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NSAID-INDUCED GASTRIC ULCERATION: PATHOPHYSIOLOGICAL MECHANISMS, THERAPEUTIC CHALLENGES AND POTENTIAL OF NATURAL PRODUCTS

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are extensively prescribed for the treatment of pain and inflammatory conditions; however, their prolonged or inappropriate use can compromise gastric mucosal integrity and contribute to the development of gastric ulcers and other gastrointestinal complications. NSAID-associated gastric injury results from a combination of interacting events rather than a single mechanism. Suppression of cyclooxygenase-dependent prostaglandin synthesis weakens important endogenous defense mechanisms, while oxidative imbalance, inflammatory signalling, altered mucosal circulation, epithelial dysfunction, and increased cellular damage further contribute to ulcer development. Conventional gastroprotective medicines are effective in reducing gastric injury, but their use may be limited by adverse effects, drug interactions, recurrence, or concerns associated with prolonged therapy. These limitations have encouraged research into naturally derived compounds with broader biological activities. Various phytochemicals, including flavonoids, polyphenols, terpenoids, alkaloids, and saponins, have demonstrated gastroprotective potential through antioxidant, anti-inflammatory, cytoprotective, acid-regulating, and mucosal barrier-supporting actions in experimental studies. Recent investigations have also highlighted molecular pathways involving nuclear factor erythroid 2-related factor 2, nuclear factor-κB, nitric oxide signalling, NLRP3 inflammasome activation, mitochondrial dysfunction, and epithelial barrier regulation as potential targets for intervention. The present review examines the development of NSAID-induced gastric ulceration, underlying cellular and molecular mechanisms, commonly employed experimental models, and currently available pharmacological approaches. Particular attention is given to natural products and their proposed mechanisms of gastric protection, together with issues related to extract standardization, safety, dose optimization, and translation of preclinical findings into clinical applications. The review further identifies important research gaps and discusses future opportunities for developing evidence-based natural gastroprotective strategies.

KEYWORDS: NSAIDs; Gastric ulcer; Gastric mucosal injury; Gastroprotection; Oxidative stress; Phytochemicals; Natural products; Gastric mucosal defense.

1. INTRODUCTION

Gastric ulceration is a common gastrointestinal disorder characterized by disruption of the gastric mucosal lining, resulting from an imbalance between damaging factors and the protective mechanisms of the stomach. The gastric mucosa is continuously exposed to hydrochloric acid, digestive enzymes, dietary substances, and other potentially harmful agents. Under normal conditions, this exposure is controlled by protective mechanisms such as mucus and bicarbonate secretion, adequate mucosal blood circulation, epithelial cell renewal, endogenous prostaglandins, and antioxidant defenses. When these protective mechanisms become insufficient, progressive mucosal damage may occur and eventually develop into ulceration.[1]

Several factors are associated with gastric ulcer development, including *Helicobacter pylori* infection,

alcohol consumption, smoking, psychological or physiological stress, excessive gastric acid secretion, and the use of ulcerogenic medicines. Among these, non-steroidal anti-inflammatory drugs (NSAIDs) are an important cause of drug-associated gastric injury because of their widespread use in the treatment of pain and inflammatory disorders. Commonly used NSAIDs include aspirin, ibuprofen, naproxen, and diclofenac. The risk of gastric complications may increase with prolonged treatment, higher doses, advanced age, previous ulcer history, or simultaneous use of other medicines that increase gastrointestinal risk.[2]

The development of NSAID-induced gastric injury involves several interconnected mechanisms. Inhibition of cyclooxygenase enzymes reduces the production of protective prostaglandins, which normally contribute to mucus and bicarbonate secretion, mucosal blood flow, epithelial repair, and maintenance of gastric integrity. NSAIDs may also promote oxidative stress, lipid peroxidation, inflammatory signalling, mitochondrial dysfunction, and epithelial cell injury. These processes can weaken the gastric barrier and increase susceptibility to acid-mediated tissue damage.[2,3]

Current management includes proton pump inhibitors, H_2-receptor antagonists, prostaglandin analogues, and other mucosal protective agents. Although these approaches have demonstrated therapeutic value, limitations associated with long-term treatment and adverse effects have encouraged investigation of additional gastroprotective strategies. Natural products have gained attention because phytochemicals such as flavonoids, polyphenols, terpenoids, alkaloids, and saponins may act through multiple protective pathways. Their reported activities include antioxidant, anti-inflammatory, cytoprotective, acid-regulating, and mucosal barrier-supporting effects. Therefore, understanding the molecular basis of NSAID-induced gastric injury and evaluating naturally derived gastroprotective agents may contribute to the identification of safer and more effective therapeutic approaches. This review focuses on the mechanisms of NSAID-induced gastric ulceration, current therapeutic strategies, experimental evidence for natural gastroprotective agents, emerging molecular targets, limitations of existing research, and future opportunities for clinical translation**.**reported to be beneficial in disorders of the digestive, circulatory, urinary and reproductive systems, as well as in various skin diseases.[3]

