International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Evaluation of the Anti-Ulcer Activity of A Polyherbal Formulation in Experimentally Induced Gastric Ulcers in Rats

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Abstract
Gastric ulcer is a multifactorial gastrointestinal disorder resulting from an imbalance between aggressive factors such as gastric acid, pepsin, non-steroidal anti-inflammatory drugs (NSAIDs), alcohol, stress, and reactive oxygen species, and protective mechanisms including mucus secretion, bicarbonate, prostaglandins, antioxidant defenses, and epithelial regeneration. Conventional anti-ulcer therapies, including proton pump inhibitors, H_2-receptor antagonists, and antacids, though effective, are often associated with adverse effects such as hypergastrinemia, renal complications, osteoporosis, and ulcer recurrence, particularly upon long-term use. Polyherbal formulations, rooted in traditional medicinal systems like Ayurveda, Siddha, and Unani, combine multiple medicinal plants to provide a synergistic and multi-targeted therapeutic approach, addressing various ulcerogenic pathways simultaneously. Experimental studies using rat models, such as ethanol-induced, aspirin-induced, pylorus ligation-induced, and stress-induced gastric ulcers, have demonstrated that polyherbal formulations significantly reduce ulcer index, decrease gastric acidity, enhance mucus production, restore antioxidant status, and protect against inflammatory and histopathological damage. The pharmacological effects are largely attributed to bioactive phytoconstituents such as flavonoids, tannins, saponins, alkaloids, and phenolic compounds. Collectively, these findings highlight the therapeutic potential of polyherbal formulations as effective, safe, and multi-mechanistic agents for the management and prevention of gastric ulcers.

Keywords: Gastric ulcer; Polyherbal formulation; Anti-ulcer activity; Gastroprotection; Experimental rat models

1. INTRODUCTION

Gastric ulcer is a chronic and recurrent gastrointestinal disorder characterized by localized erosion and necrosis of the gastric mucosal lining, which may extend into the submucosa or muscularis layer of the stomach wall. It represents a major public health problem worldwide due to its high prevalence, tendency to recur, and association with complications such as gastrointestinal bleeding, perforation, and gastric outlet obstruction. The pathogenesis of gastric ulcer is multifactorial and primarily results from an imbalance between aggressive factors and protective mechanisms within the gastric mucosa. [1]

The principal aggressive factors involved in ulcerogenesis include excessive secretion of gastric acid and pepsin, infection with *Helicobacter pylori*, prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs), alcohol consumption, smoking, stress, and oxidative damage. These factors compromise the

integrity of the gastric mucosal barrier by inducing inflammation, increasing acid output, reducing mucosal blood flow, and generating reactive oxygen species (ROS). In contrast, the defensive mechanisms of the stomach consist of mucus and bicarbonate secretion, adequate mucosal blood flow, endogenous prostaglandins, epithelial cell regeneration, and antioxidant enzymes such as superoxide dismutase, catalase, and glutathione. Disruption of this delicate balance ultimately leads to mucosal injury and ulcer formation. [2]

Conventional pharmacological therapies for gastric ulcers mainly include proton pump inhibitors (PPIs), H_2-receptor antagonists, antacids, and cytoprotective agents. Although these drugs are effective in suppressing acid secretion and promoting ulcer healing, their long-term use is often associated with adverse effects such as hypergastrinemia, vitamin and mineral deficiencies, osteoporosis, renal impairment, increased susceptibility to infections, and high rates of ulcer recurrence after drug withdrawal. These drawbacks, along with the rising incidence of drug resistance and patient non-compliance, have encouraged the search for safer and more sustainable therapeutic alternatives. [3]

In this context, herbal medicines and polyherbal formulations have gained considerable attention due to their long history of traditional use in the management of gastrointestinal disorders. Polyherbal formulations consist of a combination of two or more medicinal plants, selected based on traditional knowledge and therapeutic rationale. The concept of polyherbalism is based on the principle of synergy, where multiple bioactive constituents work together to enhance therapeutic efficacy, reduce toxicity, and target multiple pathological pathways simultaneously. In gastric ulcers, such formulations may exert anti-secretory, cytoprotective, antioxidant, anti-inflammatory, and mucosal healing effects, thereby offering comprehensive protection against ulcerogenesis. [4]

