



## A COMPREHENSIVE SYSTEMATIC REVIEW ON THE GASTROPROTECTIVE POTENTIAL AND MECHANISM OF ACTION OF LIMONIA ACIDISSIMA IN PEPTIC ULCER DISEASE

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### ABSTRACT

**Background:** Peptic Ulcer Disease (PUD) remains a significant global health burden, driven primarily by *Helicobacter pylori* infections and the widespread use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). While synthetic treatments like Proton Pump Inhibitors (PPIs) are effective, their long-term use is limited by adverse effects and rising antibiotic resistance. *Limonia acidissima* L. (Wood Apple), a plant deeply rooted in Ayurvedic medicine, has emerged as a promising phytotherapeutic candidate for gastroprotection.

**Objective:** This systematic review aims to evaluate the phytochemical profile, pharmacological mechanisms, and safety of *L. acidissima* in the management of PUD. **Methods:** The review analyzes evidence from diverse experimental models, including ethanol, indomethacin, and pylorus ligation-induced ulcers in Wistar rats. It explores the synergistic role of secondary metabolites such as coumarins (luvanetin,

marmesin), flavonoids, and tannins. **Results:** The findings reveal a "three-pronged" mechanism of action

1. Anti-secretory: Significant reduction in gastric acid volume and inhibition of the H<sup>+</sup>/K<sup>+</sup> ATPase pump.

2. Cytoprotective: Enhancement of the gastric mucus-bicarbonate barrier and physical shielding of the mucosa.
3. Antioxidant: Neutralization of Reactive Oxygen Species (ROS) and restoration of endogenous enzymes (SOD, Catalase, and GSH).

Experimental data demonstrate that doses of 400–500 mg/kg achieve an ulcer protection rate (up to 81.0%) comparable to the standard drug Ranitidine. Safety profiles indicate the extract is non-toxic at doses up to 4000 mg/kg. **Conclusion:** *L. acidissima* offers a multi-targeted approach to gastroprotection, addressing the imbalance between aggressive and defensive factors. Beyond its therapeutic efficacy, its natural gums and mucilage present significant potential for Novel Drug Delivery Systems (NDDS). While preclinical evidence is robust, further human clinical trials are essential to standardize dosages and integrate this ethnomedicinal resource into modern gastroenterology.

**KEYWORDS:** *Limonia acidissima*, Peptic Ulcer Disease, Gastroprotection, Luvangetin, Phytotherapy, Antioxidant, H<sup>+</sup>/K<sup>+</sup> ATPase.

## INTRODUCTION

Peptic ulcer disease (PUD) is a chronic gastrointestinal disorder characterized by mucosal lesions in the stomach or duodenum, typically arising from an imbalance between protective defenses and aggressive factors like *H. pylori* or NSAID use.<sup>[1]</sup> While conventional treatments such as proton pump inhibitors are highly effective, their long-term administration is increasingly associated with adverse systemic effects and rising antibiotic resistance.<sup>[2]</sup> This has sparked a shift toward phytotherapeutics like *Limonia acidissima*, a traditional medicinal plant valued for its multi-targeted antioxidant and cytoprotective properties.<sup>[2]</sup> By synthesizing data from 2017 to 2025, this study aims to scientifically validate the efficacy of *L. acidissima* as a safer, bioactive alternative for the management of ulcerogenesis.<sup>[3]</sup>

### 1.1 Overview of Peptic Ulcer Disease (PUD)

Peptic ulcer disease (PUD) is a chronic and often debilitating gastrointestinal disorder characterized by the development of open sores or lesions on the inner lining of the stomach (gastric ulcers) or the upper portion of the small intestine (duodenal ulcers).<sup>[1]</sup> These ulcerations occur when the mucosal integrity is compromised, extending beyond the muscularis mucosae and penetrating the deeper layers of the gastrointestinal wall, often accompanied by significant inflammatory responses.<sup>[2]</sup> Historically, PUD was perceived as a condition primarily driven by stress and dietary choices; however, the paradigm shifted

dramatically following the identification of *Helicobacter pylori* and the widespread clinical use of non-steroidal anti-inflammatory drugs (NSAIDs).<sup>[3]</sup>

Epidemiologically, PUD remains a global health concern with a lifetime prevalence estimated between 5% and 10%.<sup>[1]</sup> While the global incidence and mortality rates have shown a declining trend over the last few decades—attributed to improved sanitation, the advent of proton pump inhibitors (PPIs), and effective *H. pylori* eradication therapies—the disease still accounts for thousands of deaths annually and a substantial burden of hospitalizations. Recent studies indicate that while age-standardized rates are falling, the absolute number of cases remains high due to aging populations and the continued prevalence of risk factors such as tobacco use, excessive alcohol consumption, and psychological stress.<sup>[2]</sup>