2. EPIDEMIOLOGY AND CLINICAL SIGNIFICANCE

2.1 Upper Gastrointestinal and Ulcer Bleeding

- **Epidemiological Significance:** Gastrointestinal (GI) bleeding is the **most common GI** diagnosis requiring hospitalization in the United States, with more than **500,000** admissions annually. Upper GI bleeding (UGIB) specifically accounts for nearly 80% of patients visiting emergency departments being admitted with that principal diagnosis. While mortality in the US is relatively uncommon at approximately **2%**, preventing further bleeding is the primary clinical goal.
- **Clinical Significance:** Ulcer bleeding is the most common cause of UGIB. Risk stratification using tools like the Glasgow-Blatchford score is clinically significant for identifying very-low-risk patients who can be safely managed as outpatients, thereby reducing hospitalizations and costs. For hospitalised patients, a restrictive red blood cell transfusion threshold of **7 g/dL** has been shown to reduce further bleeding and mortality compared to more liberal policies.[4]

2.1.1 Peptic Ulcer Disease (PUD)

- **Epidemiological Significance:** Approximately 1 out of 12 people in the United States is affected by PUD. Historically, most ulcers were associated with *H. pylori* infection, but recent data shows a decline, with only one-fourth of duodenal and one-sixth of gastric ulcers currently linked to the bacterium. The strongest risk factors are now Helicobacter pylori infection and long-term NSAID use.
- **Clinical Significance:** The combination of *H. pylori* and NSAID use is particularly dangerous, synergistically increasing the risk of bleeding ulcers more than sixfold. Clinical manifestations include epigastric pain, bloating, and nausea. Major complications include life-threatening gastrointestinal bleeding, perforation (leading to peritonitis), and gastric outlet obstruction due to chronic inflammation or scarring.[4,5]

2.1.2 Corneal Ulcers

- **Epidemiological Significance:** The annual incidence of corneal ulcers in the US is estimated between 30,000 and 75,000. Keratitis, the precursor to these ulcers, is responsible for approximately one million clinic and emergency department visits annually. They are much more common in contact lens wearers, with the highest rates of bacterial ulcers seen in females aged 25 to 34. Notably, 12.2% of all corneal transplant**s** are performed to manage infectious keratitis.
- **Clinical Significance:** A corneal ulcer is a vision-threatening ocular emergen**cy** that can lead to significant morbidity, including corneal scarring, perforation, glaucoma, cataracts, and permanent vision loss. Prompt identification and emergent ophthalmologic evaluation within 12 to 24 hours are critical.[5]

2.1.3 Venous Leg Ulcers (VLU)

- **Epidemiological Significance:** VLUs are the most common type of chronic wound in the lower extremity, affecting an estimated 1% to 3% of the older adult population in the US and Europe.

Incidence is higher in women and increases with aging and obesity.[6]

- **Clinical Significance:** These ulcers represent a massive economic burden, costing the US healthcare system approximately $14.9 billion annually. They are late indicators of chronic venous insufficiency and are associated with a twofold higher risk of all-cause mortality. VLUs carry the highest recurrence rate among chronic wounds, with only 60% achieving closure at six months, severely impacting patient quality of life through pain, malodor, and social isolation.[6,7]

2.1.4 Pressure Ulcers

- **Epidemiological Significance:** These are common in older and immobile individuals, as well as those with diabetes, vascular disease, or malnutrition.
- **Clinical Significance:** Pressure ulcers often cause severe pain and can lead to social avoidance behaviors. Clinical management focuses on optimizing hydration, circulation, and nutrition to promote wound healing.[8]

2.1.5 Zollinger-Ellison Syndrome (ZES)

- **Epidemiological Significance:** ZES is a rare condition affecting 0.1 to 3 per million people, with an average age of onset around 41 years and a slight male preponderance. Approximately 25% to 30% of cases are associated with Multiple Endocrine Neoplasia type 1 (MEN1).[9]
- **Clinical Significance:** It is characterized by gastrinomas that secrete gastrin autonomously, causing massive acid hypersecretion (often five times normal levels). This results in severe, recurrent peptic ulcers that are often treatment-resistant and located in atypical distal sites like the jejunum. Clinical manifestations also include chronic secretory diarrhea, malabsorption (steatorrhea), and severe esophageal complications like Barrett's esophagus.[9,10]

2.2 MAJOR CAUSES OF GASTRIC ULCERATION

Gastric ulceration develops when the protective capacity of the gastric mucosa is insufficient to counteract damaging influences. Several factors can disturb this balance and contribute to mucosal injury. The major causes of gastric ulceration include *Helicobacter pylori* infection, prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs), excessive gastric acid and pepsin activity, alcohol consumption, smoking, physiological and psychological stress, and disturbances in gastric mucosal defense.[11]

2.2.1 Helicobacter pylori Infection

Helicobacter pylori is an important infectious factor associated with peptic ulcer disease. The bacterium can colonize the gastric mucosa and produce substances that contribute to epithelial injury and inflammation. Persistent infection can alter the local gastric environment, weaken mucosal defenses, and promote inflammatory responses, thereby increasing susceptibility to ulcer formation.[12]

