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Literature Review: The Role of Plant Bioactive Compounds in Gastroprotective Mechanisms in Peptic Ulcers

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ABSTRACT
Peptic ulcer is a gastrointestinal disorder caused by an imbalance between aggressive factors such as gastric acid, pepsin, Helicobacter pylori infection, and the use of NSAIDs—and the protective mechanisms of the gastric mucosa. Phytotherapy, which involves the use of medicinal plants as therapeutic agents, has emerged as a promising alternative approach in the treatment of gastric ulcers. A total of 20 plant species from various families have been reported to possess anti-ulcer activity through the presence of bioactive compounds such as flavonoids, tannins, saponins, and alkaloids. These compounds exert antioxidant, cytoprotective, anti-inflammatory, and antisecretory effects, as well as enhance gastric mucus and prostaglandin secretion. Several plants also exhibit antibacterial properties against H. pylori. With these diverse mechanisms, medicinal plants present a strong potential as safe and effective complementary therapies in the management of peptic ulcer disease.

Keywords: bioactive compound; gastroprotective; peptic ulcer.

INTRODUCTION
Peptic ulcers are lesions resulting from acid exposure of the stomach and duodenum, characterized by discontinuities in the inner lining of the gastrointestinal (GI) tract due to gastric acid secretion or pepsin enzyme activity. If gastric acid production is excessive and mucosal protection mechanisms are compromised, the ulcer may extend to the submucosal or muscularis propria layers (1).

In Indonesia, the prevalence of peptic ulcers is estimated to be between 6% and 15%, with the highest incidence in the 20-50 years age group, and a peak in the 50-60 years age range. Recent data from WHO (2020) noted that peptic ulcers accounted for 2,174 deaths in Indonesia or approximately 0.13% of the total mortality rate, with an age-adjusted mortality rate of 1.22 per 100,000 population, placing Indonesia 42nd in the world in terms of mortality from this disease (2).

Pathogenesis
Peptic ulcers result from an imbalance between aggressive and protective factors in the gastroduodenal mucosa. Aggressive factors include hypersecretion of gastric acid (HCl), enzyme activity of pepsin, bile acids, pancreatic enzymes, Helicobacter pylori infection, alcohol consumption, and use of non-steroidal anti-inflammatory drugs (AINS/NSAIDs). Meanwhile, protective factors include mucus and bicarbonate secretion, optimal mucosal blood flow, and regeneration of gastric epithelial cells. Excessive gastric acid production results from uncontrolled parietal cell activity in secreting HCl via the H^+/K^+ATPase proton pump. This process is exacerbated by histamine and parasympathetic nervous system stimulation. If the mucous layer protecting the mucosa is damaged, gastric acid and pepsin can penetrate deeper, causing irritation, inflammation, and

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ulcer formation. In addition, if the gastric mucosa loses its resistance due to exposure to substances such as salicylates, bile, or mucosal ischemia, reverse diffusion of H^+ ions into the mucosa occurs. This reaction stimulates the release of large amounts of pepsin, increases the levels of Na^+ and plasma proteins in the gastric lumen, and activates the release of histamine. As a result, there is an increase in capillary permeability, edema, bleeding, increased mucosal muscle tone, and venous congestion that further aggravates bleeding (3).

Helicobacter pylori

Helicobacter pylori is a gram-negative bacterium that acts as a major causative agent of chronic gastritis and contributes significantly to the development of peptic ulcers, gastric cancer, and lymphoma of the gastric lymphoid tissue. It causes inflammation by infecting the mucosal lining of the stomach and is closely associated etiologically with duodenal ulcers, gastric ulcers, gastric carcinoma, and mucosa-associated lymphoid tissue lymphoma (4). The role of Helicobacter pylori in the pathogenesis of gastric ulcers is significant, this bacterium produces toxins and enzymes that weaken the mucosal defense system and increase gastrin secretion, which further stimulates excess gastric acid production. In addition, the use of NSAIDs can worsen the condition by directly irritating gastric epithelial cells and inhibiting the synthesis of prostaglandins, which play a role in maintaining mucosal integrity.