Scientific evaluation and validation of polyherbal formulations are essential to substantiate their traditional claims and to understand their mechanisms of action. Experimentally induced gastric ulcer models in rats are widely employed for this purpose, as they closely mimic the pathophysiological features of human gastric ulcers. These models allow systematic assessment of parameters such as ulcer index, gastric acidity, mucus content, histopathological changes, and antioxidant status, providing reliable evidence of anti-ulcer potential. [5]

Therefore, the present review focuses on the evaluation of the anti-ulcer activity of polyherbal formulations using experimentally induced gastric ulcer models in rats. It aims to highlight the scientific rationale, experimental approaches, and therapeutic significance of polyherbal formulations as promising alternatives for the management of gastric ulcers. [6]

Pathophysiology of Gastric Ulcer Formation:

a) **Imbalance Between Aggressive and Protective Factors** Gastric ulcer formation primarily results from an imbalance between aggressive factors such as gastric acid, pepsin, and inflammatory mediators, and protective mechanisms including mucus–bicarbonate secretion, prostaglandins, antioxidant enzymes, and epithelial regeneration. When this balance is disturbed, the gastric mucosa becomes vulnerable to injury. [7]

b) **Excessive Gastric Acid and Pepsin Secretion** Hypersecretion of gastric acid and pepsin leads to direct erosion of the gastric epithelial lining. Prolonged exposure to these aggressive secretions damages the mucosal surface, initiating ulcer formation and delaying healing. [8]

c) **Decreased Gastric Mucus and Bicarbonate Secretion**

The mucus–bicarbonate barrier protects the gastric mucosa from acidic and enzymatic injury. Reduction

in mucus thickness and bicarbonate secretion weakens this barrier, allowing acid and pepsin to penetrate and damage the epithelial cells. [9]

d) **Reduced Prostaglandin Synthesis**

Prostaglandins are essential for maintaining mucosal integrity by enhancing mucus secretion, regulating gastric blood flow, and promoting epithelial cell turnover. Inhibition of prostaglandin synthesis, particularly by NSAIDs, compromises mucosal defense and facilitates ulcer development. [10]

e) **Increased Oxidative Stress and Lipid Peroxidation**

Oxidative stress plays a significant role in gastric ulcer pathogenesis. Excessive generation of reactive oxygen species causes lipid peroxidation of gastric cell membranes, leading to cellular injury and disruption of antioxidant defense mechanisms. [11]

f) **Release of Inflammatory Cytokines**

Inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) are released during gastric mucosal injury. These cytokines enhance inflammation, increase vascular permeability, and aggravate tissue damage. [12]

g) **Microcirculatory Disturbances and Ischemia**

Reduced gastric mucosal blood flow results in inadequate oxygen and nutrient supply, leading to ischemic damage. Impaired microcirculation delays healing and worsens the severity of gastric ulcers. [13]

h) **Delayed Epithelial Cell Regeneration**

Rapid epithelial regeneration is essential for healing damaged gastric mucosa. Impaired cell proliferation and delayed tissue repair prolong ulcer persistence and increase the risk of complications. [14]

i) **Role of Polyherbal Formulations in Modulating Pathophysiology**

Polyherbal formulations act on multiple pathways involved in gastric ulcer formation. By simultaneously reducing acid secretion, enhancing mucosal defense, combating oxidative stress, suppressing inflammation, and promoting epithelial regeneration, they provide superior and holistic gastroprotection compared to single-drug therapy. [15]

2. Polyherbal Formulation: Concept and Rationale

The concept of polyherbal formulation is deeply embedded in traditional systems of medicine such as Ayurveda, Siddha, and Unani, where the therapeutic use of combinations of medicinal plants has been practiced for centuries. Unlike single-herb therapy, polyherbalism is based on the holistic principle that diseases are multifactorial in nature and therefore require multi-targeted therapeutic interventions. According to classical Ayurvedic philosophy, the rational combination of herbs in a formulation not only enhances therapeutic efficacy but also balances the pharmacological actions and minimizes the risk of adverse effects associated with individual components. [16]

Polyherbal formulations contain a diverse range of bioactive phytoconstituents such as flavonoids, alkaloids, tannins, saponins, terpenoids, glycosides, and phenolic compounds. These constituents act through complementary and synergistic mechanisms, resulting in improved pharmacodynamic outcomes. In the context of gastric ulcer management, polyherbal formulations are particularly advantageous because ulcerogenesis involves multiple pathological pathways, including hypersecretion of gastric acid, oxidative stress, inflammation, mucosal damage, and impaired healing. [17]