2.2.2 Non-Steroidal Anti-Inflammatory Drugs

NSAIDs are among the major drug-related causes of gastric mucosal injury. Common examples include aspirin, ibuprofen, naproxen, and diclofenac. These drugs inhibit cyclooxygenase enzymes and reduce the formation of protective prostaglandins. Reduced prostaglandin activity can decrease mucus and bicarbonate secretion, impair mucosal blood flow, and interfere with epithelial repair. NSAIDs may also contribute to oxidative stress and inflammatory tissue damage.[13]

2.2.3 Gastric Acid and Pepsin

Hydrochloric acid and pepsin are essential for normal digestion but can contribute to ulcer formation when mucosal protection is compromised. Excessive acid exposure or inadequate buffering by mucus and bicarbonate can facilitate penetration of hydrogen ions into damaged mucosal tissue. Pepsin can further contribute to the breakdown of cellular and protein components of the injured mucosa.[14]

2.2.4 Alcohol Consumption

Excessive alcohol exposure can damage the gastric epithelial barrier and increase mucosal permeability. Alcohol may promote oxidative stress, inflammatory responses, and disruption of the protective mucus layer, making the gastric mucosa more susceptible to acid-mediated injury.[15]

2.2.5 Smoking

Tobacco smoking has been associated with impaired gastric mucosal defense and delayed ulcer healing. Components of tobacco smoke may affect mucosal blood circulation, promote oxidative stress, and interfere with protective and repair mechanisms.[16]

2.2.6 Physiological and Psychological Stress

Severe physiological stress, including trauma, burns, surgery, or critical illness, can contribute to stress-related gastric mucosal injury. Psychological stress may also influence gastric function and inflammatory responses. Alterations in mucosal blood flow and increased susceptibility to acid-related injury can contribute to ulcer development under severe stress conditions.[17]

2.2.7 Impairment of Gastric Mucosal Defense

The stomach possesses several protective mechanisms, including mucus and bicarbonate secretion, epithelial regeneration, adequate blood supply, prostaglandin production, and antioxidant defenses. Disturbance of one or more of these mechanisms can increase vulnerability to gastric injury. Thus, ulcer formation generally results from an imbalance between aggressive factors, such as acid, pepsin, NSAIDs, and inflammatory mediators, and protective factors responsible for maintaining mucosal integrity.[18]

2.3 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Non-steroidal anti-inflammatory drugs (NSAIDs) constitute an important group of medicines widely used for the management of pain, inflammation, and fever. They are frequently prescribed or used for conditions such as osteoarthritis, rheumatoid arthritis, musculoskeletal disorders, headache, dysmenorrhea, and other painful inflammatory conditions. Their therapeutic effects are primarily associated with inhibition of cyclooxygenase (COX) enzymes, which are involved in the conversion of arachidonic acid into prostaglandins and related lipid mediators. Although suppression of prostaglandin synthesis contributes to the desired anti-inflammatory and analgesic effects, it can also interfere with physiological processes responsible for maintaining gastrointestinal mucosal integrity.[19]

NSAIDs can be broadly differentiated according to their relative selectivity toward the COX-1 and COX-2 isoenzymes. Conventional or non-selective NSAIDs inhibit both COX-1 and COX-2 to varying degrees. Examples include aspirin, ibuprofen, naproxen, indomethacin, and diclofenac. Preferential COX-2 inhibitors, such as meloxicam and etodolac, exhibit greater activity toward COX-2 than COX-1, although their selectivity varies with dose. Selective COX-2 inhibitors, commonly referred to as coxibs, were developed with the objective of providing anti-inflammatory effects while reducing some of the gastrointestinal effects associated with inhibition of COX-1.[19,20]

2.3.1 Classification of NSAIDs

NSAIDs may be classified according to their chemical structure or their relative inhibition of cyclooxygenase enzymes. A simplified pharmacological classification is presented below.

Category	Examples	General COX activity
Non-selective NSAIDs	Aspirin, ibuprofen, naproxen, indomethacin, diclofenac	COX-1 and COX-2 inhibition
Preferential COX-2 inhibitors	Meloxicam, etodolac	Greater COX-2 activity than COX-1
Selective COX-2 inhibitors	Celecoxib, etoricoxib	Predominantly COX-2 inhibition

The degree of COX inhibition is influenced by the individual drug, dose, duration of treatment, and pharmacological characteristics. Therefore, classification based only on selectivity provides a general framework rather than an absolute description of gastrointestinal risk.[21]

2.3.2 Mechanism of Action of NSAIDs

The principal pharmacological action of NSAIDs involves inhibition of cyclooxygenase enzymes. These enzymes catalyze an important step in the metabolism of arachidonic acid, leading to the formation of prostaglandins and other prostanoid mediators. Reduction in prostaglandin synthesis decreases inflammatory signalling and contributes to the analgesic and antipyretic effects of NSAIDs.[22]

COX-1 is constitutively expressed in many tissues and contributes to several physiological functions. Within the gastrointestinal tract, COX-1-derived prostaglandins participate in maintaining mucosal defense by supporting mucus and bicarbonate secretion, mucosal blood flow, and epithelial homeostasis. In contrast, COX-2 is commonly induced during inflammatory responses and contributes to the production of inflammatory prostaglandins. However, the functions of COX-2 are not restricted exclusively to inflammation, and its role can vary according to tissue, disease state, and stage of injury or repair.[23]

2.3.3 Therapeutic Uses of NSAIDs

NSAIDs are used in a wide range of clinical conditions because of their analgesic, antipyretic, and anti-inflammatory properties. Common applications include.

