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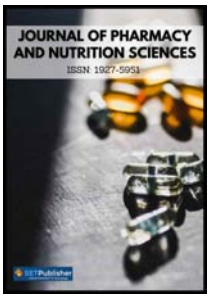

Potential Effect of Medicinal Plants on the Prevention of Gastric Ulcer: Mechanism of Actions

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Abstract:

Medicinal plants have been widely studied to identify plant-based anti-gastric ulcer medicines. The mechanism of gastroprotective action is important to discover the potential lead compounds for drug development. All relevant articles between 2011 and 2021 focusing on Malaysian plants were collected and analyzed to understand the underlying pathways. Keywords include peptic ulcer, gastric ulcer, NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), *Helicobacter pylori*, medicinal plant, gastroprotection, antiulcer, acid secretion, cytoprotective, and digestion processes were applied in the search engines. Twenty-two of the plants had been reported based on the collected data. The review concludes that Malaysian plants could protect the gastric wall against necrotizing agents like ethanol and NSAIDs. This is mainly due to four critical defensive mechanisms: cytoprotective barriers, regulation of heat-shock protein 70 (HSP70) and pro-apoptotic protein (BAX), gastric acid secretion, and antioxidant capability. The mechanisms have been illustrated in the schematic diagrams for better understanding.

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INTRODUCTION

Gastric ulcer, also known as stomach ulcer, is a sore or lesion that develops on the stomach lining resulting from continuous erosion and injury of the stomach wall. It occurs mostly because of infection by the bacterium of *Helicobacter pylori* (*H. pylori*), stress, alcohol consumption, smoking, and long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen sodium [1]. The most common symptoms are pain, nausea, heartburn, appetite change, and breathing problem. If the disease is not treated properly, it can cause bleeding, weight loss, interruption of mucosal integrity, and ultimately peptic ulcer formation. A peptic ulcer is related to a sore inside the stomach lining or the small intestine's upper portion.

Gastric ulcer is a chronic, recurrent disease with a medical challenge [2]. It is a worldwide medical problem with approximately 5 to 10% of development risk in a lifetime [3]. A systematic review conducted in the United States concluded that the annual rate of peptic ulcer bleeding ranged from 19 to 57 cases per 100,000 individuals [4, 5]. The prevalence of gastric ulcers is affected by several factors such as ethnic background, geographical landscape, and occupation [5]. Epidemiological studies have reported that the frequency of gastrointestinal ulcers caused by *H. pylori* varied among different ethnic groups in Malaysia [6]. The lower incidence was found among Malays, about 10-25%, compared to the Chinese, between 35 and 55%, and the Indian population accounted for 50 to 60% [6].

The standard treatment for gastric ulcers is reducing gastric acidity and strengthening the gastric mucosal barrier. The drugs are mainly antacids, proton pump inhibitors, histamine receptor antagonists, as well as antibiotics to inhibit the growth of *H. pylori.* The existing gastric ulcer therapy has limited efficacy and possesses severe side effects such as thrombocytopenia, acute interstitial nephritis, nephrotoxicity, hepatotoxicity, anaphylaxis, gynecomastia, constipation, and diarrhea [7, 8]. Ulcer often recurs even after treatment, which could be due to the ineffectiveness of drug treatment. Therefore, researchers are looking for alternative therapy using medicinal plants. Many medicinal plants have been proven for their gastrointestinal protective and antiulcer property particularly Malaysian herbs. The therapeutic property was mainly attributed to phytochemicals exhibiting remarkable antioxidant activity [9, 10]. Nowadays, many studies have focused on using bioactive compounds from medicinal plants to treat gastric ulcers [11]. The recent review of Beiranvand [12] highlights that gastric ulcer is preventable and treatable, most probably by medicinal plants and their phytochemicals.

Researchers have discovered Malaysian herbs' anti-acid, anti-peptic, gastroprotective, and antiulcer properties for over a decade. The experimental models for antiulcer activity were the cold restraint, stress-induced ulcer model, diclofenac-induced ulcer model in rats, acidified ethanol-induced ulcer in mice, and water immersion stress-induced ulcer in rats. Table **1** lists research outcomes of Malaysian medicinal plants reported for preventing gastric ulcers. The scientific and local names of the registered plants and their parts and the extraction solvents are presented in the table. The ulcer induction model and the ulcer inhibition percentage are also recorded. Each paper has been carefully reviewed to investigate the gastroprotection mechanism contributed by medicinal plants commonly used by indigenous people from Malaysia.

Ethnomedicines have proved that herbal plants have been traditionally used in local therapy for ages to prevent and cure a wide range of diseases, including gastrointestinal ulcers. It has been documented to be complementary and alternative medicine. For instance, *Etlingera elatior* was reported to possess antibacterial properties [13], *Pandanus amaryllifolius* was reported to possess anticancer properties [14], *Acronychia pedunculata* was applied as an anti-inflammatory and analgesic agent [15], *Cassia alata* was used to cure skin diseases [16], and *Hibiscus sabdariffa* Linn had been used for antidiabetic and as a wound healing agent [17]. Malaysian medicinal plants are revered for their gastric protection property and healing capability. This article reviews the plausible mechanism attributed to medicinal plants in gastric protection via cytoprotection, up-regulation of heat-shock protein 70 (HSP70) and down-regulation of pro-apoptotic protein (Bax), balancing acid/bicarbonate secretions, and ability to scavenge free radicals through enzymatic and non-enzymatic antioxidant activities.