Rationale for Polyherbal Formulation in Ulcer Management

- **Synergistic Interaction of Phytoconstituents:** When multiple medicinal plants are combined, their

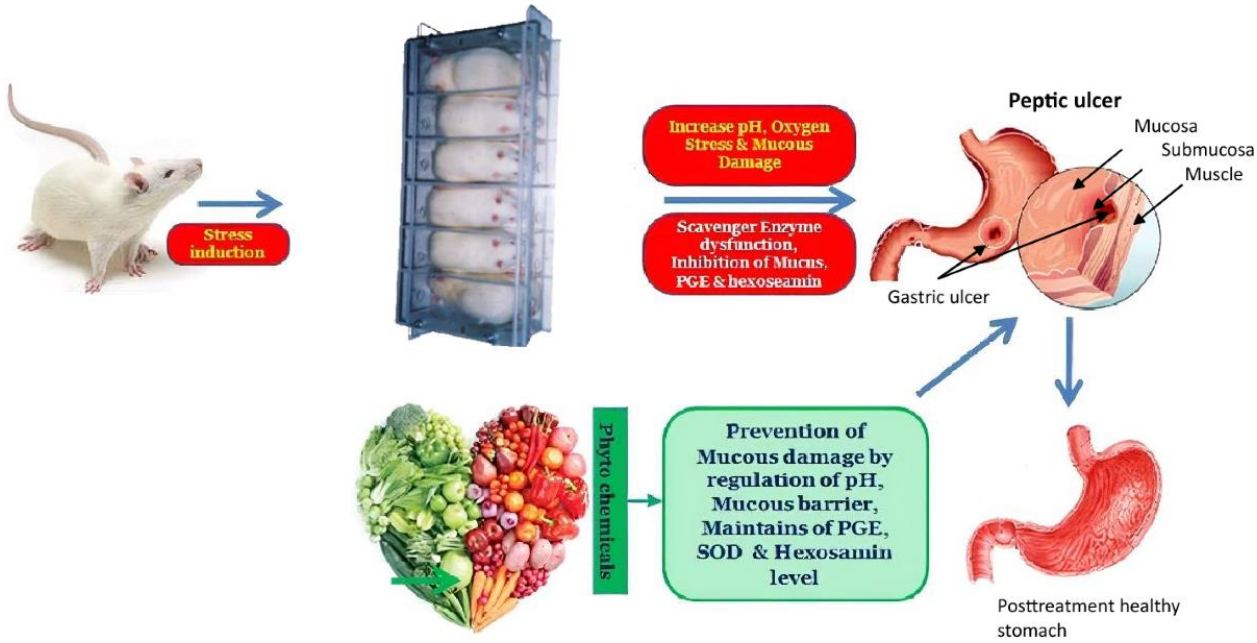
bioactive compounds interact synergistically to enhance overall anti-ulcer efficacy. For example, one herb may reduce gastric acid secretion while another strengthens mucosal defense or promotes epithelial regeneration. This synergism allows the formulation to achieve greater therapeutic effects than individual herbs used alone. [18]

- **Multi-targeted Pharmacological Action:** Gastric ulcers are not caused by a single factor; therefore, effective management requires modulation of several ulcerogenic mechanisms. Polyherbal formulations can simultaneously exert anti-secretory, cytoprotective, antioxidant, anti-inflammatory, and antimicrobial effects, particularly against *Helicobacter pylori*. This broad spectrum of action makes them more effective in preventing ulcer formation and accelerating healing. [19]
- **Enhanced Antioxidant and Cytoprotective Effects:** Oxidative stress plays a crucial role in gastric mucosal injury. Many medicinal plants included in polyherbal formulations are rich in natural antioxidants that scavenge free radicals, reduce lipid peroxidation, and enhance endogenous antioxidant enzyme activity. Additionally, these formulations promote mucus secretion, improve mucosal blood flow, and stimulate prostaglandin synthesis, thereby strengthening the gastric mucosal barrier. [20]
- **Reduced Dose Requirement and Improved Safety Profile:** Due to synergistic effects, lower doses of individual herbs are required in polyherbal formulations to achieve the desired therapeutic outcome. This dose-sparing effect reduces the risk of toxicity and adverse reactions, making polyherbal therapies safer for long-term use compared to conventional synthetic drugs. [21]
- **Improved Patient Compliance and Reduced Adverse Effects:** Polyherbal formulations are generally well tolerated and associated with fewer side effects, which improves patient adherence to therapy. Their natural origin and traditional acceptance further enhance patient confidence and compliance, especially in chronic conditions such as peptic ulcer disease. [22]

