract	Obligatory immobilization stress	Wistar albino male rats (250–270 g) 1 mL before 1 h stress induction Omeprazole (20 mg), Famotidine (30 mg)	Number of ulceration areas was prominently decreased	[120]
<i>Artemisia annua</i>	Dried ground plant material crude ethanolic extract	Hypothermic restraint stress (HRS)	Wistar albino male rats (200–300 g) 100 mg before 30 min stress induction Carbenoxolone (200 mg)	The increase in prostaglandin levels resulted in a 29.4% inhibition of ULI and a 46.7% increase in the production of gastric mucosa adherent mucus	[121]
<i>Stryphnodendron adstringens</i>	Bark acetone extract	HRS	Male albino rats (80–200 g) 100, 400 and 800 mg before 1 h stress induction Ranitidine (50 mg)	Prevented gastric lesions	[122]
<i>Turnera ulmifolia</i>	Aerial parts aqueous extract	HRS	Male Swiss albino mice (30–40 g) and Wistar rats (200–220 g) 100, 250, 500, and 1000 mg before 1 h stress induction Cimetidine (100 mg)	The aqueous extract of <i>Turnera ulmifolia</i> aerial parts effectively prevented the development of stress-induced lesions	[123]
<i>Petroselinum crispum</i>	Aerial parts ethanolic extract	HRS	Wistar albino rats (150–200 g) 1 and 2 g 3 h before stress induction	Decreased dose dependent intraluminal bleeding and gastric lesions	[124]
<i>Barleria lupulina</i>	Methanolic fraction	Wrapped in a soft wire mesh stress	Albino (Wistar) rats (180–200 g) 200 mg immediate induction Famotidine (30 mg)	Significantly reduced the incidence and severity of ulceration	[125]
Gentian	Gentian root methanolic extract	Water immersion restraint stress (WIRS)	Male Donryu (180–200 g) 2.58 mg and 167 mg Cimetidine (60 mg)	Dose-dependent protective effects against GU	[126]
<i>Commiphora opobalsamum</i>	Aerial parts ethanolic extract	HRS	Wistar albino rats (150–200 g) 250 and 500 mg 1 h before stress induction	Absence of hemorrhagic necrosis, inhibition of the intraluminal bleeding score, gastric lesion score, and mucin-secreting superficial epithelium	[127]
<i>Solanum nigrum</i>	Fruits methanolic extract	Cold restraint stress (CRS)	Male albino Wistar rats (120–150 g) 200 and 400 mg, 3 days Omeprazole 10 mg	Significantly inhibited the gastric lesions 76.6%, dose-dependent protective effect against GU	[128]
<i>Tinospora malabarica</i>	Stem aqueous and alcoholic extracts	CRS	Swiss albino mice (20–25 g) and wistar rats (160–200 g) 500 mg for 10 days <i>Withania somnifera</i> (100 mg)	The study found that there were reductions in liver and adrenal gland weights, along with decreased RBC, WBC, and DLC counts, as well as lower levels of glucose, cholesterol, triglycerides, BUN, and cortisol. Additionally, improvements in anoxia tolerance and swimming endurance time were noted, concluding that these changes were harmless	[129]

(Continued)

Table I (Continued).