DIFFERENT PROTECTIVE MECHANISMS AGAINST GASTRIC ULCER

Based on the data collected from the literature, the underlying mechanism of gastroprotective effects attributed to medicinal plants could be credited to four key defensive factors: cytoprotective, molecular,

Table 1: Gastroprotective Activity and Mechanisms of Malaysian Medicinal Plants from (2011-2021)

Name of plants	Part of plant	Solvent of extraction	Mode of induction (duration)	Type of animal	Antiulcer activity	Cytoprotective / anti-inflammatory activity	Antisecretory protection	Enzymatic antioxidant	Ref.
Phyllanthus niruri (Amin Buah)	Leaf	Ethanol	Absolute ethanol (1.5 h)	Swiss albino rats	10 % at 1000 mg/kg	Inhibited leukocyte infiltration	NT	NT	[59]
Lentinus squarrosulu (Kulat Putih)	Mycelia	Water	Absolute ethanol (0.5 h)	Sprague-Dawley rats	85 % at 200 mg/kg	Inhibitory action on serum TNF-α and IL-1β levels, Inhibition of a neutrophil influx in the gastric mucosa	NT	NT	[60]
Bauhinia purpurea (purple bauhinia)	Leaf	Water	Absolute ethanol and indomethacin using pyloric ligation (1 h)	Sprague-Dawley rats	75.3 % and 39.1 % at 1000 mg/kg after ethanol and indomethacin induction, respectively	Lack of leukocyte infiltration and cellular debris	Reduced pH Increased total acidity without altering the gastric volume	NT	[61]
Boesenbergin A (BA), a chalcone isolated from *Boesenbergia rotunda*	Leaf	Methanol	Ethanol (1 h)	Sprague-Dawley rats	69% at 20 mg/kg	Lowered GSH & MDA, Lowered cytokines (TNF-α and IL-6), Lowered plasma NO level, Increased NP-SH levels, Upregulated HSP and Downregulated iNOS in immunohistochemical and gene expression studies	NT	NT	[24]
Boesenbergia rotunda (fingerroot)	Leaf	Methanol	Ethanol (1 h)	Sprague-Dawley rats	95.22% at 400 mg/kg	Inhibited leukocyte infiltration of stomach wall, Suppression of neutrophil infiltration during inflammation, Enhancing the peptic ulcer healing and inhibitory effects on both COX-1 & -2 enzymes	Increased pH of stomach content	Reduced oxidative stress by lowering MDA level	[58]

(Table 1). Continued.

Name of plants	Part of plant	Solvent of extraction	Mode of induction (duration)	Type of animal	Antiulcer activity	Cytoprotective / anti-inflammatory activity	Antisecretory protection	Enzymatic antioxidant	Ref.
Muntingia calabura (kerukup siam)	Leaf	Methanol	Pylorus ligation (6 h)	Sprague-Dawley rats	7.6% at 500 mg/kg	Raised the amount of mucus secreted by the gastric mucosal cells, Strengthened gastric mucosal barrier	Reduced the volume of gastric secretion and total acidity in the stomach.	Inhibited superoxide dismutase activity.	[62]
Annona muricata (soursop or graviola)	Leaf	Ethyl acetate	Ethanol (1 h)	Sprague-Dawley rats	Inhibited the ulcer lesion index at 400 mg/kg	Suppressed neutrophil infiltration, Inhibited gastric damage from ethanol Increased PGE-2 in the stomach homogenate tissue	Reduced gastric acidity	Cellular antioxidants maintained ROS at their physiological levels to attenuate tissue damage	[28]
Melastoma malabathricum L. (Senduduk)	Leaf	Methanol	Pylorus-ligation (1 h)	Sprague-Dawley rats	54.33 ± 4.82 % at 500 mg/kg	Increased gastric mucus secretion, Enhanced gastric mucosal barrier Modulated nitric oxide and sulphydryl group	Reduced gastric content Increased gastric pH Increased gastric wall mucus Reduced total and free acidity	Enzymatic (SOD, CAT, GTP and myeloperoxidase) and non-enzymatic (anti-lipid peroxidation) antioxidant defense	[29]
Parkia speciose (stink bean)	Leaf	Ethanol	Ethanol (1 h)	Sprague-Dawley rats	95 % 400 mg/kg	Inhibited leukocyte infiltration	Reduced gastric content Increased mucus content	Decreased MDA, Elevated GSH and SOD	[63]
Tabernaemontana divaricata (crepe jasmine)	Flower	Methanol	Aspirin & Ethanol (1 h)	Wistar rats	1.50 ± 0.46 reduction in ulcer index at 500 mg/kg	Elevated NPSH content	Increased mucin content Decrease total protein content in gastric juice	Raised catalase and superoxide dismutase. Declined MDA level Reduced lipid peroxidation (MDA).	[64]
Clausena excavate (Pink Lime-Berry)	Leaf	Methanol	Ethanol (1 h)	Sprague-Dawley rats	87.8% at 400 mg/kg	Decreased mucosal damage Reduced edema and leukocyte infiltration, and epithelial loss.	Increased gastric pH, Increased mucus content	Increased SOD, CAT, and GPx	[65]

(Table 1). Continued.