Several medicinal plants are frequently incorporated into polyherbal anti-ulcer formulations due to their well-documented gastroprotective properties. These include *Glycyrrhiza glabra* (licorice), known for its mucosal protective and anti-inflammatory effects; *Azadirachta indica* (neem), which exhibits antioxidant and anti-ulcer activity; *Aloe vera*, recognized for its healing and cytoprotective properties; *Musa paradisiaca* (banana), which enhances mucus secretion and epithelial regeneration; *Ocimum sanctum* (holy basil), valued for its anti-stress and antioxidant effects; and *Terminalia chebula*, which possesses strong antioxidant and gastroprotective activity. The rational combination of such herbs forms the scientific basis for the development of effective polyherbal formulations for the management of gastric ulcers. [23]

3. Experimental Animals

Experimental animals play a crucial role in the preclinical evaluation of anti-ulcer activity, as they provide a reliable and reproducible model for studying gastric mucosal injury and the protective effects of therapeutic agents. Among various laboratory animals, Wistar albino rats are most commonly employed in anti-ulcer studies due to their well-characterized physiology, ease of handling, and close resemblance to humans in terms of gastric acid secretion, mucosal defense mechanisms, and response to ulcer-inducing agents. [24]



Wistar albino rats exhibit predictable gastric responses to chemical, physical, and stress-induced ulcer models, making them suitable for evaluating the efficacy of polyherbal formulations. Their stomach anatomy and biochemical pathways involved in ulcerogenesis allow accurate assessment of parameters such as ulcer index, gastric acidity, mucus content, and histopathological alterations. [25]

Details of Experimental Animals: [26]

- **Species:**

Wistar albino rats

- **Body Weight:**

150–250 g, selected to ensure uniformity and to minimize variability in experimental outcomes

- **Sex:**

Either sex (male or female), with animals distributed equally among experimental groups wherever possible

- **Age:**

Young adult rats are generally preferred, as they exhibit stable physiological and metabolic functions

Housing and Maintenance Conditions:

The animals are housed under standard laboratory conditions to ensure their health and to avoid external stress factors that could influence the experimental results. [27]

- **Temperature:** Maintained at 22 ± 2 °C
- **Relative Humidity:** 45–65%
- **Light/Dark Cycle:** 12 h light and 12 h dark cycle
- **Caging:** Polypropylene cages with sterile bedding material
- **Diet:** Standard laboratory pellet diet
- **Water:** Provided ad libitum

Animals are allowed to acclimatize to laboratory conditions for at least 7 days prior to the initiation of the experiment. During this period, they are observed daily for signs of illness or abnormal behavior. [28]

Ethical Considerations:

All experimental procedures involving animals are carried out in strict accordance with ethical standards to ensure animal welfare. [29]

- Experiments are conducted as per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India
- The experimental protocol is reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of the respective institution
- Efforts are made to minimize animal suffering by using the minimum number of animals required to obtain statistically significant results
- Proper anesthesia and humane handling methods are employed during experimental procedures and sacrifice
- Thus, the use of Wistar albino rats under controlled and ethically approved conditions provides a scientifically valid and ethically responsible platform for evaluating the anti-ulcer activity of polyherbal formulations. [30]

4. Experimental Induction of Gastric Ulcers

The experimental induction of gastric ulcers in laboratory animals is a fundamental step in the scientific evaluation of anti-ulcer activity of polyherbal formulations. These experimental models are specifically designed to reproduce the pathological, biochemical, and histological features of gastric ulceration observed in humans. Since gastric ulcer disease is multifactorial in nature, no single model can explain all aspects of ulcerogenesis. Therefore, different ulcer induction methods are employed to study various mechanisms such as acid hypersecretion, breakdown of mucosal defense, oxidative stress, inflammation, prostaglandin inhibition, and stress-related gastric damage. The use of multiple models provides a comprehensive assessment of the protective and therapeutic potential of polyherbal formulations. [31]