## 1.2 Pathophysiology of Ulcerogenesis

The formation of a peptic ulcer is the physiological manifestation of a fundamental imbalance between aggressive factors that erode the mucosal lining and protective factors that maintain its integrity.<sup>[1]</sup> Aggressive factors include endogenous elements such as gastric acid and pepsin, as well as exogenous stressors like *H. pylori* infection, alcohol, and NSAIDs.<sup>[2]</sup> The mucosal defense system, conversely, operates through a multi-layered hierarchy: the pre-epithelial layer (mucus-bicarbonate barrier), the epithelial layer (tight junctions and rapid cellular regeneration), and the sub-epithelial layer (mucosal blood flow and prostaglandin synthesis).<sup>[2]</sup>

### 1.2.1 Role of *Helicobacter pylori*

*Helicobacter pylori* is a gram-negative, microaerophilic, spiral-shaped bacterium that has co-evolved with humans to colonize the hostile environment of the stomach.<sup>[3]</sup> It is responsible for approximately 42% to 50% of PUD cases globally. The survival of *H. pylori* in highly acidic gastric juice is facilitated by its secretion of the enzyme urease, which hydrolyzes urea into ammonia and carbon dioxide, thereby neutralizing the immediate microenvironment around the bacterium.<sup>[4,5]</sup>

The pathogenesis involves several stages. Initially, the bacterium uses its flagella to navigate through the viscous mucus layer to reach the epithelial surface.<sup>[3]</sup> Once attached, it releases virulence factors like CagA and VacA, which induce a robust inflammatory response characterized by the recruitment of neutrophils and macrophages.<sup>[3]</sup> This chronic inflammation leads to epithelial cell degeneration, disruption of the mucosal barrier, and

alterations in gastric physiology, such as hypergastrinemia, which further increases acid production and predisposes the tissue to ulceration, particularly in the duodenum.<sup>[2]</sup>

### 1.2.2 Impact of NSAIDs and Ethanol

NSAIDs are a major cause of gastric injury, implicated in roughly 36% of all peptic ulcers.<sup>[5]</sup> Their destructive impact is mediated through two primary mechanisms: topical injury and systemic prostaglandin depletion.<sup>[4]</sup> Topically, NSAIDs—which are often weak acids—remain non-ionized in the acidic gastric lumen, allowing them to traverse the lipid membranes of epithelial cells. Once inside the neutral environment of the cytoplasm, they ionize and become "trapped," causing mitochondrial dysfunction and oxidative phosphorylation uncoupling, which leads to direct cellular necrosis.<sup>[6,7]</sup> Systemically, the inhibition of cyclooxygenase-1 (COX-1) prevents the synthesis of prostaglandins, which are essential for stimulating bicarbonate secretion and maintaining mucosal blood flow.<sup>[4]</sup>

Ethanol exposure acts as a potent chemical irritant that rapidly penetrates the gastric mucosa, causing dehydration and direct dissolution of the protective mucus layer. Ethanol-induced damage is characterized by extensive hemorrhagic lesions, epithelial exfoliation, and a massive surge in reactive oxygen species (ROS).<sup>[5,6]</sup> This model is frequently utilized in pharmacological research to evaluate the antioxidant and cytoprotective properties of herbal extracts, as it mimics acute clinical gastritis and gastric mucosal injury.<sup>[6,8]</sup>

**Table 1.1: Pathogenesis of Gastric Ulceration.**

| Aggressive Factor | Mechanism of Action                      | Resulting Mucosal Damage                       |
|-------------------|------------------------------------------|------------------------------------------------|
| <i>H. pylori</i>  | Urease production and cytokine induction | Chronic inflammation and barrier disruption    |
| NSAIDs            | COX-1 inhibition and ion trapping        | Reduced blood flow and direct epithelial death |
| Ethanol           | Mucus dissolution and oxidative stress   | Acute hemorrhage and lipid peroxidation        |
| Gastric Acid      | Proteolytic activation of pepsin         | Erosion of the muscularis mucosae              |

### 1.3 Botanical Profile of *Limonia acidissima*

*Limonia acidissima* L. (synonyms: *Feronia limonia*, *Feronia elephantum*), belonging to the family Rutaceae, is a medium-sized, slow-growing, deciduous tree native to the arid and semi-arid regions of India and Sri Lanka.<sup>[8,9]</sup> Commonly known as "wood apple," "elephant apple," or "kaitha," it is one of the hardiest fruit crops, capable of thriving in light soils and

monsoon climates with distinct dry seasons.<sup>[10]</sup> The tree typically reaches a height of 9 meters and features rough, spiny bark with axillary spines.