Name of plants	Part of plant	Solvent of extraction	Mode of induction (duration)	Type of animal	Antiulcer activity	Cytoprotective / anti-inflammatory activity	Antisecretory protection	Enzymatic antioxidant	Ref.
Artocarpus obtusus (Temu tis)	Rhizome	Hexane	Ethanol (1 h)	Sprague-Dawley rats	63% at 400 mg/kg	Suppressed sub-mucosal infiltration,	Increased gastric pH,	Increased SOD level,	[66]
						Increased the NO level	Upregulated Hsp70 protein,	Decreased MDA production	
							Down-regulated Bax protein		
Polygonum chinense (Chinese knotweed)	Leaf	Water	Ethanol (1 h)	Sprague-Dawley rats	87.63% at 500 mg/kg	Inhibited leukocyte infiltration,	Hsp70 protein associated with down-regulation of Bax protein	Increased SOD level,	[67]
						Enhanced mucus secretion from gastric glands		· Decreased MDA concentration	
Polygonum minus (kesum)	Leaf	Ethyl acetate: methanol (1:1 v/v)	Ethanol (1 h)	Sprague-Dawley rats	90.30% at 100 mg/kg	Increased gastric mucus wall production, PGE2 level, level of hexosamin	Raised pH in gastric content	Increased SOD level	[51]
Enicosanthellum pulchrum (King) Heusden	Leaf and stem	Methanol	Ethanol (1 h)	Sprague-Dawley rats	· 65% at 300 mg/kg of stem extract	Reduced lipid peroxidation,	Decreased gastric acid content,	Increased GSH, NO and SOD	[37]
					· 63% at 300 mg/kg of leaf extract	Enhanced PGE2, catalase and protein concentration levels in the gastric tissue homogenate,	Down-regulated Bax protein level		
						Increased gastric mucus			
Cibotium barometz (Golden Hair Dog Fern)	Leaf	Ethanol	Ethanol (1 h)	Sprague-Dawley rats	84.28%	Reduced leukocyte infiltration in gastric wall sections,	Increased in glycoprotein and mucus in the gastric mucosa	Increased cellular antioxidant activities of SOD, CAT & GPx levels,	[33]
						Upregulated HSP70 protein,		Decreased lipid peroxidation	
						Down-regulated Bax protein.			
Arbutin from *Turnera diffusa* (damiana)	Pure compound extracted from damiana	Not available	Ethanol (1 h)	Sprague-Dawley rats	69.1% using Arbutin 60 mg/kg + aspirin	Reduced edema, inflammation and leukocytes infiltration,	Increased pH level and mucus production	Lowered the elevated TBARS level and MDA	[68]
						Modulated the levels of interleukin-6, interleukin-10 and TNF-a			

(Table 1). Continued.

Name of plants	Part of plant	Solvent of extraction	Mode of induction (duration)	Type of animal	Antiulcer activity	Cytoprotective / anti-inflammatory activity	Antisecretory protection	Enzymatic antioxidant	Ref.
Andrographis paniculata (Hempedu Bumi)	Leaf	Water and ethanol	Ethanol (1 h)	Sprague-Dawley rats	100% at 500 mg/kg	Reduced edema, inflammation and leukocyte infiltration	Increased pH level and mucus production	NT	[69]
Murraya koenigii (curry leaves)	Leaf	95% methanol	Ethanol and hydrochloric acid (4 h)	Sprague-Dawley rats	53%	Anti-inflammation	NT	NT	[26]
Berberis vulgaris (barberry)	Leaf	Ethanol	Ethanol (1 h)	Sprague-Dawley rats	50 mg/kg	Reduced macroscopic ulcer score and microscopic lesion index, Increased PGE2 concentration in gastric wall.	Increased pH level	NT	[70]
Leucas Aspera	Leaf	70% methanol	Indomethacin (1 h)	Sprague-Dawley rats	200 mg/kg	Reduced ulcer area and ulcer score	NT	NT	[71]
Momordica charantia L. (bitter melon)	Seed	Hexane	150 mM HCl and 60% ethanol, indomethacin and pylorus-ligation model (3 h)	Sprague-Dawley rats	100 mg/kg of essential oil	Suppressed the formation of edema, epithelial disruption, and mucosa erosions.	Elevated the pH, and mucus, without decreasing the total acidity of gastric juice.	NT	[72]
Centella asiatica (pegaga)	Leaf	75% ethanol	Indomethacin (5 h)	Sprague-Dawley rats	65% at 250 mg/kg	Reduced gastric lesions, Promoted the expansion of mucous gel layer, Decreased the expression of TNF-a, Suppressed the formation of MDA, Inhibited the COX-2 expression	NT	NT	[73]
NT: not tested									

Antisecretory, and antioxidant mechanisms. Each mechanism will be discussed in detail in the following subsections.