4.1 Ethanol-Induced Gastric Ulcer Model

The ethanol-induced gastric ulcer model is widely used to study acute gastric mucosal injury and to evaluate the cytoprotective potential of test formulations. Ethanol produces severe damage to the gastric mucosa by rapidly penetrating the epithelial lining of the stomach. This penetration leads to direct necrotic injury to epithelial cells and disrupts the integrity of the mucosal barrier. Ethanol exposure also stimulates excessive generation of reactive oxygen species, resulting in oxidative stress and lipid peroxidation of gastric cell membranes. These processes significantly reduce mucus production, impair microcirculation, increase vascular permeability, and promote inflammatory responses within the gastric tissue. [32]

As a result, visible hemorrhagic streaks, edema, and ulcerative lesions develop on the gastric mucosa. This model closely resembles alcohol-induced gastric injury in humans and is particularly useful for assessing the ability of polyherbal formulations to preserve mucosal integrity, enhance mucus secretion, and counteract oxidative damage. A significant reduction in ulcer index and improvement in mucosal architecture following treatment indicates strong cytoprotective and antioxidant activity. [33]

4.2 Aspirin-Induced Gastric Ulcer Model

The aspirin-induced gastric ulcer model is commonly employed to evaluate ulceration caused by non-steroidal anti-inflammatory drugs and to study the role of prostaglandins in maintaining gastric mucosal defense. Aspirin induces gastric ulcers primarily by inhibiting cyclooxygenase enzymes, which are responsible for the synthesis of prostaglandins. Prostaglandins play a vital role in protecting the gastric mucosa by stimulating mucus and bicarbonate secretion, maintaining mucosal blood flow, and supporting

epithelial cell regeneration. [34]

Inhibition of prostaglandin synthesis by aspirin results in weakened mucosal defenses, increased gastric acid secretion, reduced mucus thickness, and enhanced susceptibility of the gastric lining to acid and pepsin. Additionally, aspirin causes direct epithelial irritation and promotes inflammatory responses within the gastric tissue. These combined effects lead to erosion and ulceration of the gastric mucosa. [35]

This model closely mimics NSAID-induced gastric ulcers observed in clinical practice. It is particularly useful for evaluating the gastroprotective efficacy of polyherbal formulations that act by restoring prostaglandin levels, reducing inflammation, enhancing mucus secretion, and strengthening mucosal defense mechanisms. [36]

4.3 Pylorus Ligation-Induced Ulcer Model

The pylorus ligation-induced ulcer model is a classical experimental method used to study the role of gastric acid secretion in ulcer formation. In this model, the pyloric end of the stomach is surgically ligated, preventing the passage of gastric contents into the intestine. As a result, gastric secretions, including hydrochloric acid and pepsin, accumulate within the stomach. [37]

The continuous accumulation of gastric juice leads to increased intragastric pressure and prolonged exposure of the gastric mucosa to acid and proteolytic enzymes. This causes autodigestion of the gastric lining, resulting in ulcer formation, particularly in the glandular portion of the stomach. Oxidative stress and inflammatory changes further aggravate mucosal damage. [38]

This model is especially useful for evaluating the antisecretory and anti-acid properties of polyherbal formulations. Parameters such as gastric volume, pH, free acidity, and total acidity are measured to assess the ability of the formulation to suppress acid secretion and protect the gastric mucosa from acid-mediated injury. [39]

4.4 Stress-Induced Gastric Ulcer Model

Stress-induced gastric ulcer models, such as cold restraint stress or water immersion stress, are employed to simulate stress-related gastric lesions commonly seen in humans. Exposure to physical or psychological stress leads to activation of the hypothalamic–pituitary–adrenal axis, resulting in increased secretion of gastric acid and stress hormones. Stress also causes vasoconstriction, reduced gastric mucosal blood flow, impaired mucus secretion, and enhanced oxidative stress. [40]

These physiological changes weaken the gastric mucosal barrier and promote the formation of ulcers, particularly in the glandular region of the stomach. Stress-induced ulcers are often associated with severe oxidative damage and inflammatory infiltration of gastric tissues.