Plants	Phytochemicals	Stress Models	Animals and Treatment Conditions Along with Std Drug	Key Results	[Ref.]
<i>Cnestis ferruginea</i>	Root aqueous extract	Forced swim stress (FSS)	Sprague Dawley rats (150–200 g) and Swiss albino mice (17–25 g) 300–500 mg 1 h before stress induction. <i>P. ginseng</i> (50–200 mg)	There was a significant decrease in immobility duration and a notable increase in meantime, with no occurrence of GU	[130]
<i>Ginkgo biloba</i>	Leaves hexane extracts	Cold immobilization stress	Adult Charles Foster rats (100–150 g) 50 and 100 mg 1 h before stress induction Imipramine (15 mg - i.p)	There is significant dose-dependent antidepressant activity, along with a decrease in the number of failures to escape from a shock chamber and a reduction in the ulcer index	[131]
<i>Maytenus robusta</i>	Leaves aqueous ethanolic extract	WIRS	Male Wistar rats (200–250 g) 50, 250 and 500 mg 30 min before stress induction Cimetidine (100 mg)	Treatments on gastric conditions, highlighting the inhibition of ulcer lesions, a decrease in gastric juice volume and acidity, and an increase in gastric pH	[132]
<i>Ficus glomerata</i>	Fruit ethanolic extract	CRS	SpragueDawley rats (140–180 g) 50, 100 and 200 mg twice daily for 5 days Ranitidine (50 mg)	By inhibiting LPO, preventing oxidative damage to the stomach mucosa, and significantly lowering SOD, H+K+ATPase, and increasing CAT activity, dose-dependent suppression of ulcer index	[133]
<i>Eugenia jambolana</i>	Seeds ethanolic extract	CRS	Charles Foster strain albino mice (25–35 g) 100, 200 and 400 mg daily for 10 days	Dose-dependent decrease in ulcer index, decreased LPO level	[134]
<i>Raphanus sativus</i>	Freshly squeezed radish juice	HRS	Wistar albino rats (150–200 g) 2 and 4 mL/ 200 g before 30 min induction Ranitidine (2.5 mg)	Significantly inhibited gastric ulcer formation, significantly reduced the intensity of ulceration and intraluminal bleeding at high dose	[135]
<i>Solanum torvum</i>	Leaves aqueous and methanolic extracts	CRS	Wistar male rats (180–200 g) 250, 500 and 750 mg Ranitidine (50 mg)	Dose of 750 mg/kg 96.03% whereas aqueous extract 98.63% produced inhibition of gastric ulcerations	[136]
<i>Tinospora malabarica</i>	Dried stems aqueous, alcoholic, petroleum ether extract	WIRS	Swiss albino mice (20–25 g) and Wistar rats (160–200 g) 500 mg for 3 days Ranitidine (20 mg)	Reduction in ulcer index due to properties that include antisecretory effects, enhanced cytoprotection, and the inhibition of H2 receptors or proton pumps	[137]
<i>Olea europaea</i>	Leaf ethanolic extract	CRS	Male Wistar rats (180–220 g) 40, 80 and 120 mg 30 min before stress induction Ranitidine (50 mg)	The treatment substantially reduced gastric mucosal lesions and various histopathological changes, including congestion, hemorrhage, edema, necrosis, and inflammation, while also decreasing the number of erosions and ulcers, as well as MDA and SOD activity.	[138]
<i>Eugenia umbelliflora</i>	Leaves and fruits methanolic extract	HRS	Male Balb-C mice (20–22 g) 50, 125 and 250 mg 30 min before stress induction Cimetidine (100 mg)	Significant reduction of the lesions, enhanced gastric mucosal defensive factor	[139]
<i>Baccharis dracunculifolia</i>	Leaves essential Oil extraction by hydro-distillation technique	WIRS	Male Wistar rats (200–250 g) 50, 250 and 500 mg 30 min before the induction Cimetidine (100 mg)	The treatment led to a notable reduction in lesion index, total lesion area, and percentage of lesions, while also decreasing gastric juice volume and total acidity, and significantly increasing gastric pH	[140]