- Relief of mild-to-moderate pain
- Musculoskeletal pain
- Osteoarthritis
- Rheumatoid arthritis
- Acute inflammatory conditions
- Headache and migraine
- Dysmenorrhea
- Dental pain
- Fever

Low-dose aspirin has an additional clinical application because of its antiplatelet effect, where it may be used for prevention of thrombotic cardiovascular events in appropriate patients.

2.3.3 Adverse Effects of NSAIDs

Although NSAIDs provide substantial therapeutic benefits, their use can be associated with adverse effects involving several organ systems. Gastrointestinal complications are among the most clinically important and include dyspepsia, gastritis, gastric mucosal erosion, peptic ulceration, gastrointestinal bleeding, and, in severe cases, perforation.

The gastrointestinal toxicity of NSAIDs is particularly important because injury can develop even when symptoms are relatively mild or absent. The risk generally depends on factors such as the specific NSAID, dose, duration of exposure, patient susceptibility, previous history of ulcer disease, and concurrent use of other medicines that increase gastrointestinal risk.

Other important adverse effects associated with NSAID therapy include renal impairment, fluid retention, elevation of blood pressure, and cardiovascular complications in susceptible individuals. Therefore, selection of an NSAID requires consideration of both therapeutic benefits and individual patient risk factors.[24]

2.3.4 Relationship Between NSAID Use and Gastric Ulceration

The relationship between NSAID exposure and gastric ulceration is primarily associated with disruption of endogenous gastric defense mechanisms. Inhibition of prostaglandin synthesis can reduce mucus and bicarbonate secretion, compromise mucosal blood flow, and interfere with epithelial repair. In addition, NSAIDs may contribute to direct epithelial injury and promote oxidative and inflammatory processes.[25]

Thus, NSAID-induced gastric injury results from the combined influence of impaired mucosal defense and cellular injury rather than from increased gastric acid secretion alone. Understanding these mechanisms is essential for the development of effective preventive and therapeutic approaches, including the investigation of natural products with potential gastroprotective properties.[26]

2.4 NORMAL GASTRIC MUCOSAL DEFENSE

The gastric mucosa is continuously exposed to potentially damaging substances, particularly hydrochloric acid and pepsin. Despite this harsh environment, the stomach generally maintains its structural and functional integrity through a coordinated defense system. Gastric mucosal protection depends on several complementary mechanisms, including the mucus-bicarbonate barrier, epithelial integrity and regeneration, adequate mucosal blood flow, endogenous prostaglandins, and antioxidant defenses. The balance between these protective mechanisms and aggressive factors is essential for preventing mucosal injury and ulcer formation.[27]

2.4.1 Mucus-Bicarbonate Barrier

The mucus layer forms the first physical barrier between the gastric epithelium and the acidic gastric contents. Mucins produced by surface epithelial cells create a viscous layer that limits the movement of hydrogen ions and other potentially harmful substances toward the epithelial surface. Bicarbonate secreted by gastric epithelial cells becomes incorporated into this mucus layer and helps maintain a relatively neutral microenvironment close to the epithelial cells. Together, mucus and bicarbonate reduce the direct exposure of the gastric epithelium to gastric acid and digestive enzymes.[28]

2.4.2 Gastric Epithelial Barrier

Gastric epithelial cells provide an additional protective barrier against luminal contents. Tight junctions between adjacent epithelial cells restrict the movement of hydrogen ions and other substances through the spaces between cells. Continuous replacement of damaged epithelial cells also contributes to maintenance of mucosal integrity. Rapid epithelial restitution allows superficial defects to be covered before they progress into deeper tissue damage.[29]

2.4.3 Mucosal Blood Flow

Adequate blood circulation within the gastric mucosa is important for maintaining tissue viability and supporting repair processes. Gastric blood flow supplies oxygen and nutrients to epithelial and supporting cells and facilitates removal of potentially harmful metabolic products. It also contributes to the ability of the mucosa to recover following exposure to damaging agents.[30]

2.4.4 Role of Prostaglandins

Endogenous prostaglandins, particularly PGE_2, play an important role in gastric mucosal protection. They support mucus and bicarbonate secretion, maintain mucosal blood flow, and contribute to epithelial repair. Prostaglandins therefore represent an important link between gastric physiology and mucosal defense. Reduction in prostaglandin production can weaken several protective mechanisms simultaneously.[30,31]

2.4.5 Antioxidant Defense

The gastric mucosa possesses endogenous antioxidant systems that help control reactive oxygen species generated during normal metabolism and pathological conditions. Important antioxidant defenses include superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and glutathione peroxidase (GPx). These systems help limit oxidative damage to cellular membranes, proteins, and other cellular components.[32]