Cytoprotective Mechanism

Stomach secrets hydrochloric acid (HCl) to activate pepsin which is necessary to break down macromolecules like proteins into smaller molecules for body absorption without damaging the stomach lining wall [18]. The protection is provided by cytoprotective barriers such as mucus coats and compacted epithelial cell layers that line up the gastric lumen. This is aided by prostaglandin and non-enzymatic molecules (e.g., nitric oxide, NO) in regulating the mucus-bicarbonate and acid secretion. Many medicinal plants from Malaysia offer gastric cryoprotection in different ways, as presented in Table **1**. Interestingly, *P. minus* leaf extract offered the highest antiulcer activity (90.30% at 100 mg/kg) among the collected plant extracts. The key mechanism is the stimulation of mucus production. The gastric mucus is a gel-like substance secreted by mucus cells in the epithelial tissue lining the stomach wall [18]. Gastric mucous plays an essential role as a barrier in guarding the epithelial tissue of the stomach wall from damage by acid and pepsin activity [19]. The mucus layer generates a stable membrane of mucus on the surface of the epithelial layer to neutralize the acid, thus creating a lubricated environment to protect the stomach from any physical damage that may occur during the digestion process and trapping pathogens [19].

The disruption of the mucus layer would expose the stomach to the attack of pathogens, acids, and digestive enzymes, thus causing stomach damage [20]. One of the critical factors in maintaining the mucus layer's thickness is the production of prostaglandin [21]. Prostaglandin is produced when phospholipids in the cell membrane of gastric cells are degraded to arachidonic acid, a precursor of prostaglandin synthesis by phospholipase A2. The arachidonic acid is further degraded with cyclooxygenases (COX-1 and COX-2) to produce prostaglandin G2 (PG2). COX-1 is the constitutive form of cyclooxygenase produced due to a regular physiological stimulus. It performs a wide range of cytoprotective functions in the body, including gastrointestinal cryoprotection. COX-1 plays a vital role in regulating mucus-bicarbonate, acid secretion, and mucosal blood flow. It keeps the mucosal layer flattened and inhibits neutrophil infiltration [21]. COX-2 is the inducible enzyme producing prostaglandin during inflammation and immune responses.

COX-1 and COX-2 transform PG2 to PGH2, PGE2, PGD2, and PGF2 as precursors for prostaglandin synthesis [21]. The most prominent prostaglandin in the gastrointestinal tract is PGE2 which mediates various gastroprotective functions, as illustrated in Figure **1**. Studies have shown that nonsteroidal anti-inflammatory drugs (NSAIDs) and ethanol cause gastric ulcers, mainly due to the inhibition of prostaglandin production [22, 23]. Phenolics as secondary metabolites extracted from plants could enhance prostaglandin synthesis, thus mediating cytoprotective activity in the gastric wall [24, 25]. However, the antiulcerogenic effects of *M. koenigii* leaves were found to be contributed carbazole alkaloids [26]. The mucosal injury exhibited almost 53% inhibition. Even gastric-induced rats were orally administrated as low as 40 mg/kg of alkaloidal extract of *M. koenigii*. A review article also reported the gastroprotective and antiulcer activities of alkaloids in disease-induced animals [5].

Nitric Oxide (NO) is another essential element that plays a vital role in protecting the gastrointestinal tract from the attack of nonsteroidal anti-inflammatory drugs (NSAIDs) and ethanol. NO is synthesized from L-arginine by nitric oxide synthase (NOS) [27]. Several studies on Malaysian plants showed that NO plays a vital role in protecting the stomach wall against ethanol and NSAIDs in experimental animals—plants such as *Annona muricata* [28] and *Melastoma malabathricum* [29]. *Simba ferruginea* [27], *Zanthoxylum rhoifolium* [30], and cinnamon [23] could prevent gastric ulcers against necrotizing agents like ethanol and NSAIDs by enhancing the production of NO. This was because NO in the gastrointestinal tract increased the vasodilation that mediated the gastric blood flow, leading to the maintenance of adequate mucosal blood flow, the suppression of leukocyte-endothelial cell recruitment, and the sustenance of the integrity of gastric mucus and epithelium layer [28].

Up-Regulation of Heat-Shock Protein 70 (HSP70) and Down-Regulation of Pro-Apoptotic Protein BAX

The expression of heat shock proteins (HSPs), particularly HSP70, is important to protect the gastric wall. HSP70 exists in the stomach mucosa. The increased expression of HSP would upregulate the expression of oxidative synthetase. It boosts prostaglandin E2 production, which has a defensive effect on the mucosal layer of the stomach. HSP70 was reported to be a preventative protein to protect the gastric wall from irritant-induced agents. When stomach cells are irritated by ulcer-induction agents like