-	Saikokaryukotsuboreito	WIRS	Male Wistar rats (300–350 g) 100, 300, or 1000 mg/kg	Repeated administration of SRBT effectively enhanced anxiety levels associated with chronic stress	[141]
-	CHGZT extract suspension	WIRS	Male Wistar rats (260–280 g) 50, 250 and 500 mg before 2 or 4 h stress induction Diazepam (10 mg)	Effectively halts the progression of gastric mucosal lesions	[142]
<i>Zanthoxylum rhoifolium</i>	Stem barks ethanolic extract	HRS	Wistar rats (180–240 g) 125, 250 and 500 mg for 4 h Cimetidine (100 mg)	Inhibition of stomach lesions, nitric oxide release, K channel opening, nonprotein sulfhydryl groups involvement, CAT, and a rise in mucus secretion	[143]
<i>Aphanmixis polystachya</i>	Barks methanolic and aqueous extract	Cold Water Immersion stress (CWIS)	Wistar rats (200 g) 200 mg Pantoprazole (4 mg - i.p)	Reduction in the ulcer index	[144]
<i>Elaeis guineensis</i>	Palm vitamin E	WIRS	Male Sprague Dawley rats (200–250 g) 60 mg for 28 days before induction α -tocopherol (60 mg)	Reduced gastric lesions significantly, reduced plasma adrenalin and noradrenalin significantly	[145]
<i>Ocimum suave</i>	Leaf aqueous extract	CRS	Male Wistar rats (160–200 g) 250–500 mg for 14-day Sucralfate (200 mg)	Decreased levels of reduced glutathione, increased SOD and CAT	[146]
<i>Ficus religiosa</i>	Leaf ethanolic extract	CWIS	Wistar rats (180–200 g) and male albino mice (20–25 g) 250 and 500 mg before stress induction Ranitidine (50 mg)	There is a notable reduction in ulcer formation, no gastric secretion produced, and a significant decrease in gastric lesions	[147]
-	Curcumin	WIRS	Male Sprague Dawley rats (200–250 g) 20 mg for 7 days before stress induction Ursodeoxycholic Acid (30 mg)	Alteration in the histopathological characteristics, along with a suppression of H ⁺ , K ⁺ -ATPase mRNA expression	[148]
<i>Ladies Finger</i>	Seed aqueous and methanolic extracts	FST	Male Swiss albino mice (22±2 g) 200 mg for 7 days before stress induction Diazepam (2 mg - i.p)	Reduction in serum levels of glucose, corticosterone, cholesterol, and triglycerides	[149]
-	Fenugreek seeds Oil, ginger plant Oil, Peppermint plant Oil methanolic extract	WIRS	Male albino rats (100–120 gm) FSO - 1.0, 2.0 mL/kg GPO - 3.3, 4.3 mg/100 gm PPO - 0.81, 0.91mg/100 gm Two doses per day respectively 1 h before stress induction Ranitidine (2.7 mg/100 gm)	Ginger and fenugreek oils have demonstrated a strong antioxidant effect, evidenced by increased activities of CAT and SOD, along with reduced levels of MDA	[150]
-	Glutinous rice aqueous extract	WIRS	Male Sprague Dawley rats (230–250 g) 30 to 300 mg 30 min before the induction	Significantly block the lesions at the dose of 100 mg/kg	[151]

(Continued)

Table 1 (Continued).

Plants	Phytochemicals	Stress Models	Animals and Treatment Conditions Along with Std Drug	Key Results	[Ref.]
<i>Citrus sinensis</i>	Hesperidin from dried peel methanolic extract	HRS	Wistar rats (180–250 g) 150 to 450 mg before 1 h stress induction for 7 days Omeprazole (20 mg)	The study observed a significant decrease in total acidity, pH, free acidity, and ulcer index, alongside increased levels of SOD, GSH, and CAT at the highest dose of 450 mg/kg. Additionally, there was an increase in GSH, protein, and mucin, indicating moderate recovery of mucosal damage	[152]
-	Quercetin and triethylene glycol	Foot shock Stress	Male albino mice (20±5 g) 5, 20, 100 and 400 mg/ day for 10 days Fumaric acid (10 mg)	Suppression of transient hyperthermia and Weight loss	[153]
<i>Azadirachta indica</i>	Azadiradione ethanolic extract from seeds	CWRS	Sprague Dawley rats (180–200 g) 20 mg 45 min prior to stress induction Omeprazole (10 mg)	Azadiradione demonstrates strong antiulcer activity by inhibiting H ⁺ K ⁺ -ATPase (proton pump) through its cytoprotective and antisecretory effects	[154]
<i>Cinnamomum tamala</i>	Leaves aqueous extract	WIRS	Adult Wistar albino rats (180±20 g) 100, 200, and 400 mg/day for 7 days Lorazepam (1 mg), Imipramine (10 mg), and <i>W. somnifera</i> (100 mg)	Significant increase in entries made and time spent in open arms, open field ambulation, rearing, activity in center, self-grooming social interaction and decreased in immobility time and significantly decreases the ulcer index	[155]
<i>Fumaria indica</i>	Methanolic extract	Chronic Foot-Shock Stress	Male Charles Foster albino rats (150±10 g) MFI 60, 120 and 240 mg and MMF 1.25, 2.5 and 5 mg/ day; for 21 days <i>W. somnifera</i> root extract (100 mg)	A dose-dependent effect was observed with MFI and MMF treatments, resulting in decreased body weight, reduced ulcer index, lowered plasma corticosterone and IL-1b levels, and increased 5-HT levels in the hypothalamus	[156]
<i>Piper sarmentosum</i>	Leaves methanolic extract	RWIS	Male Wistar rats 500 mg for 28 days Omeprazole (20 mg)	Effects of a treatment that leads to a decrease in stress-induced gastric lesions, reduces gastric acid levels and MDA, while increasing PGE2 and the mRNA levels of COX-1/2	[157]
<i>Parathenium hysterophorus</i>	Leaves aqueous and alcoholic extract	WIRS	Wistar rats (150–200 g) Cimetidine (32mg - i.p)	Extracts inhibited the ulcer index at 71.11 and 87.69% respectively	[158]
<i>Sophora flavescens</i>	Oxymatrine (from root)	RWIS	Sprague Dawley male rats (180–220 g) 30, 60, and 120 mg/day for a week Omeprazole (20 mg)	There was a notable decrease in the lesion size, along with improved pathological characteristics, reduced congestion severity, and decreased tissue inflammation	[159]
-	Fluvoxamine	CRS	Male albino rats (130–150 g) 50 mg/day for 8 days	The study found that stomachs exhibited fewer and smaller ulcers with less severe hyperemia and moderate mucosal injuries, alongside decreased LPO and increased levels of SOD, CAT, and GSH	[160]