This model is useful for evaluating the adaptogenic, antioxidant, and anti-stress properties of polyherbal formulations. A reduction in ulcer severity and restoration of normal gastric architecture indicate the formulation's ability to modulate stress responses, reduce oxidative damage, and protect the gastric mucosa. [41]

In summary, the use of multiple experimental ulcer models provides a comprehensive and mechanistic understanding of the anti-ulcer potential of polyherbal formulations, supporting their therapeutic relevance in the management of gastric ulcers.

5. Evaluation Parameters

The assessment of anti-ulcer activity of polyherbal formulations involves a comprehensive evaluation of both macroscopic and microscopic parameters, along with biochemical estimations. These parameters collectively provide insight into the severity of gastric mucosal damage, the protective efficacy of the

formulation, and its possible mechanisms of action. Evaluation is typically carried out after ulcer induction and treatment, allowing comparison between control, ulcerated, standard drug-treated, and polyherbal formulation-treated groups. [42]

5.1 Ulcer Index

The ulcer index is one of the most important and commonly used parameters for assessing the severity of gastric ulceration. After sacrificing the animals, the stomach is excised, opened along the greater curvature, and examined for the presence of gastric lesions. Ulcers are scored based on their number, length, and depth, using a standardized scoring system. Hemorrhagic spots, erosions, and deep ulcers are carefully noted.

The ulcer index is calculated using appropriate formulas that take into account the total number of ulcers and their severity. A significant reduction in ulcer index in animals treated with the polyherbal formulation, compared to the ulcer control group, indicates strong gastroprotective and ulcer-healing activity. [43]

5.2 Gastric Volume and pH

Measurement of gastric juice volume and pH provides valuable information regarding the antisecretory activity of the formulation. After pylorus ligation or ulcer induction, gastric contents are collected, centrifuged, and the supernatant is analyzed.

An increase in gastric volume and a decrease in pH indicate excessive acid secretion, which contributes to ulcer formation. Polyherbal formulations with anti-ulcer potential typically reduce gastric juice volume and increase gastric pH, reflecting suppression of acid secretion and improved gastric environment. These changes suggest a protective effect against acid-mediated mucosal damage. [44]

5.3 Total and Free Acidity

Total acidity and free acidity of gastric juice are determined by titrimetric analysis using standardized sodium hydroxide solution and suitable indicators such as Topfer's reagent and phenolphthalein. Free acidity represents the concentration of free hydrochloric acid, while total acidity includes both free and combined acids present in the gastric juice.

A reduction in total and free acidity following treatment with the polyherbal formulation indicates effective inhibition of gastric acid secretion. This parameter is particularly useful in models such as pylorus ligation-induced ulcers, where acid hypersecretion plays a major role in ulcerogenesis. [45]

5.4 Mucus Content

Gastric mucus forms a critical protective barrier that shields the gastric epithelium from acid, pepsin, and other damaging agents. Estimation of mucus content is performed by measuring the amount of adherent mucus present on the gastric mucosa, often using staining or scraping methods.

An increase in mucus content in treated animals suggests enhanced mucosal defense and cytoprotective activity. Polyherbal formulations rich in flavonoids, tannins, and polysaccharides are known to stimulate mucus secretion and strengthen the gastric mucosal barrier, thereby preventing ulcer formation and promoting healing. [46]

5.5 Antioxidant Parameters

Oxidative stress plays a key role in gastric mucosal injury. Therefore, assessment of antioxidant parameters is essential to understand the protective mechanism of polyherbal formulations. Gastric tissue homogenates are prepared and analyzed for levels of endogenous antioxidant enzymes and oxidative stress markers.

Superoxide dismutase (SOD) and catalase (CAT) are evaluated to determine the enzymatic antioxidant defense system, while reduced glutathione (GSH) levels indicate non-enzymatic antioxidant capacity.

Malondialdehyde (MDA), a marker of lipid peroxidation, reflects the extent of oxidative damage to gastric tissues. [47]

An increase in SOD, CAT, and GSH levels along with a decrease in MDA concentration in treated groups indicates effective antioxidant and free radical scavenging activity of the polyherbal formulation, contributing to gastric mucosal protection.

5.6 Histopathological Examination

Histopathological examination of gastric tissue provides confirmatory and visual evidence of the anti-ulcer activity observed in macroscopic and biochemical evaluations. Gastric tissue samples are fixed in formalin, processed, sectioned, and stained, commonly using hematoxylin and eosin.