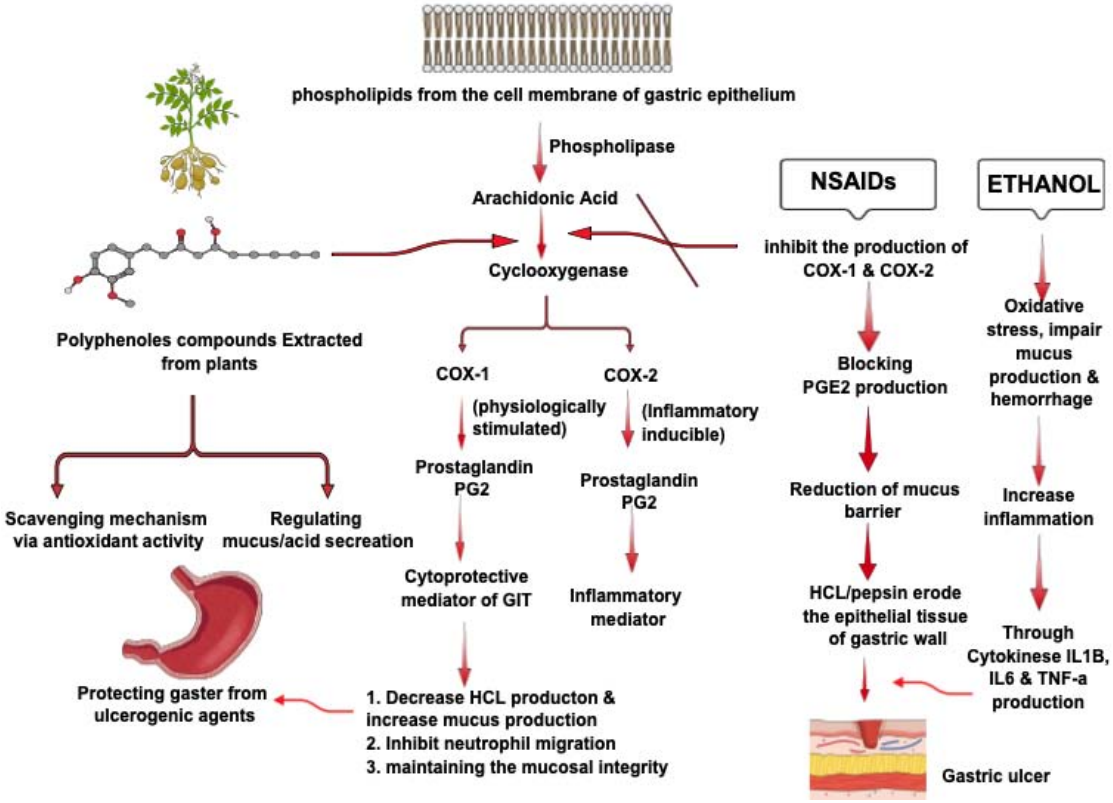

Figure 1: The main pathway of prostaglandin and mucus production in the gastrointestinal tract and how NSAIDs and ethanol are acting as necrotizing agents that cause gastric ulcers. Plants, however, can alleviate the necrotizing effects of NSAIDs and ethanol and enhance the gastric protection activity of the stomach.

ethanol, NSAIDs, and *H. pylori,* HSPs are expressed and induced to resist cells from the irritation [31].

Furthermore, HSP70 is crucial in healing gastric ulcers. The ulcer healing process involves cell proliferation and angiogenesis in margin tissue [32]. HSP70 acts as a molecular chaperone expressed in response to stress. The primary function of Hsp70 is to bind to the protein substrates and stabilize them against denaturation. Research also found that HSP70 mediated cell apoptosis by deactivating protein kinase JNK that inhibited protein Bax, thus reducing cell apoptosis. HSP70 could also reduce the inflammation of gastric mucosa by inhibiting the NF-kB and IL-8 and making IL-8 and NF-kB more effective in preventing the occurrence of chronic atrophic gastritis [32].

On the other hand, Bax is a critical protein from the Bcl-2 family that is linked to apoptosis during mitochondrial damage. Therefore, it has a key role in disrupting the integrity of the stomach mucosal layer [33]. Plants such as *Cibotium barometz* [33], *Annona muricata* [28], and *Vitex pubescent* [34] were found to have protective actions by up-regulation of HSP70 and down-regulation of Bax. The event may prevent the initiation of damage to the gastric epithelium by delaying a stress-induced apoptotic program. This would inhibit the trigger of gastric ulcers and consequently promote healing.

Antisecretory Action of Acid Mechanism

The secretion of HCl from the parietal cells of the lining epithelium of the stomach is essential for digestion [31]. Acid secretion is regulated by the proton pump enzyme (H^+-K^+-ATPase), which is promoted by gastrin, histamine, and acetylcholine, as illustrated in Figure **2**. Gastrin is the gastrointestinal hormone secreted by endocrine G-cells in the gastric pits. It plays a vital role in the process of HCl secretion in two ways. Firstly, gastrin released from the blood vessels activates cholecystokinin2 (CCK2)-receptors on the parietal cells (P-cells) to enhance HCl production. Secondly, gastrin binds to the CCK2 receptors on the enterochromaffin-like cells to stimulate histamine secretion, activating histamine type-2 (H2) receptors on the P-cells to produce HCl. Histamines are the most prominent molecules produced from the spherical endocrine cells called enterochromaffin-like cells (ECL) in the epithelial layer of the stomach. They play a functionally important role in stimulating parietal cells through H2 receptors to