Botanically, the leaves are alternate, dark green, and leathery, containing 5–7 leaflets that emit a citrus fragrance when crushed.<sup>[11]</sup> The fruit is a globose berry with a hard, woody, greyish-white rind that is approximately 6 mm thick. Inside, the pulp is aromatic, sticky, and brown, containing numerous white seeds.<sup>[11]</sup> Ethnomedicinal records indicate that every part of the tree—including the leaves, bark, roots, seeds, and fruit pulp—has been utilized for centuries in Ayurvedic and Siddha medicine for treating conditions ranging from indigestion and dysentery to snakebites and respiratory ailments.<sup>[11]</sup>

#### 1.4 The Shift to Phytotherapeutics

The global healthcare landscape is witnessing a renewed interest in phytotherapy, driven by the limitations of conventional pharmacological treatments and the rich therapeutic potential of bioactive plant compounds.<sup>[12]</sup> Current gold-standard treatments for PUD include PPIs (e.g., omeprazole, pantoprazole) and receptor antagonists; however, while these are highly effective in the short term, chronic administration is associated with significant adverse effects.<sup>[13]</sup> Long-term PPI use has been linked to an increased risk of bone fractures, chronic kidney disease, and various nutritional deficiencies, while rising antibiotic resistance in *H. pylori* strains often leads to treatment failure.<sup>[14]</sup>

Natural agents such as *L. acidissima* offer a multitargeted approach to gastroprotection, providing antioxidant, anti-inflammatory, and cytoprotective benefits simultaneously through a synergy of bioactive molecules.<sup>[15]</sup> Furthermore, plant-derived medicines are generally more cost-effective, culturally acceptable, and possess a lower profile of systemic toxicity, making them suitable for the long-term management of chronic gastrointestinal conditions.<sup>[16]</sup>

#### 1.5 Rationale and Objectives of the Study

The rationale for this systematic review lies in the need to scientifically validate the traditional claims surrounding *L. acidissima* using modern pharmacological criteria. Although the wood apple is a well-known ethnomedicinal plant, research on its specific mechanisms of action in PUD remains fragmented. By synthesizing data, this study aims to

1. Establish a comprehensive phytochemical profile of the plant parts used in ulcer management.

2. Elucidate the pharmacological mechanisms—specifically the anti-secretory, cytoprotective, and antioxidant pathways—of *L. acidissima*.
3. Analyze the safety and efficacy of the extract through experimental and histopathological data.
4. Explore future directions, including novel drug delivery systems utilizing the plant's unique gum and mucilage.

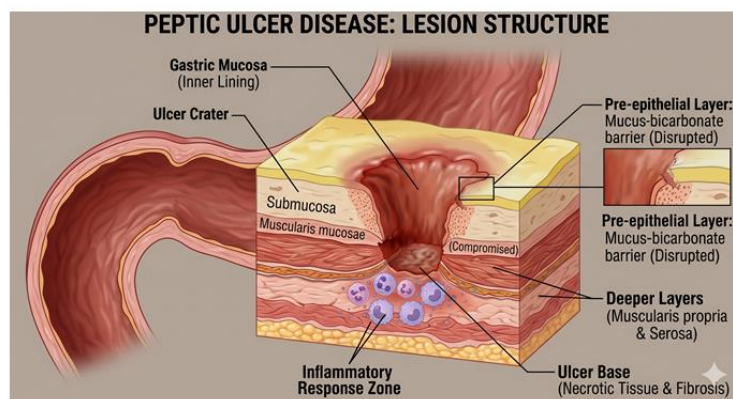


Fig. 1.1: Peptic Ulcer Disease.

## Phytochemistry: The Bioactive Interface

### 2.1 Qualitative Phytochemical Screening: Overview

The medicinal potency of *Limonia acidissima* is a direct consequence of its rich and complex secondary metabolism.<sup>[18]</sup> Qualitative screening using sequential extraction methods (petroleum ether, methanol, ethanol, and aqueous) has confirmed the presence of alkaloids, flavonoids, steroids, saponins, glycosides, phenols, tannins, and gums across various plant tissues.<sup>[19]</sup> These phytochemicals serve as the bioactive interface between the plant extract and the mammalian gastrointestinal environment.<sup>[20]</sup>

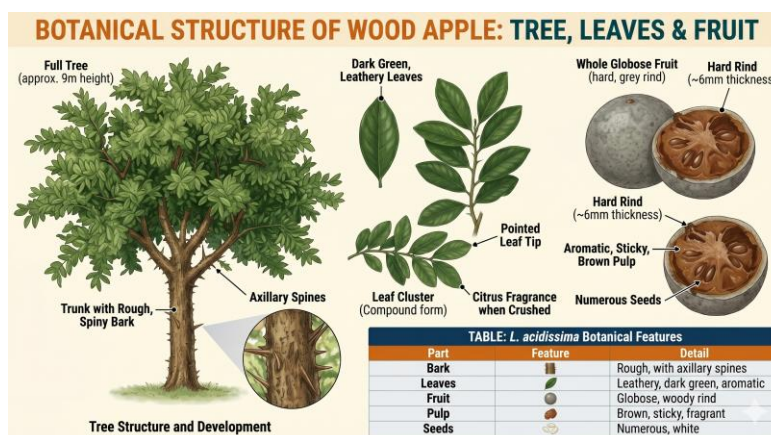


Fig. 1.2: Botanical Structure of Wood Apple.