Microscopic examination reveals structural changes such as epithelial erosion, ulceration, edema, hemorrhage, inflammatory cell infiltration, and necrosis. In animals treated with polyherbal formulations, preservation of normal mucosal architecture, reduced inflammatory infiltration, regeneration of epithelial cells, and healing of ulcerated areas are commonly observed.

Thus, histopathological findings support and validate the protective and therapeutic effects of polyherbal formulations against experimentally induced gastric ulcers. [48]

6. Future Perspective:

6.1 Need for Safer and Long-Term Anti-ulcer Therapies

The adverse effects and relapse associated with prolonged use of conventional anti-ulcer drugs highlight the need for safer alternatives. Polyherbal formulations, due to their natural origin and multi-targeted action, offer potential for long-term management of gastric ulcers with improved safety and patient tolerance. [49]

6.2 Scientific Validation of Traditional Polyherbal Formulations

Although polyherbal medicines have been traditionally used for ulcer treatment, systematic scientific validation is essential. Future studies should focus on evidence-based evaluation using standardized experimental models to bridge the gap between traditional knowledge and modern pharmacology.

6.3 Standardization and Quality Control

Ensuring consistency in raw materials and finished formulations remains a major challenge. Advanced analytical tools such as HPTLC, HPLC, and LC–MS should be employed to standardize polyherbal formulations and maintain batch-to-batch uniformity, which is critical for reproducibility and regulatory acceptance. [50]

6.4 Identification of Bioactive Phytochemical Markers

Isolation and characterization of key bioactive compounds responsible for anti-ulcer activity will help in understanding therapeutic mechanisms. Marker-based standardization will also improve formulation reliability and quality assurance.

6.5 Elucidation of Molecular and Cellular Mechanisms

Future research should explore molecular pathways involved in gastroprotection, including modulation of inflammatory mediators, prostaglandin synthesis, oxidative stress pathways, and epithelial regeneration. Such studies will strengthen the mechanistic basis of polyherbal anti-ulcer therapy. [51]

6.6 Comprehensive Toxicological and Safety Evaluation

Despite their natural origin, polyherbal formulations require thorough toxicological evaluation. Sub-acute, chronic, and reproductive toxicity studies are necessary to establish safety profiles and support long-term clinical use.

6.7 Development of Novel Drug Delivery Systems

Incorporating polyherbal extracts into advanced delivery systems such as gastro-retentive tablets, mucoadhesive formulations, nanoparticles, or sustained-release systems can enhance gastric residence time and therapeutic efficacy. [52]

6.8 Enhancement of Bioavailability and Therapeutic Efficacy

Poor solubility and stability of herbal constituents often limit their effectiveness. Future formulation strategies should aim to improve bioavailability and ensure sustained action at the gastric mucosa.

6.9 Clinical Trials and Human Validation

Translation of preclinical findings into clinical practice requires well-designed randomized controlled trials. Clinical studies will help establish efficacy, safety, optimal dosage, and patient compliance of polyherbal anti-ulcer formulations. [53]

6.10 Role in *Helicobacter pylori* Management

With increasing antibiotic resistance, polyherbal formulations possessing antimicrobial and anti-inflammatory properties may serve as alternative or adjunct therapies for *H. pylori*-associated gastric ulcers.

6.11 Integration into Modern Healthcare Systems

With adequate scientific evidence and regulatory support, polyherbal anti-ulcer formulations can be integrated into mainstream healthcare as cost-effective and patient-friendly therapeutic options. [54]

7. Mechanisms of Anti-ulcer Activity of Polyherbal Formulation

Polyherbal formulations exhibit significant anti-ulcer activity through a multifaceted and synergistic mode of action, targeting several interconnected pathways involved in the pathogenesis of gastric ulcers. Unlike conventional single-target drugs, polyherbal formulations provide holistic gastroprotection by simultaneously reducing aggressive factors and strengthening mucosal defense mechanisms. The combined presence of diverse phytoconstituents such as flavonoids, tannins, saponins, alkaloids, and phenolic compounds plays a pivotal role in mediating these protective effects. [55]

7.1 Inhibition of Gastric Acid Secretion

Excessive secretion of gastric acid and pepsin is a major causative factor in ulcer development. Polyherbal formulations exert an antisecretory effect by modulating acid-producing pathways in the stomach. Certain phytoconstituents inhibit proton pump activity, suppress histamine-mediated acid release, and reduce vagal stimulation of gastric secretion. This leads to a decrease in gastric volume, free acidity, and total acidity, thereby minimizing acid-induced mucosal damage and promoting ulcer healing. [56]