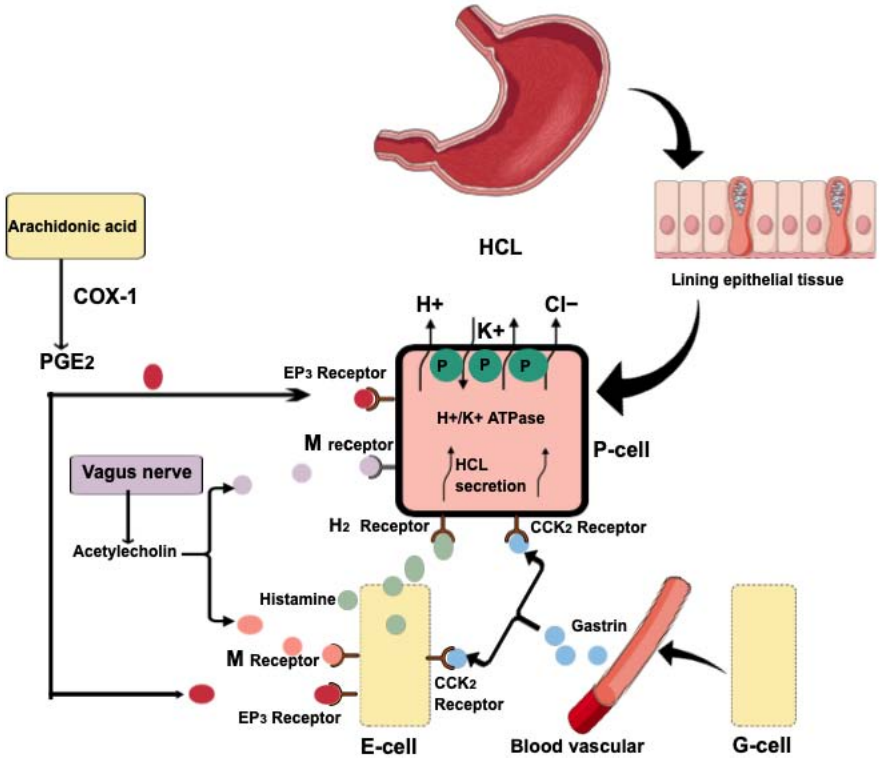

Figure 2: The mechanisms for regulating HCl secretion by P-cell in the epithelium layer of the stomach lining, mediated by GI endocrine hormones (like gastrins and histamines) and a neurotransmitter (acetylcholine). Gastrin released from the blood vessels directly activates CCK2 receptors from the P-cell to enhance HCl production. It indirectly binds to the CCK2--receptors on the enterochromaffin-like cells to stimulate histamine secretion. This leads to the activation of H2 receptors on the P-cell to increase HCl formation. Acetylcholine released by the vagus nerve activates the M-receptor from the P-cell and E-cell to enhance HCl production. P-cell (parietal cell); GI (gastrointestinal); CCK2 (cholecystokinin receptor); E-cell (enterochromaffin-like cell); PGE2 (prostaglandin E2); EP3 (prostaglandin E receptor 3); M Receptor (muscarinic receptor); H2 receptors (histamine receptor) [20, 41].

stimulate HCl production [31]. Histamine secretion is promoted mainly by gastrin and neural mediators through the vagal nerve part of the parasympathetic nervous system by secreting acetylcholine [32]. Acetylcholine is directly involved in gastric acid secretion by activating muscarinic receptors (M-receptors) linked to the parietal cells and indirectly activating histamines released by binding to the M-receptors on the ECL [35].

Plants rich in magnesium and potassium can neutralize acid because they increase and maintain the alkalinity in the gastric lumen [36, 37], which protects the mucosal layer of the stomach lining. Malaysian plants are rich in phenolic compounds that regulate H^+-K^+-ATPase and proton pump enzymes [38, 39]. Additionally, Malaysian plants have been shown to increase prostaglandin production, which in turn blocks parietal cells and enterochromaffin-like cells to inhibit the production of excessive HCl. Isackson & Ashley [40] proved that blocking histamine receptors on the parietal cells leads to a decrease in the production of gastric acid.

Antioxidant Mechanism

Oxidative stress is influential in causing illnesses, including gastric ulcers, resulting from a wide range of human pathogens. NSAIDs, alcohol, and stress are three primary sources disturbing mucosal resistance against free radicals [42-44]. The process of generating free radicals is illustrated in Figure **3**. To eliminate oxidative stress and prevent gastric ulcer formation, Malaysian medicinal plants rich in antioxidant compounds are widely used for gastroprotection and gastric ulcer healing as a traditional remedy. The high antioxidant activity of medicinal plants is mainly due to the presence of phenolic compounds [45, 46] and other plant-derived compounds [47].