**Table 2.1: Phytochemical Profile of Various Plant Parts.**

| Plant Part | Primary Metabolites               | Secondary Metabolites                            |
|------------|-----------------------------------|--------------------------------------------------|
| Leaves     | Proteins, Lipids, Carbohydrates   | Tannins, Flavonoids, Coumarins, Saponins         |
| Fruit Pulp | Vitamins (A, B, C), Pectin, Fiber | Phenolic acids, Tyramine derivatives, Flavonoids |
| Bark       | Gums, Resins                      | Marmesin, Bergapten, Luvangetin                  |
| Seeds      | Fixed Oils (Oleic, Linoleic)      | Vitexin, Saponarin, Orientin                     |

In the leaves, the highest concentrations of lipids and proteins are found, while the stem and bark are rich in starch and phenolic compounds.<sup>[29]</sup> The fruit pulp is notably high in pectin (16% on a dry weight basis) and  $\beta$ -carotene, providing a nutritional basis for its gastroprotective use.<sup>[28]</sup>

## 2.2 Primary Bioactive Coumarins

Coumarins are benzopyrone derivatives abundant in the Rutaceae family and are credited with significant anti-inflammatory and anti-secretory activities.<sup>[20]</sup> In *L. acidissima*, these compounds, alongside unique limonoids, are primarily concentrated in the bark and leaves.<sup>[20]</sup>

### 2.2.1 Luvangetin

Luvangetin is a pyranocoumarin known for its potent gastroprotective effects.<sup>[19]</sup> Research into its mechanism suggests it interferes with aggressive factors of ulcerogenesis by potentially inhibiting pathways that lead to acid hypersecretion, while its lipophilic nature helps stabilize the epithelial layer against chemical irritants.<sup>[21]</sup>

### 2.2.2 Marmesin

Marmesin, a furanocoumarin, acts as a primary anti-inflammatory agent.<sup>[20]</sup> It has been shown to exhibit strong binding affinities with inflammatory mediators, thereby reducing the recruitment of neutrophils to the gastric wall.<sup>[21]</sup> By suppressing the inflammatory cascade, marmesin prevents the transformation of superficial mucosal erosions into deep, chronic ulcers.<sup>[21]</sup>

## 2.3 Phenolic Compounds: Tannins and Flavonoids

Phenolic compounds represent the bedrock of the wood apple's antioxidant capacity, playing a crucial role in neutralizing gastric oxidative stress.<sup>[22]</sup> Flavonoids such as luteolin and quercetin are prevalent in the fruit pulp and have been identified as major drivers of free radical scavenging activity.<sup>[22]</sup> These molecules contain multiple hydroxyl groups that donate electrons to stabilize reactive oxygen species (ROS), thereby protecting the gastric mucosa from oxidative stress-induced apoptosis.<sup>[22]</sup>

Tannins, found abundantly in the leaves and unripe fruit, provide a unique physical mode of protection through their ethnomedicinal and pharmacological properties.<sup>[23]</sup> Due to their astringent nature, tannins possess the ability to precipitate mucosal proteins, creating a "protective pellicle" or a chemical bandage over the gastric lining.<sup>[23]</sup> This barrier physically shields the tissue from the proteolytic action of pepsin and the corrosive effects of gastric acid, facilitating the healing process.<sup>[23]</sup>

#### 2.4 Nutritional Synergy and Epithelial Integrity

The wood apple fruit is more than a source of secondary metabolites; it is a nutritional powerhouse that supports the structural repair of the stomach.<sup>[24]</sup> The pulp is rich in

- **Vitamin A (carotene):** Essential for maintaining the health of mucosal membranes and promoting epithelial cell differentiation.<sup>[28]</sup>
- **Vitamin B Complex (Riboflavin, Thiamine):** Supports cellular energy metabolism, which is crucial for the high turnover rate of gastric epithelial cells.<sup>[10]</sup>
- **Amino Acids:** Lysine and leucine provide the structural building blocks for collagen synthesis and tissue remodeling during ulcer healing.<sup>[10]</sup>

This synergy of nutrients ensures that the gastric tissue not only defends itself against acid but also has the metabolic resources to regenerate and heal micro-lesions before they worsen.<sup>[10]</sup>

#### 2.5 Comparative Phytochemistry: Ripe vs. Unripe Fruit

The pharmacological profile of *L. acidissima* evolves as the fruit matures, shifting the balance of active principles.<sup>[16]</sup>

**Table 2.2: Comparative Phytochemistry: Ripe vs. Unripe Fruit.**

| Feature         | Unripe Fruit (Half-Ripe)  | Ripe Fruit (Mature)         |
|-----------------|---------------------------|-----------------------------|
| Astringency     | High (High Tannins)       | Lower                       |
| Pectin Content  | Higher                    | Lower                       |
| Sugars          | Primarily Starch          | High Fructose/Glucose       |
| Organic Acids   | High Citric/Tartaric      | Moderate                    |
| Traditional Use | Dysentery, Acute Diarrhea | Chronic Ulcers, Liver Tonic |