<i>Periplaneta americana</i>	Kangfuxin	WIRS	Male Sprague Dawley rats (180–220 g) 2.5, 5 and 10 mL/day Sanjuweitai Granules group (1850 mg/day, i.g) Omeprazole (20 mg/day, i.p)	The treatment reduces gastric ulcer area, enhances the healing of ulcerated tissue, and increases levels of PGE2 by 52% and COX-1 by 30%. It also improves various biochemical markers: MOD (54%), SOD (58%), CAT (39%), and NO (11%), as well as inflammatory markers TNF- α (9%), IL-6 (11%), MMP-9 (54%), and MMP-2 (53%). Additionally, there is an increase in the expression of IGF-1, PTEN, and Akt proteins	[161]
<i>Gynura cusimbua</i>	Leaves aqueous Extract	CWRS	Albino rats (20 \pm 2 g) 500–2000 mg 30 min to 3 h Omeprazole (2 mg)	An aqueous extract lowered the ulcer index significantly at a dosage of 2000 mg/Kg	[162]
<i>Borago officinalis</i>	Methanolic, organic and aqueous extract	WIRS	Male Sprague Dawley rats (235–370 g) 25, 50, 100, 250, and 500 mg 5, 10, 20, 30, and 40 mg stress induction immediate drug administration respectively Omeprazole (20 mg)	Lower the number of stomach ulcers and the severity score	[163]
-	Resveratrol	Electrical foot shock Stress	Mice (20–30 g) 20, 40 and 80 mg for 7 days Fluvoxamine maleate (20 mg)	The study found reduction in immobility time and a decrease in the expression of CRF mRNA in the amygdala	[164]
<i>Nymphaea lotus</i>	Leaf methanol extract	Hypothermic stress	Rats (160–180 g) 200, 400 and 600 mg for 2 weeks Omeprazole (25 mg)	Significantly prevented peptic ulcers in a dose-dependent manner	[165]
<i>Piper sarmentosum</i>	Leaves methanolic extract	WIRS	Male Wistar rats 500 mg for 28 days treatment Omeprazole (20 mg)	Significantly lowered gastric lesion scores, induced gastric MDA levels, reduced gastric SOD activity, mRNA of SOD, iNOS. Significantly reduced TNF- α , IL-1 β , IL-6	[166]
<i>Fridericia chica</i>	Leaves hydroethanolic extract	WRS	Albino mice (25–45 g) 1, 5 and 20 mg 30 min before stress induction Cimetidine (50 mg)	The ulcerated area was reduced by 80.34% at 1 mg. This was due to dependent increased mucus production, activating K ⁺ ATP channels and α 2-adrenoreceptors, triggering the release of PGs, increasing CAT and GSH activities, and lowering MPO activity and MDA levels	[115]
<i>Sterculia coccinea</i>	Jack leaves ethanolic extract	WIRS	Wistar male rats (150–250 g) 50, 100, and 200 mg for 7 days Ranitidine (27 mg)	The administration of the extract led to a reduction in the number of ulcers, ulcer score, ulcer area, and ulcer index.	[167]
<i>Terminalia argentea</i>	Leaves hydroethanolic extract	WRS	Albino Wistar (150–200 g) 2, 10, and 50 mg 30 min before stress induction Cimetidine (100 mg)	Reduced the ulcerated area dose dependently, lowered acid secretion	[168]
-	Ellagic acid	WRS	Male Wistar rats 5 mg, 10 mg, and 20 mg	The treatment resulted in lower ulcer scores and indices in a dose-dependent way, reducing TNF- α , IL-1 β , and MDA levels while increasing PGE1 and GSH. Immunohistochemical analysis showed elevated Nrf2 and HO-1 levels, alongside decreased NF- κ B and COX-2 levels in the groups treated with EA	[169]
-	Wenweishu Granule	WIRS	Male Sprague Dawley rats (200–220 g) 2.0g/kg/d, WWS-M (n=10, 4.0g/kg/d), and WWS-H (n=10, 8.0g/kg/d for 7 days) Ranitidine (0.0315g/kg/d)	The study indicates an improvement in ulcer index, with elevated levels of SOD and GSH-px, alongside reduced levels of inflammatory markers IL-1 β , IL-6, TNF- α , and MDA. Additionally, there is a suppression of phosphorylation in Akt and PI3K proteins	[170]