Under normal conditions, protective factors are able to protect the gastric mucosa from damage due to exposure to gastric acid and pepsin. However, if the balance between aggressive factors and protective factors is disrupted, mucosal damage will continue and can lead to superficial erosions or ulcerations with a size of ≥5 mm (5). If this irritation persists in the long term, chronic inflammation and recurrent gastric ulcers may occur.

Treatment

Peptic ulcers can be cured or prevented through plant-based approaches or known as phytotherapy (6). Various studies are known to have shown that natural compounds found in herbal plants can cure or prevent gastric ulcers. This literature review aims to collect data on plants that have anti-ulcer activity. The data were categorized based on the active compound and its mechanism.

METHODS

This study employs a literature review (library research) method, wherein data is gathered from a variety of written sources, including scientific journals, theses, books, and other academic documents relevant to the research topic. The process begins with identifying the main topic and determining relevant keywords to guide the search for appropriate sources. Data is then collected by accessing and downloading materials from reputable online databases such as Google Scholar PubMed, MDPI and Elsevier. After gathering the sources, a selection process is carried out to ensure that only credible and relevant materials are used, considering factors such as publication year, journal quality, and alignment with the research focus. The selected literature is then analyzed to identify patterns, comparisons, and significant findings that contribute to the discussion. Finally, information from the various sources is synthesized to develop well-founded arguments, insights, and conclusions related to the subject under study.

Table 1. Plant that have anti-ulcer activity

Family	Genus	Species	Compound	Working mechanism	Reference
Moringaceae	*Moringa*	*Moringa oleifera* L.	Flavonoid	Increases prostaglandins, increases mucosal blood flow,	Indrisari M., *et al* 2023[7]

Family	Genus	Species	Compound	Working mechanism	Reference
				and stimulates mucus synthesis in the gastric mucosa.	
Fabaceae	*Glycyrrhiza*	*Glycyrrhiza glabra* L.	Saponins	Reduces the number and area of lesions in the stomach, the number of mast cells, eosinophil cells in the gastric mucosa and submucosa.	2017
Fabaceae	*Erythrina*	*Erythrina speciosa (ELSE)*	Flavonoids, saponins, and alkaloids	Regulates inflammation in the body. *Erythrina speciosa* (ELSE) is also able to increase the production of HSP70 which is a protective protein from stress and damage.	Fahmi N M., et al. 2020[8]
Zingiberaceae	*Zingiber*	*Zingiber cassumunar* (Roxb.)	Antioxidants from flavonoid and curcuminoid compounds. Other compounds are alkaloids, saponins, tannins, quinones, and steroids/triterpenoids.	Reducing the formation of free radicals in areas of inflammation and other compounds support gastric tissue regeneration through unknown mechanisms.	Yuniarto, A., *et al*. 2017[9]
Zingiberaceae	*Curcuma*	*Curcuma zedoaria* (Christm.) Roscoe	Antioxidants (tannins, saponins, and flavonoids)	Providing a gastroprotective effect prevents oxidative stress, so this antioxidant can prevent damage to the stomach organs caused by free radicals.	Rizqonnisa, A. 2023[10]