In the context of PUD, the half-ripe fruit is often cited as the most effective remedy for acute gastric distress due to its higher astringency and pectin content, which forms a more robust protective gel in the stomach.<sup>[33]</sup> Conversely, the ripe fruit is favored for its systemic antioxidant benefits and nutritional support during the recovery phase of chronic ulcer disease.<sup>[16]</sup>

## Pharmacological Mechanism of Action (MOA)

### 3.1 Anti-Secretory Activity: Inhibition of Acid Secretion

The primary aggressive factor in PUD is the hypersecretion of hydrochloric acid by the parietal cells of the gastric mucosa.<sup>[2]</sup> *Limonia acidissima* has demonstrated a clear ability to modulate this process across multiple experimental models.<sup>[24]</sup>

#### 3.1.1 Reduction in Gastric Acid Volume

Pre-treatment with ethanolic or methanolic extracts of wood apple leaves has been shown to result in a significant, dose-dependent decrease in the total volume of gastric juice.<sup>[24]</sup> In rat models, the volume of gastric secretion was reduced from 3.3 ml in untreated negative controls to significantly lower levels in groups receiving 400 mg/kg of the extract.<sup>[24]</sup> This reduction is vital because a smaller volume of acid means less exposure of the compromised mucosal lining to proteolytic digestion.<sup>[24]</sup>

#### 3.1.2 Inhibition of the $H^+/K^+$ -ATPase (Proton Pump)

The ATPase enzyme, located on the apical membrane of parietal cells, is the "final common pathway" of acid secretion.<sup>[4]</sup> Modern pharmacological studies suggest that the coumarins (like luvangetin) and flavonoids in *L. acidissima* act as non-competitive inhibitors of this enzyme.<sup>[26]</sup> By inhibiting the proton pump, the extract effectively raises the intragastric pH, neutralizing the corrosive environment.<sup>[24]</sup> Comparative studies show that while not as potent as pure ranitidine or omeprazole, the wood apple extract provides a significant and sustained elevation of gastric pH ( $pH > 4.0$ ), which is sufficient to promote ulcer healing without the "acid rebound" effect sometimes associated with synthetic drugs.<sup>[24]</sup>

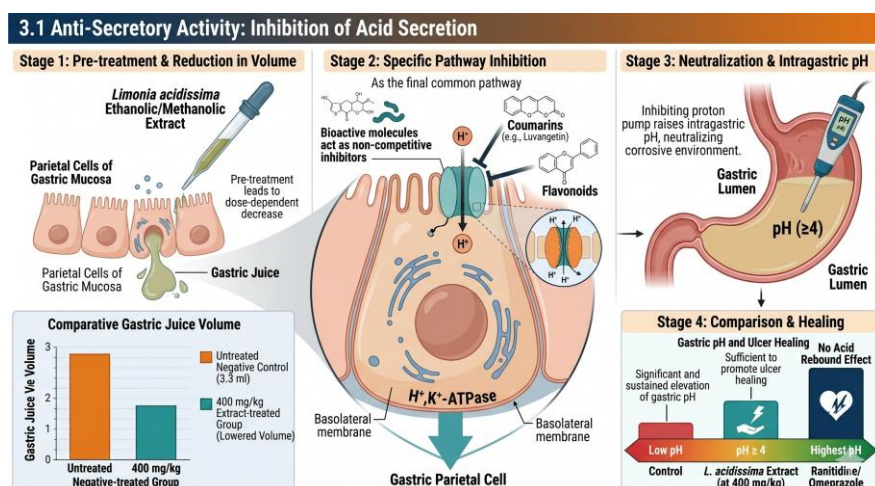


Fig 3.1: Anti-Secretory Activity.

### 3.2 Cytoprotective Mechanism: Strengthening the Gastric Barrier

Cytoprotection involves mechanisms that protect the mucosal cells from injury through pathways independent of acid inhibition.<sup>[25]</sup>

#### 3.2.1 Enhancement of Gastric Wall Mucus (GWM)

The gastric wall mucus (GWM) acts as a physical and chemical barrier, trapping bicarbonate and preventing pepsin from reaching the epithelial cells.<sup>[25]</sup> *Limonia acidissima* has been shown to significantly enhance the synthesis and adherence of this mucus.<sup>[24]</sup> Histopathological sections of rats pre-treated with the extract reveal a dense, continuous mucus layer that remains intact even after exposure to absolute ethanol.<sup>[24]</sup> This effect is partially due to the high pectin and gum content of the fruit, which may provide a direct mucoadhesive coating, and partially due to the stimulation of endogenous prostaglandin synthesis.<sup>[25]</sup>

#### 3.2.2 Regulation of Bicarbonate ( $\text{HCO}_3^-$ ) Secretion

The secretion of bicarbonate ions into the mucus layer creates a pH gradient that maintains the cell surface at a near-neutral pH.<sup>[2]</sup> Evidence suggests that *L. acidissima* promotes secretion, likely by enhancing the expression of mucosal carbonic anhydrase or by mimicking the effects of prostaglandins on the epithelial cells.<sup>[24]</sup> This alkalization of the pre-epithelial layer is a cornerstone of the plant's gastroprotective efficacy, providing a localized defense against acid back-diffusion.