Phenolics are the most prominent secondary metabolites or phytochemicals in plants. They have gained public attention as natural antioxidants because of their capacity to act effectively as free radical scavengers and metal chelators [48]. The underlying mechanism of antioxidation attributed to phenolic acids involves the active hydroxyl groups attached to

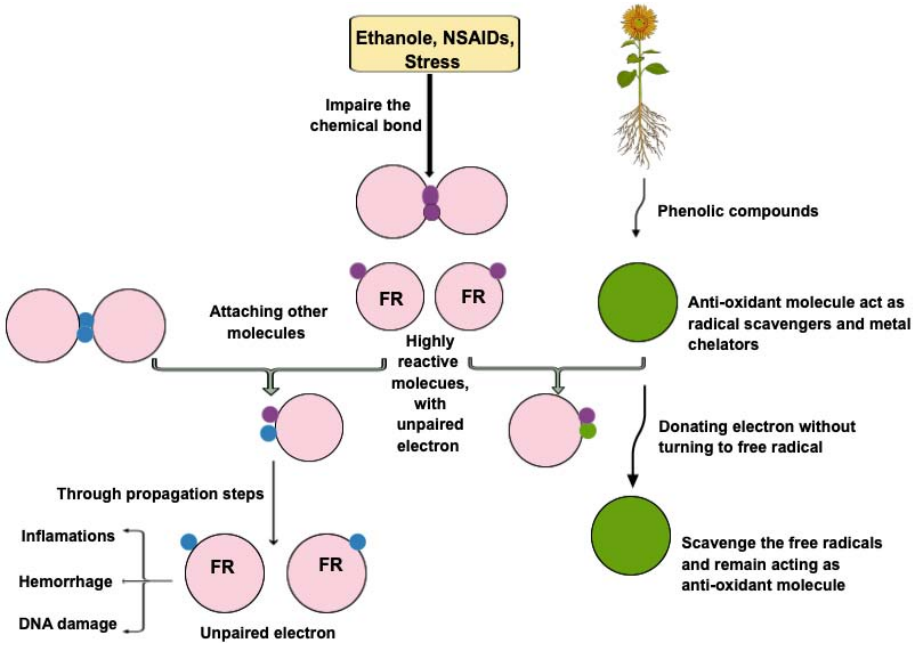

Figure 3: Illustrates the free radical (FR) generation by necrotizing agents like ethanol, NSAIDs, and stress. The scavenging activity of phenolic compounds extracted from plants in terminating FR formation is also depicted.

benzene rings. The hydroxyl groups react with reactive oxygen and nitrogen species to terminate the regeneration of new radicals, as seen in Figure **3** [49]. Phenolic acid also suppresses the formation of free radicals by chelating metallic ions [50]. Additionally, phenolic compounds extracted from medicinal plants have an affinity for intermingling with proteins, including acetylcholinesterase, due to the hydrogen-bonding potential of the hydroxyl groups and the hydrophobic benzenoid rings. The presence of phenolic acids could inhibit enzymes like acetylcholinesterases which involve in radical generation [50].

Table **2** summarizes Malaysian medicinal plants' non-enzymatic antioxidant capacity, total phenolic content, and phytochemicals. Using different assays, plants show high antioxidant capabilities through enzymatic and non-enzymatic reactions. SOD (superoxide dismutase) and CAT (catalase) are the standard enzymatic assays that researchers widely applied. While DPPH (2,2-diphenyl-1-picryl-hydrazine-hydrate), FRAP (Ferric reducing antioxidant power assay), and TBARS (Thiobarbituric acid reactive substance) are the most commonly used non-enzymatic protocols to measure the antioxidant activity of plants. The results showed that plants rich in phenolic acids have high antioxidant abilities with a low ulcer index. A positive correlation was established between antioxidants, phenolic contents, and antiulcer activity in the selected Malaysian plants [51, 52]. That was supported by other studies using plants that originated from other regions. The antioxidative Zerumbone extracted from *Zingiber zerumbet* provided gastroprotection by maintaining mucus integrity and up-regulation of HSP-70 [10]. Gallic acid extracted from several plants promoted gastroprotection against ethanol-induced gastric ulcers in rats through the antioxidant, Nrf2/HO-1 signaling, and anti-apoptosis mechanism by regulating Bax, Bcl-2, and Caspase-3 [53]. Hiruma-Lima *et al*. [54] suggested that flavonoid glycosides, the main antioxidant compounds isolated from *Alchornea castaneaefolia*, were responsible for antiulcer activity against the HCl/ethanol-induced ulcer model. The active antioxidant compound, Carlina oxide, played an essential role in the gastroprotective activity of *Carlina centifolia* against absolute ethanol-induced gastric ulcers. Studies suggested that the antiulcer activity of *Bauhinia purpurea* aqueous leaf extract was attributed to the antioxidant activity of saponins or sugar-free polyphenol compounds [55. 56]. Gallic acid, the main antioxidant compound of *Zingiber officinale*, has been proven to contribute to ulcer prevention activity against HCl/ethanol-induced ulcer model [57]. Furthermore, Abdelwahab *et al*. [58] showed that the mechanism of antiulcer activity of *Boesenbergia rotunda* L. was related to the antioxidant activity rather than nitric oxide and COX pathways.