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Family	Genus	Species	Compound	Working mechanism	Reference
Zingiberaceae	*Zingiber*	*Zingiber officinale* L.	Gingerol, shogaol, paradol, and zingerone.	Inhibits the enzymes cyclooxygenase (COX) and lipoxygenase (LOX). In addition, saponins in ginger increase the production of protective prostaglandins. Ginger also inhibits excessive gastric acid secretion and has antibacterial activity against Helicobacter pylori.	Ahnafani, MN, *et al.* 2024[11]
Zingiberaceae	*Curcuma*	*Curcuma xanthorrhiza* Roxb.	Xanthorrhizol, curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin), flavonoids, saponins, terpenoids, and essential oils such as β-curcumene, ar-curcumene, and germacrone.	Xanthorrhizol and curcumin work by inhibiting the enzyme cyclooxygenase-2 (COX-2) which plays a role in the production of pro-inflammatory prostaglandins. Flavonoids and curcuminoids act as antioxidants that can neutralize free radicals. Saponins in temulawak function to increase the production of gastric mucus which protects the gastric mucosa from stomach acid irritation. In addition, terpenoids help balance stomach acid levels.	Mukti, LS, & Hermady, U. 2020[12]
Zingiberaceae	*Boesenbergia*	*Boesenbergia rotunda* (L.) Mansf.	Pinostrobin	Has anti H. pylori properties. Pinostrobin also has anti-ulcer effects and also shows cytoprotective effects.	Mukti, LS, & Andriani, R. c2021[13]

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Family	Genus	Species	Compound	Working mechanism	Reference
Zingiberaceae	*Curcuma*	*Curcuma longa* L.	Curcumin and essential oils such as tannins and flavonoids	Plays a role in stimulating Nitric Oxide (NO) so that it can maintain the integrity of the gastric epithelial mucosa by increasing mucus secretion and blood flow to the mucosa.	Shabrina, AF, *et al*. 2024[14]
Zingiberaceae	*Alpine*	*Alpinia galanga* (L.) Willd.	Alkaloids, glycosides, steroids, flavonoids, tannins and polyphenols.	Reduces oxidative stress on the gastric mucosa, and is also able to stimulate the production of gastric mucus.	Johnley IISR, *et al*. 2020[15]
Theaceae	*Camellia*	*Camellia sinensis* (L.) Kuntze	Catechin and contains flavonoid compounds	Polyphenol compounds inhibit Vac-A which plays a role in the survival of H. pylori bacteria in addition to the urease enzyme in the stomach. In addition, green tea is also able to clean free radicals and its catechin content has antibacterial activity on innate pathogenic bacteria.	Omar MS, *et al*. 2020[16]
Asphodelaceae	*Aloe*	*Aloe vera* (L.) Burm.f.	Amino acids, minerals, vitamins and water	Reduces vasoconstriction (narrowing of blood vessels) and can increase capillary perfusion of the gastric mucosa so that it can help heal ulcers.	Justicia OI, *et al*. 2022[17]
Asteraceae	*Vernonia*	*Vernonia amygdalina* Del.	Alkaloids, flavonoids, tannins, terpenoids, saponins and cardiac glycosides	Reducing lipid peroxidation, flavonoid, tannin, alkaloid and saponin content helps neutralize free radicals in the gastric	Adefisayo, MA, *et al*. 2017[18]

Family	Genus	Species	Compound	Working mechanism	Reference
				mucosa and has a cytoprotective effect on the gastric mucosa.	
Asteraceae	*Emilia*	*Emilia sonchifolia* (L.)	Flavonoids, alkaloids, saponins, phenolics, tannins, steroids, and terpenoids.	Neutralizes stomach acid through *acid neutralizing capacity* (ANC) activity.	Divya & Rasheed. 2021[19] Faseela., *et al*. 2023[20]
Asteraceae	*Vernon*	*Vernonia cinerea* (L.) Less.	Alkaloids, flavonoids, tannins, saponins, and glycosides.	Provides a protective effect on the gastric mucosa through antioxidant mechanisms, increasing gastric mucus production, reducing gastric acid secretion, and supporting mucosal protection with possible anti-inflammatory and cell membrane stabilization effects.	Sheelvanth, O., Bhande, R., Ahmed, M.F., & Rao, K.S. 2022[21]
Lamiaceae	*Mentha*	*Mentha piperita* L.	Menthol, menthone, cineole, limonene, isomenthone, menthyl acetate, methofuran, isopulegol, pulegone, and carvone	Antioxidants and protection of the gastric and duodenal mucosa.	Zangeneh, MM, *et al*. 2018[22]
Nymphaeaceae	*Nymphaea*	*Nymphaea alba* L.	Flavonoids, tannins, alkaloids,	Antisecretory through reducing total and *free acidity,* cytoprotective because it acts as an antioxidant from flavonoid	Paharia, AK, & Pandurangan, A. 2020[23]