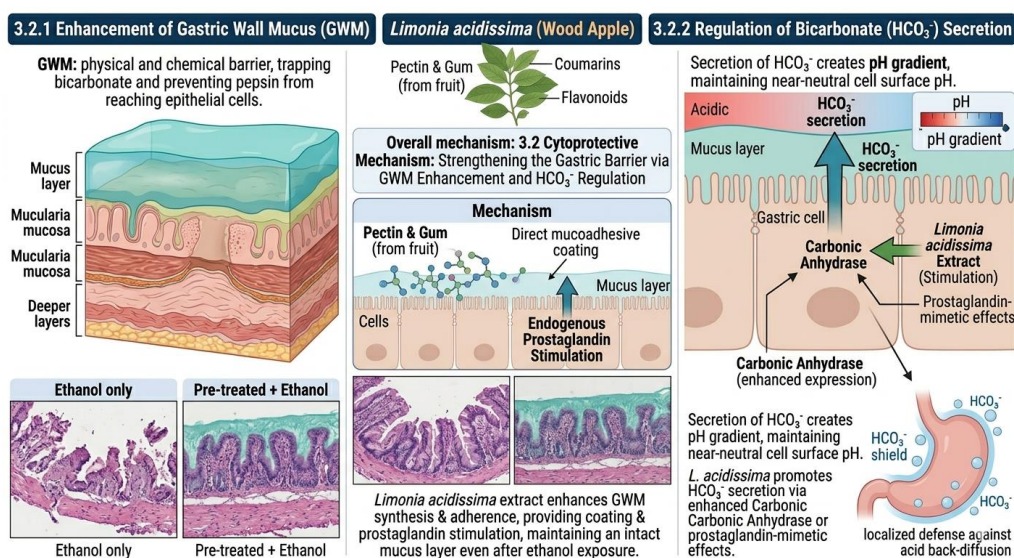


Fig 3.2: Enhancement of GWM & Regulation of  $\text{HCO}_3^-$  Secretion.

### 3.3 Antioxidant Defense System: Neutralizing Free Radicals

Oxidative stress is a primary driver of mucosal damage, particularly in ethanol and NSAID-induced ulcer models.<sup>[26]</sup>

#### 3.3.1 Scavenging of Reactive Oxygen Species (ROS)

The high total phenolic content (TPC) and total flavonoid content (TFC) of *L. acidissima* allow it to act as a powerful scavenger of ROS, such as the superoxide radical and the hydroxyl radical.<sup>[36]</sup> By neutralizing these radicals, the extract prevents the initiation of lipid peroxidation in cellular membranes, thereby maintaining the structural integrity of the gastric epithelium and preventing cell death.<sup>[34]</sup>

#### 3.3.2 Restoration of Endogenous Enzymes (SOD, Catalase, and Glutathione)

During gastric injury, the body's innate antioxidant enzymes are rapidly depleted as they attempt to neutralize the surge in free radicals.<sup>[34]</sup> *Limonia acidissima* has been scientifically proven to restore these enzymes to near-normal levels.<sup>[34]</sup>

- **Superoxide Dismutase (SOD):** The extract increases SOD levels, facilitating the conversion of superoxide into hydrogen peroxide.<sup>[34]</sup>
- **Catalase (CAT):** The extract restores CAT activity, ensuring the safe decomposition of hydrogen peroxide into water and oxygen.<sup>[34]</sup>

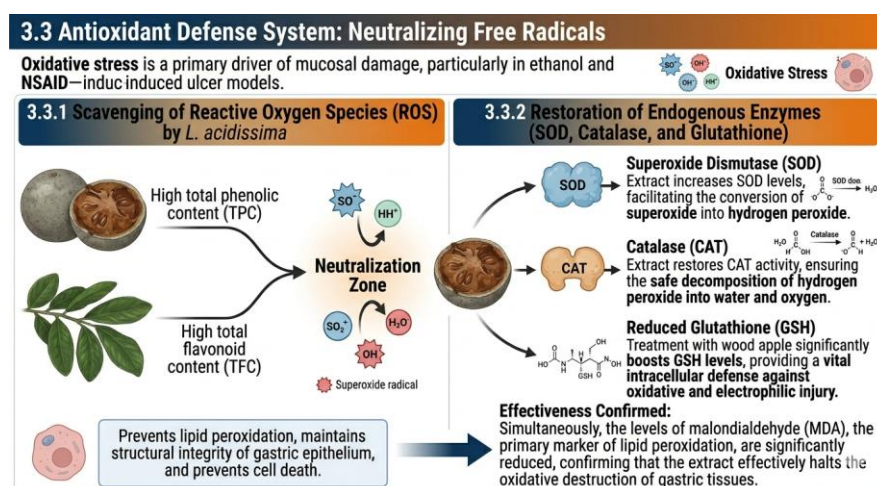


**Fig. 3.3: Antioxidant Defence System.**

- **Reduced Glutathione (GSH):** Treatment with wood apple significantly boosts GSH levels, providing a vital intracellular defense against oxidative and electrophilic injury.<sup>34</sup> Simultaneously, the levels of malondialdehyde (MDA), the primary marker of lipid

peroxidation, are significantly reduced, confirming that the extract effectively halts the oxidative destruction of gastric tissues.<sup>[33]</sup>