2.5 Integrated Gastric Mucosal Protection

Gastric protection is therefore not dependent on a single mechanism. Mucus and bicarbonate, epithelial integrity, mucosal circulation, prostaglandins, and antioxidant defenses function together to maintain the gastric barrier. NSAIDs can interfere with several of these mechanisms, particularly through inhibition of prostaglandin synthesis and enhancement of oxidative and inflammatory processes. Understanding normal mucosal defense is therefore essential for explaining the subsequent molecular events involved in NSAID-induced gastric ulceration.[33]

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2.6 Integrated Gastric Mucosal Protection

Gastric mucosal protection depends on the coordinated action of several defense mechanisms that maintain the balance between aggressive factors and protective factors. The mucus–bicarbonate barrier forms the first line of defense by limiting the penetration of hydrogen ions and maintaining a relatively neutral environment near the gastric epithelium. The epithelial barrier and tight junctions further restrict acid back-diffusion and protect underlying tissues.[40]

Prostaglandins, particularly PGE_2, play an important role by promoting mucus and bicarbonate secretion, maintaining mucosal blood flow, and supporting epithelial repair. Adequate mucosal blood circulation supplies oxygen and nutrients while assisting the removal of harmful metabolic products. The gastric mucosa also contains antioxidant defenses, including superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and glutathione peroxidase (GPx), which help neutralize reactive oxygen species and reduce oxidative damage.[40,41]

Additionally, epithelial restitution and regeneration enable rapid repair of superficial mucosal injuries. Together, these mechanisms maintain gastric mucosal integrity. Disruption of multiple protective pathways, particularly reduced prostaglandin production, impaired blood flow, oxidative stress, and epithelial damage, can increase susceptibility to gastric ulceration. This integrated defense system is particularly important in understanding NSAID-induced **gastric** injury, where several protective mechanisms may be simultaneously compromised.[41]

Gastric mucosal protection involves coordinated pre-epithelial, epithelial and sub-epithelial defenses that maintain mucosal integrity against acid, pepsin, NSAIDs and other irritants. The mucus-bicarbonate layer forms the primary barrier, while tight epithelial junctions prevent hydrogen-ion back-diffusion. Prostaglandins, nitric oxide and hydrogen sulfide enhance mucus and bicarbonate secretion, maintain mucosal blood flow and support epithelial repair. Antioxidant systems, including glutathione, catalase and superoxide dismutase, neutralize reactive oxygen species and limit oxidative damage. Growth factors promote epithelial restitution, proliferation and angiogenesis. Together, these mechanisms reduce inflammation and oxidative injury while facilitating **mucosal regeneration and ulcer healing**.

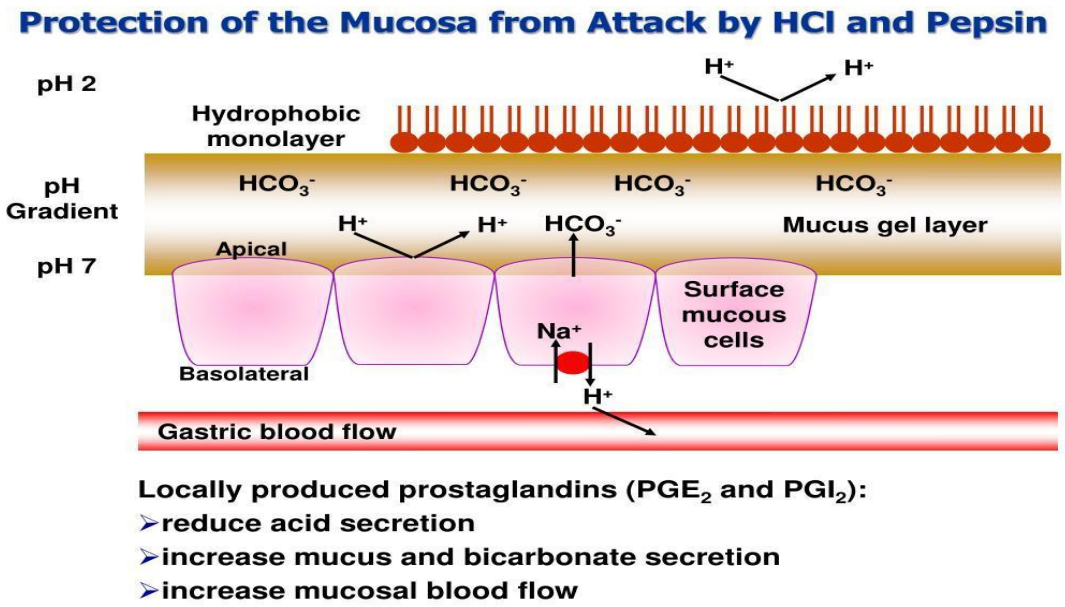

Figure 1: Schematic representation of the gastric mucosal barrier and its major protective mechanisms. Adapted from M. Komorniczak, Wikimedia Commons, CC BY-SA 3.0.