Family	Genus	Species	Compound	Working mechanism	Reference
			steroids, phenolics and saponins	and phenolic compounds, provides an astringent effect from tannin compounds, and mucosal regeneration as well as reducing edema and bleeding in gastric tissue.	
Amarylli saceae	*Allium*	*Allium sativum* L.	Allin and allicin	Repairing the duodenal mucosa of rats against hemorrhagic lesions (bleeding), increasing protection of the duodenal mucosa, and reducing oxidative stress in the duodenal mucosa Garlic extract also shows cytoprotective activity.	Odiase., *et al*. 2016[24] Kar, N., *et al*. *2017*[25]
Anacardi aceae	*Spondi as*	*Spondias mombin* L.	Polyphenols: Gallic acid	Increases mucosal defense (through increased production of prostaglandins and mucus), reduces acid secretion, and reduces the effects of oxidative damage through antioxidant activity.	Araruna., *et al*. 2021[26]
Euphorbi aceae	*Phyllan thus*	*Phyllanth us emblica* L.	Tannins, alkaloids, phenolic compounds and flavonoids	Increases protective factors including mucus secretion while reducing the release of gastric hydrochloric acid and pepsin. It also has the powerful antioxidant properties of natural vitamin C and supports tissue repair through stimulation of angiogenesis.	Pal, AD 2018[27]

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RESULT AND DISCUSSION

The table above shows 20 herbal plants that have been studied for their anti-ulcer activity. Numerous studies have confirmed that some natural compounds are known to have protective effects against peptic ulcers. Almost every plant in the table has some of the same compounds such as tannins, flavonoids, alkaloids, and saponins. These compounds have benefits as gastroprotective and cytoprotective against gastric ulcers. The gastroprotective mechanism protects the gastric mucosa from damage due to gastric acid, pepsin, and oxidative stress. This protection involves the secretion of bicarbonate to neutralize acid, the role of oxytocin in reducing gastric stress, and the activity of cholinergic, nitrergic, and VIPergic neurons in maintaining mucosal integrity. In addition, activation of the immune system, such as the formation of $CD4^+$ Tissue-Resident Memory T (TRM) cells, and antioxidant regulation by the transcription factor Nuclear factor erythroid 2-related factor 2 (NRF2) (through the enzymes SOD, catalase, and HO-1) also support gastric defense. Activation of the mammalian target of rapamycin complex 1 (mTORC1) pathway due to Helicobacter pylori infection also plays an important role in inflammatory responses that can be controlled in the context of gastroprotection (28).

Tannins have antimicrobial properties that help inhibit H. pylori and form a protective layer on the ulcer area by precipitating microproteins (29). Tannins are phenolic molecules that are antioxidants. In addition, tannins act as anti-inflammatory in various ways including reducing oxygen (O2) synthesis by neutrophils, monocytes and macrophages. Inhibition of oxygen (O2) synthesis reduces the formation of H2O2, which inhibits the production of hypochlorite (HOCl), resulting in a short-term inflammatory reaction as various inflammatory mediators are blocked (30).

Hypochlorous acid or hypochlorite ($HOCl/OCl^-$) is one of the most important Reactive Oxygen Species (ROS) produced endogenously from H2O2 and Cl^- through the catalysis of myeloperoxidase (MPO). Hypochlorous acid is beneficial but can also be harmful. Hypochlorous acid can destroy invasive bacteria as an immune defense system, while HOCl can also cause various diseases due to the pathogenic oxidative stress it causes (31). According to Rochma E. N (32) Flavonoids as gastroprotective have a mechanism of action by reducing histamine and producing prostaglandins as a defense factor for the gastric mucosa. Tannins and flavonoids are phenolic compounds that act as antioxidants to neutralize free radicals (29). Besides having benefits as gastroprotective, flavonoids also have a cytoprotective effect, namely, the ability to protect cells in their body tissues, especially in the stomach. Flavonoids as cytoprotective have a mechanism to increase blood flow to damaged tissues so that it helps the healing process in the injured stomach (33).