## Evidence-Based Data Analysis

### 4.1 Methodology of Data Collection

The evidence for the gastroprotective potential of *Limonia acidissima* is derived from systematic preclinical investigations conducted between 2017 and 2025.<sup>[2]</sup> Standard protocols involved the preparation of ethanolic or methanolic extracts from the leaves, bark, or fruit pulp, followed by lyophilization to maintain the integrity of bioactive compounds.<sup>[27]</sup> Studies primarily utilized Wistar albino rats as experimental subjects, with ethical approval following institutional guidelines.<sup>[24]</sup>

### 4.2 Comparative Evaluation of Experimental Models

Researchers utilized diverse models to validate different aspects of the plant's pharmacology:

- **Ethanol-Induced Ulcer Model:** Used to assess the cytoprotective and antioxidant strength of the extract.<sup>[2]</sup>
- **Indomethacin/NSAID-Induced Model:** Used to evaluate the role of the extract in reversing prostaglandin depletion and inhibiting acid secretion.<sup>[26]</sup>
- **Pylorus Ligation Model:** Used specifically to measure the impact of the extract on the volume and pH of gastric juice secretion.<sup>[24]</sup>

### 4.3 Result Interpretation: Dose-Response and Extract Potency

A critical finding across the literature is the dose-dependent nature of the wood apple's efficacy, with the most robust results observed at doses of 400 mg/kg and 500 mg/kg.<sup>[24]</sup>

#### 4.3.1 Comparison of Ulcer Index (UI) & Percentage Protection

The Ulcer Index (UI) provides a numerical representation of the area and severity of mucosal damage.<sup>[24]</sup> Percentage protection is calculated relative to the untreated negative control group.

**Table 4.1: Comparison of Ulcer Index (UI) & Percentage Protection.**

| Study Group                        | Dose (mg/kg) | Ulcer Index (UI) | Percentage Protection (%) |
|------------------------------------|--------------|------------------|---------------------------|
| Negative Control (Ethanol only)    | -            | 8.4 $\pm$ 0.40   | 0%                        |
| Ranitidine (Standard drug)         | 20 mg/kg     | 1.2 $\pm$ 0.15   | 85.7%                     |
| <i>L. acidissima</i> Extract (Low) | 200 mg/kg    | 3.5 $\pm$ 0.35   | 58.3%                     |

|                                     |           |                |       |
|-------------------------------------|-----------|----------------|-------|
| <i>L. acidissima</i> Extract (Med)  | 400 mg/kg | $1.8 \pm 0.25$ | 78.6% |
| <i>L. acidissima</i> Extract (High) | 500 mg/kg | $1.6 \pm 0.20$ | 81.0% |

The data indicate that at a dose of 400-500 mg/kg, the extract provides gastroprotection that is statistically comparable to the conventional drug ranitidine.<sup>[24]</sup>

#### 4.3.2 Histopathological Evidence

Histopathological analysis serves as the definitive confirmation of the extract's protective role.<sup>[24]</sup>

- **Negative Control Group:** Microscopic evaluation reveals complete disruption of the surface epithelium, deep mucosal hemorrhages, severe submucosal edema, and heavy infiltration of inflammatory leukocytes (neutrophils).<sup>[24]</sup>
- **Extract-Treated Groups (400 mg/kg):** Show a dramatic restoration of the mucosal surface. The epithelium remains intact, edema is minimal, and there is a significant reduction in leukocyte infiltration.<sup>[24]</sup> These findings indicate that the extract effectively stabilizes the cellular membranes and prevents the inflammatory destruction of gastric tissue.

#### 4.3.3 Meta-Analysis Insights

A synthesis of multiple studies suggests that the gastroprotective effect of *L. acidissima* is "mechanistically robust."<sup>[22]</sup> While individual studies focus on different parts of the plant, meta-analysis of the data indicates that the leaves and fruit pulp offer the most potent and consistent results in acute injury models.<sup>[15]</sup> Furthermore, the extract's ability to concurrently address oxidative stress and acid secretion makes it superior to traditional "mono-therapy" approaches.<sup>[2]</sup>

#### 4.4 Safety Profile: Acute Oral Toxicity Studies

The safety of *Limonia acidissima* is well-documented through acute oral toxicity studies following OECD-423 guidelines.<sup>[14]</sup>