release in some cases, and modulation of stress-hormone-related endpoints (eg, reduced plasma corticosterone in chronic paradigms)—indicating antioxidant, mucoprotective and HPA-modulating actions.

Water-Immersion Restraint Stress (WIRS / RWIS)

In WIRS (and its rotating variants, RWIS), a broad set of phytochemicals - including *Piper sarmentosum* extracts,¹⁵⁷ *Maytenus robusta*,¹³² *Baccharis dracunculifolia* essential oil,¹⁴⁰ *Borago officinalis* extracts,¹⁶³ *Periplaneta americana* (Kangfuxin)¹⁶¹ (Table 1) consistently reduced ulcer indices and lesion areas, lowered gastric juice acidity, and improved histopathology. Mechanistic readouts across studies showed decreased lipid peroxidation (MDA), increased antioxidant enzyme activities (SOD, CAT, GSH), enhanced PGE₂ and COX-1/2 expression, reduced proinflammatory cytokines (TNF- α , IL-6, IL-1 β) and modulation of PI3K/Akt signaling in some herbal formulas. These patterns indicate that in WIRS models phytochemicals act through combined antioxidant, anti-inflammatory, antisecretory and mucosal-protective mechanisms.

Cold Restraint Stress (CRS) and Cold Water Immersion Stress (CWIS / CWRS)

Plants (Table 1) such as *Solanum nigrum*,¹²⁸ *Ficus glomerata*,¹³³ *Ficus religiosa*,¹⁴⁷ and *Elaeis guineensis* (palm vitamin E)¹⁴⁵ (Table 1) have been evaluated in cold-stress paradigms. Reported effects include dose-dependent inhibition of lesion formation, reductions in mucosal congestion/hemorrhage, and restoration of antioxidant defenses (\uparrow SOD, \uparrow CAT, \downarrow MDA). Some extracts also increased mucus production and attenuated H⁺/K⁺-ATPase activity or expression, suggesting both cytoprotective and antisecretory roles under cold-stress conditions.

Repeated Social Defeat Stress

Repeated social defeat stress (RSDS) is a commonly used model involving a C57BL/6J male mouse (the intruder) that interacts with a larger, aggressive male CD1 mouse for 10 minutes each day over a period of 10 consecutive days. During these interactions, the intruder is typically investigated and attacked by the CD1 mouse, with different resident aggressors introduced on alternating days without removal from their home cage.^{174–177} A standardized combination of *Centella asiatica*, *Echinacea purpurea*, and *Zingiber officinale* effectively prevented behavioral and molecular effects of chronic social defeat stress in mice, including social avoidance, memory issues, and depressive behavior. It increased BDNF/TrkB expression and normalized inflammatory cytokines and pain-related gene expression, highlighting the potential of botanical combinations for stress-related disturbances.¹⁵³ Longer-term stress models evaluating *Fumaria indica*,¹⁵⁶ *Tinospora malabarica*,¹²⁹ and other adaptogenic/anti-stress botanicals reported dose-dependent decreases in ulcer indices, reductions in plasma corticosterone, decreased systemic inflammatory markers (eg, IL-1 β) and sometimes increases in central 5-HT levels, indicating both systemic stress-attenuation and local gastric cytoprotection. These results support utility of certain phytochemicals (Table 1) for chronic stress settings where neuroendocrine dysregulation drives mucosal vulnerability.