3. ANIMAL MODELS, EVALUATION PARAMETERS, CURRENT TREATMENT AND LIMITATIONS

3.1.1 Animal Models of NSAID-Induced Gastric Ulceration

Experimental animal models are widely used to investigate the mechanisms of gastric mucosal injury and to evaluate potential gastroprotective agents before clinical investigation. Among the available models, NSAID-induced ulceration using indomethacin or aspirin is commonly employed because these agents reproduce important features of drug-associated gastric injury. The severity of experimentally induced lesions can be influenced by the selected drug, dose, route of administration, and duration of exposure. Other experimental approaches, including ethanol-induced gastric injury, stress-related models, and pylorus ligation, may also be used to investigate specific aspects of gastric damage and mucosal protection. Selection of an appropriate model is important because different models reproduce different pathological mechanisms.[42]

3.1.2 Evaluation Parameters

The effectiveness of a gastroprotective treatment can be assessed using macroscopic, biochemical, physiological, and histological parameters. Macroscopic evaluation commonly includes ulcer number, ulcer severity, ulcer index, and percentage protection. Gastric secretion studies may include gastric volume, pH, free acidity, and total acidity. Biochemical assessment can provide information about oxidative and inflammatory damage through parameters such as malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and myeloperoxidase (MPO). Histopathological examination provides structural evidence of epithelial disruption, edema, hemorrhage, inflammatory-cell infiltration, and tissue necrosis. Combining several parameters provides a more reliable assessment than depending on ulcer scoring alone.[43]

3.1.3 Current Pharmacological Treatment

Management of gastric ulceration generally aims to reduce aggressive factors and strengthen mucosal protection. Proton pump inhibitors, including omeprazole and pantoprazole, suppress gastric acid secretion and are commonly used for acid-related disorders. Histamine H_2-receptor antagonists such as famotidine provide another approach to reducing acid secretion. Prostaglandin analogues such as misoprostol can help compensate for reduced prostaglandin-mediated protection and have particular relevance in NSAID-associated injury. Mucosal protective agents, including sucralfate and bismuth-containing preparations, can provide additional protection to damaged gastric tissue. Treatment selection depends on the underlying cause, severity of injury, patient risk factors, and concurrent medications.[44]

3.1.4 Limitations of Current Treatment

Although conventional gastroprotective medicines are effective, several limitations remain. Long-term pharmacological treatment may be associated with adverse effects, drug interactions, recurrence, and problems related to patient adherence. Furthermore, acid suppression does not necessarily address all mechanisms involved in NSAID-induced gastric injury, such as oxidative stress, mitochondrial dysfunction, and inflammatory signalling. These limitations have encouraged investigation of therapies capable of influencing multiple pathological pathways simultaneously. Natural products and their bioactive constituents have consequently attracted increasing interest as potential complementary gastroprotective agents. However, their efficacy, safety, standardization,

pharmacokinetic properties, and clinical relevance require systematic evaluation before they can be considered reliable thalternatives.[44,45]

3.2 NATURAL PROTECTIVE STRATEGIES AND EMERGING MECHANISMS OF GASTROPROTECTION

Natural products have received increasing attention as potential gastroprotective agents because many plant-derived compounds possess multiple biological activities that may be relevant to gastric mucosal protection. Unlike approaches that primarily focus on reducing gastric acidity, naturally occurring phytochemicals may influence several processes involved in ulcer development, including oxidative stress, inflammation, epithelial damage, mucus secretion, and cellular repair.[46] Flavonoids, phenolic compounds, terpenoids, alkaloids, tannins, and saponins have therefore been investigated in experimental models of gastric injury. However, evidence obtained from animal studies should be interpreted cautiously, as differences in extract composition, dose, experimental model, and study design can influence the observed gastroprotective response.[47]

3.2.1 Mechanisms of Natural Gastroprotection

The protective effects of natural products are generally associated with several complementary mechanisms. One of the most frequently investigated mechanisms is antioxidant activity. Excessive production of reactive oxygen species can promote lipid peroxidation and cellular damage during gastric injury. Phytochemicals with antioxidant properties may help reduce oxidative damage and support endogenous defense systems such as superoxide dismutase, catalase, glutathione, and glutathione peroxidase.[48]

Anti-inflammatory activity represents another important mechanism. Several natural compounds have been investigated for their ability to influence inflammatory mediators and signalling pathways associated with gastric injury. Reduction of inflammatory cytokines and modulation of pathways such as nuclear factor-κB may help limit the progression of mucosal damage. Some compounds may also support mucus production, bicarbonate secretion, mucosal circulation, and epithelial regeneration, thereby strengthening endogenous gastric defense.[49]

Natural compounds may additionally influence gastric acid secretion and pepsin activity. Their gastroprotective effects may therefore result from a combination of reduced aggressive influences and enhanced mucosal defense. This multi-target nature is one reason why phytochemicals continue to be investigated as potential gastroprotective candidates.[50]

3.2.2 Emerging Molecular Targets

Recent research has expanded beyond conventional measurements such as ulcer index and gastric acidity toward molecular mechanisms underlying gastroprotection. The nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is of particular interest because it regulates several cellular antioxidant and cytoprotective responses. Activation of Nrf2-associated pathways may enhance the expression of protective enzymes and improve the ability of cells to withstand oxidative stress.[51]