7.2 Enhancement of Mucus and Bicarbonate Secretion

The gastric mucus–bicarbonate barrier serves as the first line of defense against acidic and enzymatic injury. Polyherbal formulations stimulate mucus secretion and enhance bicarbonate production, resulting in increased thickness and viscosity of the protective mucosal layer. This barrier prevents direct contact between gastric acid and epithelial cells, reducing erosion and ulcer formation. Flavonoids and polysaccharides are particularly known for their mucus-enhancing properties. [57]

7.3 Antioxidant and Free Radical Scavenging Activity

Oxidative stress plays a central role in gastric mucosal injury through the generation of reactive oxygen species. Polyherbal formulations are rich in natural antioxidants that neutralize free radicals and inhibit lipid peroxidation. These formulations significantly increase endogenous antioxidant enzymes such as superoxide dismutase, catalase, and reduced glutathione while reducing malondialdehyde levels. This

antioxidant defense prevents cellular damage and preserves gastric mucosal integrity. [58]

7.4 Anti-inflammatory Action

Inflammation is a critical contributor to ulcer progression and delayed healing. Polyherbal formulations exhibit potent anti-inflammatory effects by inhibiting the release of pro-inflammatory mediators such as tumor necrosis factor-α, interleukins, and cyclooxygenase-2. Reduction in inflammatory cell infiltration and edema in gastric tissues leads to decreased mucosal injury and accelerated ulcer healing. Alkaloids and flavonoids play a key role in modulating inflammatory pathways. [59]

7.5 Strengthening of Gastric Mucosal Barrier

Polyherbal formulations enhance the structural and functional integrity of the gastric mucosa by improving mucosal blood flow, stabilizing epithelial cell membranes, and promoting prostaglandin synthesis. Prostaglandins are essential for maintaining mucosal defense, stimulating mucus secretion, and regulating blood circulation in gastric tissues. Tannins contribute by forming a protective protein layer over the ulcerated surface, preventing further damage. [60]

7.6 Promotion of Tissue Regeneration and Healing

Effective ulcer management requires not only protection but also regeneration of damaged tissues. Polyherbal formulations stimulate epithelial cell proliferation, collagen synthesis, and angiogenesis, leading to faster regeneration of the gastric lining. Improved cellular turnover and restoration of normal mucosal architecture result in effective ulcer healing and reduced chances of recurrence. [61]

7.7 Role of Phytochemical Constituents

The therapeutic efficacy of polyherbal formulations is largely attributed to the synergistic interaction of multiple phytochemicals:

- Flavonoids: Antioxidant, anti-secretory, and cytoprotective effects
- Tannins: Protein precipitation and formation of protective mucosal layer
- Saponins: Enhancement of mucus secretion and mucosal defense
- Alkaloids: Anti-inflammatory and acid secretion modulation
- Phenolic compounds: Free radical scavenging and anti-ulcer activity

In summary, polyherbal formulations exert anti-ulcer effects through a comprehensive and synergistic mechanism that addresses both the causative and protective aspects of gastric ulcer disease. Their ability to inhibit acid secretion, enhance mucosal defenses, reduce oxidative stress and inflammation, and promote tissue repair makes them promising therapeutic agents for the prevention and management of gastric ulcers. [62]

CONCLUSION

Polyherbal formulations exhibit robust anti-ulcer activity by modulating multiple interrelated mechanisms involved in ulcerogenesis, including inhibition of gastric acid secretion, enhancement of mucosal defense, antioxidant and free radical scavenging activity, anti-inflammatory effects, and promotion of tissue repair and regeneration. Experimental evidence from various rat models indicates that these formulations not only reduce ulcer severity and restore gastric biochemical parameters but also improve mucosal integrity and accelerate healing of damaged tissue. The synergistic actions of diverse phytochemicals such as flavonoids, tannins, saponins, alkaloids, and phenolic compounds contribute to their superior efficacy and favorable safety profile compared to conventional single-drug therapy. With further standardization, mechanistic exploration, toxicological evaluation, and clinical validation, polyherbal formulations hold considerable promise as safe, effective, and holistic therapeutic agents for the long-term management,

prevention, and healing of gastric ulcers.

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