Forced Swim Test

The Forced Swim Test (FST) is utilized to assess “depression-like” behavior in animals by placing them in a water-filled cylinder, where, after initially trying to escape, they eventually exhibit a floating or immobile posture.¹⁷⁸ *Cnestis ferruginea* root extract showed strong anti-stress effects in mice and rats, linked to phytochemicals like alkaloids and flavonoids. It was safe at high doses, improved stress test performance, and protected against gastric ulcers.¹³⁰

Acute Electric Foot-Shock Stress

Acute electric foot-shock stress (AEFSS) is induced in a 26 cm \times 21 cm \times 26 cm Plexiglas chamber with a grid floor of stainless steel rods. The method involves delivering 0.6-mA electrical shocks lasting 1 second, with 30-second intervals, for a total duration of 1 hr.¹⁷⁹ Despite the effectiveness of standard regimens, their therapeutic utility is limited by their frequently unavoidable adverse effects. Herbal remedies, on the other hand, have been shown in clinical and experimental research to provide therapeutic benefits for stomach ulcers with fewer adverse effects. Daily oral doses of quercetin and triethylene glycol (TEG) reduced stress-induced hyperthermia and body weight loss in mice. Quercetin had dose-dependent antidepressant effects and additional anxiolytic activity, while both compounds desensitized stress

responses, with quercetin offering broader benefits.¹⁵³ In models that combine psychological/physical stressors (forced swim, foot-shock, electrical shock), compounds such as resveratrol,¹⁶⁴ quercetin and triethylene glycol,¹⁵³ *Cnestis ferruginea*,¹³⁰ and *Fumaria indica*¹⁵⁶ reduced behavioral stress markers and contributed to gastric protection. Reported gastric outcomes include decreased ulcer indices, reduced LPO, and increased SOD/CAT/GSH, while central measures (eg, reduced CRF mRNA in the amygdala with resveratrol) suggest a brain–gut axis modulation that may complement direct mucosal effects.

Models Emphasizing Antisecretory / Proton Pump Effects

Some phytochemicals showed antisecretory activity or direct proton-pump inhibition. Azadiradione (from *Azadirachta indica*)¹⁵⁴ suppressed H⁺/K⁺-ATPase activity or expression; these effects were associated with decreased gastric acidity and marked reduction of lesions in stress models. Such findings highlight that certain plant metabolites can provide both cytoprotective and antisecretory mechanisms—useful when acid hypersecretion contributes to stress ulcers.

Mechanistic Summary Across Models

Across diverse stress models, consistent mechanistic themes emerge (Figure 3): (1) antioxidant actions (↓MDA, ↑SOD/CAT/GSH), (2) anti-inflammatory effects (↓TNF- α , IL-6, IL-1 β ; ↓NF- κ B activation in some reports), (3) enhanced mucosal defenses (↑mucin, ↑PGE₂, ↑NO where appropriate), (4) antisecretory or proton-pump modulation (↓acid, ↓H⁺/K⁺-ATPase), and (5) neuroendocrine modulation in chronic/behavioral models (↓corticosterone/CRF expression). These complementary mechanisms explain the reproducible reduction in ulcer indices and improved histology observed with many phytochemical-rich extracts and isolated compounds.

Conclusion

This review emphasizes that stress-induced gastric ulceration arises from complex neuroendocrine and oxidative interactions that compromise gastric mucosal defense. Phytochemicals derived from medicinal plants provide multi-faceted protection by enhancing prostaglandin synthesis, modulating cytokines, scavenging free radicals, and promoting angiogenesis and mucosal regeneration. Comparative analysis of experimental models reveals consistent cytoprotective patterns among flavonoids, terpenoids, and alkaloids, validating their therapeutic promise. Future studies should prioritize standardized extraction, bioavailability profiling, and molecular docking analyses to identify high-affinity targets. Integration of omics technologies and clinical validation will further translate these insights into effective, low-toxicity therapies. In conclusion, phytochemical-based interventions represent a viable and sustainable avenue for managing stress-related gastric disorders.

Author Contributions

PRS: Conceptualization and Supervision; PRS and PP: Original draft writing; PP, RA, and AS: Visualization (designed the figures and table); AS: Review and editing. AS and RA are Senior Authors. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that no conflicts of interest exist.

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