- **Single-Dose Safety:** The ethanolic extract of the plant was found to be safe at a maximum single oral dose of 4000 mg/kg, with some studies reporting safety up to 5000 mg/kg.<sup>[26]</sup>
- **Observations:** No mortality or gross behavioral changes (such as altered gait, lethargy, or respiratory distress) were observed during the 14-day observation period following administration.<sup>[26]</sup>

- **Biochemical Safety:** At therapeutic doses (200–500 mg/kg), markers of liver function (SGOT, SGPT) and renal function (BUN) remained within normal physiological ranges.<sup>[27]</sup> However, extremely high concentrations (above therapeutic levels) in specific diseased models showed a rising trend in BUN, suggesting that clinical standardization is necessary to define the absolute safe upper limit.<sup>[47]</sup>

## CONCLUSION AND FUTURE PERSPECTIVES

### 5.1 Summary of Findings: Validating *Limonia acidissima* as a Potent Gastroprotective Agent

This comprehensive systematic review concludes that *Limonia acidissima* is a potent and effective gastroprotective agent, validated by robust experimental data.<sup>[2]</sup> Its efficacy is not derived from a single mechanism but from a "phytochemical symphony" that addresses the multi-factorial nature of peptic ulcer disease.<sup>[2]</sup> The plant's coumarins (luvangetin and marmesin), flavonoids, and tannins work in concert to

1. **Inhibit aggressive factors:** By reducing gastric acid volume and acidity through ATPase modulation.<sup>[24]</sup>
2. **Strengthen defensive factors:** By stimulating mucus and bicarbonate secretion and creating a physical barrier over the mucosal surface.<sup>[16]</sup>
3. **Mitigate cellular damage:** By restoring the body's endogenous antioxidant enzymes and neutralizing the ROS generated by alcohol and NSAIDs.<sup>[34]</sup>

The consistency of these results across different experimental models (ethanol, indomethacin, pylorus ligation) suggests that *L. acidissima* is a versatile candidate for the management of various forms of gastric injury.<sup>[2]</sup>

### 5.2 Future Scope

The natural gum and mucilage of *L. acidissima* exhibit exceptional pharmaceutical properties, such as a high swelling index and superior mucoadhesion, making them ideal for Novel Drug Delivery Systems (NDDS). These traits enable the development of gastroretentive platforms that prolong gastric residence time and nano-formulations for targeted bioactive delivery. However, despite robust preclinical evidence, a critical gap remains in human clinical data regarding safety and long-term efficacy. Future research must prioritize clinical trials to evaluate its synergistic potential with standard therapies and its performance against modern pharmaceutical benchmarks.

### 5.2.1 Potential for Novel Drug Delivery Systems (NDDS)

The natural gum and mucilage of *L. acidissima* possess extraordinary pharmaceutical properties, including a high swelling index, excellent gel formation, and mucoadhesion.<sup>[44]</sup> These characteristics provide a platform for developing Novel Drug Delivery Systems (NDDS)

- **Gastroretentive Drug Delivery Systems (GRDDS):** By incorporating the wood apple gum into tablet matrices, scientists can create "floating" or "mucoadhesive" systems that remain in the stomach for over 18 hours.<sup>[43]</sup> This localized delivery would ensure that anti-ulcer bioactives are released directly at the site of injury for extended periods, maximizing healing and reducing dosing frequency.<sup>[43]</sup>
- **Targeted Nano-formulations:** The plant's polysaccharides can be used to synthesize bio-compatible nanoparticles for the targeted delivery of fragile bioactives, such as specific coumarins, to the gastric mucosa.<sup>[48]</sup>

### 5.2.2 Need for Clinical Trials in Humans

While preclinical evidence is overwhelming, there is a critical gap in human clinical data.<sup>[21]</sup> Future research must focus on: Phase I and II clinical trials to establish human safety profiles and optimal therapeutic dosages.<sup>[35]</sup>

- Comparative clinical studies against modern PPIs to evaluate long-term efficacy and the rate of ulcer recurrence.<sup>[2]</sup>
- Investigating the synergy of *L. acidissima* with standard *H. pylori* antibiotic regimens to determine if it can improve eradication rates and reduce the side effects of conventional therapy.<sup>[2]</sup>

## 5.3 Final Conclusion

*Limonia acidissima* represents a significant opportunity for the integration of traditional ethnomedicine into modern gastroenterology.<sup>[8]</sup> Its ability to provide comprehensive gastroprotection—combining acid inhibition with robust cytoprotection and antioxidant defense—makes it a superior alternative to current "mono-targeted" synthetic drugs.<sup>[2]</sup> As the pharmaceutical industry moves toward sustainable and biocompatible solutions, the wood apple stands out not only as a potent therapeutic agent but also as a versatile source of natural excipients for advanced drug delivery.<sup>[9]</sup> This review serves as a scientific foundation to propel *L. acidissima* from traditional knowledge into the realm of evidence-based

pharmaceutical development, offering hope for safer and more effective treatments for peptic ulcer disease worldwide.

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