The nuclear factor-κB (NF-κB) pathway is another important target because of its central role in inflammatory signalling. Excessive activation of inflammatory pathways can increase the production of mediators such as tumour necrosis factor-α and interleukins, thereby contributing to mucosal injury. Other pathways of interest include NLRP3 inflammasome signalling, PI3K/Akt, mitogen-activated protein kinase pathways, nitric oxide signalling, and mitochondrial mechanisms. Investigation of these pathways may help explain why certain natural compounds produce gastroprotective effects across several experimental parameters.[52]

3.2.3 Gut Microbiota and Gastric Injury

The gastrointestinal microbiota is increasingly being considered as an additional factor in NSAID-associated gastrointestinal injury. NSAID exposure may alter microbial composition and intestinal barrier function, potentially contributing to inflammatory responses and gastrointestinal damage. This has created interest in the possibility that natural products may provide benefits not only through direct antioxidant or anti-inflammatory actions but also through modulation of microbial communities and their metabolites.[53]

The relationship between natural products, gut microbiota, and gastric protection remains an emerging area of research. Some phytochemicals can influence microbial composition and may interact with microbial metabolism to produce biologically active metabolites. Nevertheless, the specific contribution of these changes to NSAID-induced gastric ulcer prevention requires further investigation. Future studies combining microbiome analysis with biochemical, histological, and molecular assessments may provide a more complete understanding of this relationship.[54]

Overall, natural gastroprotective strategies represent a promising research area because their effects may involve multiple complementary pathways. However, standardized extracts, well-characterized active constituents, appropriate dosing, safety assessment, and adequately designed clinical studies are required before experimental findings can be translated into established therapeutic applications.[54,55]

3.3 SAFETY, STANDARDIZATION AND TRANSLATIONAL CHALLENGES

Although natural products have demonstrated promising gastroprotective effects in experimental studies, their therapeutic development requires careful consideration

of safety, quality, consistency, and clinical relevance. The perception that plant-derived preparations are inherently safe can be misleading, particularly when concentrated extracts, isolated phytochemicals, or prolonged treatments are involved. A natural product intended for gastroprotective use should therefore undergo systematic safety evaluation before its therapeutic potential can be established.[56]

- Safety Considerations

Safety assessment should include both acute and repeated-dose toxicity studies. Parameters such as changes in body weight, food and water consumption, behaviour, organ weight, hematological indices, serum biochemical markers, and histopathological changes can provide information regarding possible systemic toxicity. The safety profile of a compound may also depend on its dose, extraction method, route of administration, treatment duration, and chemical composition.[57]

Another important consideration is the possibility of herb–drug interactions. Patients with gastric disorders may already be receiving proton pump inhibitors, antiplatelet agents, anticoagulants, analgesics, or other medicines. Bioactive constituents present in plant extracts may influence drug-metabolizing enzymes or transport systems and could potentially alter the pharmacological activity of concurrently administered medicines. Consequently, gastroprotective natural products should be evaluated not only for their individual safety but also for their compatibility with commonly used therapeutic agents.[58]

3.3.1 Standardization of Plant Materials and Extracts

Variation in plant material is one of the major challenges in natural-product research. Differences in species, geographical origin, cultivation conditions, harvesting period, plant part, drying conditions, extraction solvent, extraction temperature, and storage can substantially alter the concentration of biologically active constituents. As a result, two extracts prepared from the same plant may not necessarily produce equivalent pharmacological effects.[59,60]

Standardization is therefore essential for reproducible research. Botanical authentication should be accompanied by appropriate physicochemical and phytochemical characterization. Where possible, extracts should be standardized using characteristic marker compounds or groups of bioactive constituents. Techniques such as high-performance liquid chromatography, gas chromatography, liquid chromatography–mass spectrometry, and spectroscopic methods may be useful for establishing chemical profiles.[61]

A standardized preparation also makes it easier to compare results between independent studies and to establish a relationship between chemical composition and biological activity. Without adequate characterization, differences in reported gastroprotective activity may reflect variations in the preparation rather than genuine differences in therapeutic potential.[61,62]

3.3.2 Dose and Pharmacokinetic Considerations

Dose selection represents another important translational challenge. Many experimental studies demonstrate gastroprotective activity at doses that cannot be directly extrapolated to humans. Animal dose, route of administration, absorption, metabolism, tissue distribution, and elimination all influence the biological response. Pharmacokinetic investigations are therefore necessary to determine whether potentially active constituents reach appropriate concentrations at relevant sites.[63]

Bioavailability can also limit the usefulness of certain phytochemicals. Some compounds exhibit poor aqueous solubility, rapid metabolism, limited intestinal absorption, or extensive first-pass metabolism. Formulation approaches, including suitable delivery systems and standardized extracts, may improve exposure; however, these approaches require independent safety and efficacy evaluation.[64]

3.3.3 Translational Challenges

A major limitation in natural-product gastroprotection is the gap between preclinical evidence and clinical application. Animal models are valuable for understanding mechanisms and screening candidate agents, but they cannot completely reproduce human gastric physiology, comorbidities, medication use, and long-term exposure. Therefore, promising experimental findings should be followed by carefully designed clinical investigations.[64,65]

Clinical studies should establish appropriate dose ranges, treatment duration, safety parameters, pharmacokinetic characteristics, and meaningful clinical outcomes. Comparison with established gastroprotective medicines would also help determine whether a natural product provides an additional therapeutic advantage rather than simply demonstrating biological activity.[66]