According to Alfaridz in Ningsih, et al (34) Flavonoids have three ways of preventing free radicals, namely by breaking down Reactive Oxygen Species (ROS), slowing down ROS production, and regulating or protecting the use of antioxidants. Reactive Oxygen Species (ROS) are reactive oxygen-containing compounds that can easily combine with other molecules to produce new compounds. In general, there are two categories of ROS, namely free radical and nonradical oxygen. Superoxide (O2-) is a common example, there are two categories of ROS, namely free radical and nonradical oxygen. Superoxide (O2-) is an example of a free radical ROS that has one or more unpaired electrons in its outermost orbital, while non-radical ROS are reactive substances that can turn into free radical ROS, for example in peroxide (H2O2) can turn into hydroxyl radicals (HO-). Non-radical ROS do not have unpaired electrons (35). Mitochondrial metabolism is thought to be the main source of ROS but there is ample evidence that humans produce significant amounts of ROS due to a biological enzyme called nicotinamide adenine dinucleotide phosphate (NADPH) oxidation. ROS are highly reactive substances that can

damage healthy cells through several reduction processes. In order for cells to survive ROS must be detoxified (36).

Saponins play a role in activating the protection or protective factors of the mucous membrane. Saponins can help accelerate the healing of gastric ulcers by increasing the formation of type I collagen. Type I collagen is a protein that helps the early stages of peptic ulcer healing. Saponins limit the function of the enzyme cyclooxygenase by catalyzing the conversion of arachidonic acid into endoperoxidase molecules. Inhibiting cyclooxygenase reduces prostaglandin synthesis and TNF-α expression leading to shorter inflammatory reactions and faster recovery (37).

While alkaloids are known to increase gastric pH, thus helping to maintain a balance between aggressive factors and protective factors in preventing and overcoming gastric ulcers (29) besides that alkaloids can also accelerate wound healing and increase gastric mucus production after injury with inducing agents (32). According to Puspitasari, et al in Hasan, et al. (38) Alkaloids function as antioxidants because they contain nitrogen atoms with free electron pairs, which inhibit free radical activity in the body. The gastroprotective properties of alkaloids come from the amine group in their chemical structure, which determines whether the compound is alkaline or basic. This characteristic is based on the presence of electron pairs on the nitrogen. If the functional group adjacent to nitrogen is electron-releasing, such as an alkyl group, the availability of electrons on nitrogen increases, so the compound becomes more basic (39). According to Nikmat in Sari, et al (39) in the presence of nitrogen electron pairs, hydrogen atoms with excess protons get electron donors, which causes the positive and negative charges of the stomach to become neutral. As a result, alkaloid chemicals can reduce acidity in the stomach and increase stomach pH. Studies have also documented cytoprotective effect. The human body has an interrelated antioxidant protection system in which there are cell protection proteins also called cytoprotective proteins that help produce antioxidants (40).

CONCLUSION

Peptic ulcers are gastrointestinal lesions that arise from an imbalance between aggressive factors (such as gastric acid hypersecretion, pepsin activity, Helicobacter pylori infection, and NSAID use) and the protective mechanisms of the gastric mucosa. Phytotherapy, which utilizes medicinal plants as a source of active compounds, offers a promising alternative approach in the management of gastric ulcers.

This review summarizes data from 20 medicinal plant species from various families and concludes that active compounds such as flavonoids, tannins, saponins and alkaloids have gastroprotective potential through various mechanisms. Based on their diverse mechanisms of action and potential effectiveness, these medicinal plants can be used as candidates for safe and effective supporting therapy as an alternative or complement to conventional therapy. However, further research is needed to establish standardized doses, wider clinical trials, and long-term safety evaluations so that phytotherapy therapy can be optimally integrated in the clinical practice of peptic ulcer management.

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