CONCLUSION

Based on the data collected from the literature, we conclude that the twenty-two studied Malaysian plants

Table 2: Non-Enzymatic Antioxidant Capacity, Total Phenolic Content and Phytochemicals in Malaysian Medicinal Plants

Scientific and common name of plants	Non-enzymatic antioxidant capacity	Total phenolic content (mg GAE/g)	Phytochemical screening	Reference
Phyllanthus niruri (Amin Buah)	PDF: IC_{50}= 6.85 ± 1.80 µmol L^{-1}	NT	Quercetin 3-O-glucoside, catechin, quercetin 3-O-α-rhamnoside, epicatechin, rutin, chlorogenic acid (5-O-caffeoyl quinic acid), gallic acid, ellagic acid, corilagin (galloyl HHDP hexoside), apigenin, geraniin (hemiacacetal forms), ellagitannin, malic acid, quinic acid, caffeic acid, phyllanthin, and hypophyllanthin	[74,75]
Lentinus squarrosulus (Kulat Putih)	PDF: 94.7 %	Positive	NT	[76]
Bauhinia purpurea (Purple Bauhinia)	DPPH: 57.7 ± 0.1 % at 500 mg/mL	25.707	Saponins, flavonoid glycosides and high polyphenolic compounds	[55,77,78]
Muntingia calabura L. (*A*skerukup Siam)	DPPH: 266.67 ± 3.09 µmol TE/g	22.28 ± 0.10	Flavonoids, tannins, polyphenols, saponins, steroids and triterpenes	[79]
Boesenbergia rotunda (*F*ingerroot)	DPPH: 4.29 ± 0.55 mg ascorbic acid equivalent/g	6.19 ± 0.39	Five secondary metabolites consisted of three flavanones (pinostrobin, pinocembrin and alpi-netin) and two chalcones (panduratin and cardamon)	[80,81]
Annona muricata L. (Soursop and Graviola)	PDF: 90.8 %	46.96 mg GAE/mL	Acetogenins, alkaloids, phenols, terpenoids, tannins and flavonoids	[82;83]
Melastoma malabathricum L. (*S*enduduk)	DPPH: IC_{50} = 692 µg/mL	671.51 ± 50.07	Two amides (auranamide and patriscabratine), triterpene (α-amyrin), and three flavonoids (quercitrin, quercetin and kaempferol-3-O-(2″,6″-di-O-p-trans-coumaroyl)-β-glucoside	[84,85]
Parkia speciose (Stink bean)	DPPH: 66.3 ± 4.9 %; IC50 = 86.7 ± 5.80 mg/mL	26.3	Phenolic acids, flavonoids, alkaloids, saponins, terpenoids, cyclic polysulfides and tannins	[86,87]
Tabernaemontana divaricata (Crepe jasmine)	NT	NT	Tocopherol, cycloartenol, docosane, eicosane, ergost-5-en-ol, ibogaine-18-carboxylic acid 12-methoxy-methyl ester, 9-octadecenoic acid, 11-octadecenoic acid methyl ester, 9,12-octadecadienoic acid, palmitic acid, squalene, stigmasterol, tetracosane and urs-12-en-24-oic acid 3-oxo methyl ester	[64]
Corchorus olitorius (Jute)	NT	NT	Six phenolic antioxidative compounds (5-caffeoylquinic acid/chlorogenic acid, 3,5-dicaffeoylquinic acid, quercetin 3-galactoside, quercetin 3-glucoside, quercetin 3-(6-malonylglucoside), and quercetin 3-(6-malonylgalactoside)	[88]
Clausena excavata (Pink lime-berry)	PDF: > 80 %	522.0 ± 11.6	Quercetin-rhamnose- hexose-rhamnose, myricetin glucoside conjugate, myricetin 3-O-rhamnosyl-glucoside 7-O-rhamnoside, kaempferol conjugate caffeic acid, 8-geranyloxy psoralen, furocoumarin, flavonoids, and phenolic acid	[89]
Polygonum chinense (Chinese knotweed)	NT	NT	Triterpene compound–squalene, and a plasticizer compound–1,2-benzene dicarboxylic acid, mono[2-ethylhexyl] ester. [90]	[90]
Enicosanthellum pulchrum (King Heusden)	DPPH: 60.4 ± 0.02 %	NT	Cinnamic acid, aporphine alkaloids liridine and lysicamine	[91,92]
Polygonum minus (Kesum)	DPPH: 89.5 ± 1.07 %; IC_{50} = 430.0 ± 0.04 mg/mL (bark); IC50 = 640.0 ± 0.05 mg/mL (twig)	207 ± 0.011	Gallic acid, rutin, coumaric acid and quercetin	[51,93]
*Cibotium barometz (*Golden hair dog fern)	FRAP: 35.1 mmol FeSO4 equivalents/mg sample	0.37−266.00	1-nonadecene, Z-5-nonadecene, octacosanol, and 1-tetracosanol/1-heneicosanol	[94]
Andrographis paniculata (Hempedu Bumi)	DPPH: IC_{50} = 10.9 mg/mL	NT	Andrographolide	[69,95]
NT: not tested				

significantly revealed a wide range of gastroprotection capabilities. The mechanism of gastric protection could occur via four possible pathways; cytoprotection, HSP70 upregulation and pro-apoptotic protein Bax downregulation, inhibition of acid secretion, and antioxidation. Most of the plants showed high enzymatic and non-enzymatic antioxidant activities. The alkaline property of phenolic compounds plays a crucial role in attenuating and regulating gastric mucus and acid secretion, which are mediated by prostaglandins, gastrin, histamine, and the gastrointestinal neurotransmitter acetylcholine. Although gastroprotective mechanisms have been reported, future studies are highly recommended to identify the complex function of bioactive compounds in gastric protection.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing does not apply to this article because no new data were created or analyzed in this study.

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