3.4 RESEARCH GAPS AND FUTURE PERSPECTIVES

Despite considerable research into natural gastroprotective agents, several important gaps remain. A large proportion of the available evidence is derived from experimental animal models, while well-controlled human studies remain comparatively limited. Consequently, the clinical significance of many reported gastroprotective effects remains uncertain.[67]

3.4.1 Lack of Standardized Experimental Approaches

Different studies frequently use different animal species, ulcer-inducing agents, doses, treatment schedules, extraction procedures, and outcome measures. This variation makes direct comparison between studies difficult. Future research should use better-defined

experimental protocols and report methodological details sufficiently to allow reproducibility.[68]

3.4.2 Identification of Active Constituents

In many investigations, the activity of a crude plant extract is reported without establishing which constituents are responsible for the observed effect. Future studies should combine pharmacological screening with phytochemical characterization to identify active molecules or synergistic combinations. This could provide a clearer relationship between chemical composition and gastroprotective activity.[69]

- Greater Emphasis on Molecular Validation

Demonstrating changes in biochemical markers is not always sufficient to establish a specific molecular mechanism. Future research should use complementary approaches such as gene-expression analysis, protein analysis, pathway-specific inhibitors, molecular docking where appropriate, and other mechanistic techniques to validate proposed targets.[69,70]

Particular attention may be directed toward pathways associated with oxidative stress, inflammation, mitochondrial function, apoptosis, epithelial repair, and mucosal barrier integrity. Nrf2/HO-1, NF-κB, NLRP3 inflammasome, PI3K/Akt, MAPK, nitric oxide signalling, and tight-junction pathways represent potentially important areas for investigation.[70]

3.4.3 Integration of the Gut Microbiome

The possible contribution of gut microbiota to NSAID-associated gastrointestinal injury represents an emerging research area. Future studies could combine conventional ulcer models with microbiome analysis to determine whether changes in microbial composition contribute to the protective effects of natural products. Metabolomic approaches may further help identify microbial metabolites involved in these interactions.[80]

3.5 Advanced Formulation Strategies

Poor solubility, instability, limited absorption, and rapid metabolism can restrict the effectiveness of certain phytochemicals. Future research may therefore investigate suitable formulation strategies, including nano-sized delivery systems, lipid-based systems, phytosomes, or other approaches designed to improve bioavailability. However, increased delivery efficiency must be accompanied by appropriate toxicity and pharmacokinetic assessment.[81]

3.5.1 Combination Therapy

Another promising direction is the investigation of natural products as complementary agents rather than direct replacements for established medicines. Combination approaches may allow different mechanisms to be targeted simultaneously, such as acid suppression together with antioxidant, anti-inflammatory, or mucosal protective activity. Such strategies require careful evaluation of efficacy, safety, pharmacokinetic interactions, and optimal dosing.[82]

3.5.2 Need for Clinical Translation

The most important research gap remains the limited translation of promising laboratory findings into clinical evidence. Future clinical trials should use standardized preparations with clearly defined chemical profiles and scientifically justified doses. Appropriate patient selection, adequate sample sizes, validated clinical outcomes, and long-term safety monitoring will be essential.[83]

Overall, future research should move from simply demonstrating that a plant extract reduces ulcer scores toward establishing which constituents are responsible, which molecular pathways are affected, what dose is appropriate, how safe the preparation is, and whether the effect is reproducible in humans. Such a systematic approach would strengthen the evidence base for natural gastroprotective agents and improve the possibility of developing scientifically validated interventions for NSAID-associated gastric injury.[84]

3. CONCLUSION

NSAID-induced gastric ulceration is a complex gastrointestinal complication resulting from the interaction of several damaging processes, including suppression of cyclooxygenase-mediated prostaglandin synthesis, impairment of gastric mucosal defense, oxidative stress, inflammatory signalling, mitochondrial dysfunction, and epithelial cell injury. Although conventional gastroprotective medicines have an established role in preventing and managing gastric complications, their limitations and the multifactorial nature of NSAID-associated injury continue to encourage the search for additional therapeutic strategies.

Natural products and their bioactive constituents represent a promising area of research because their potential effects extend beyond simple acid suppression. Flavonoids, polyphenols, terpenoids, alkaloids, and other phytochemicals have demonstrated antioxidant, anti-inflammatory, cytoprotective, and mucosal protective properties in experimental models. Emerging pathways involving Nrf2/HO-1, NF-κB, NLRP3 inflammasome, nitric oxide signalling, mitochondrial function, and epithelial barrier regulation may provide important targets for future gastroprotective research.

However, promising preclinical findings should not be considered equivalent to established clinical efficacy. Variability in plant materials, extraction methods, phytochemical composition, experimental models, dosage, and study design remains a major challenge. Greater emphasis on extract standardization, identification of active constituents, pharmacokinetic evaluation, toxicity studies, molecular validation, and well-designed clinical trials is required. Future research should therefore focus on converting mechanistic and

experimental evidence into reproducible, safe, and clinically relevant gastroprotective interventions for patients exposed to NSAID-associated gastric injury.

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