The Promising Therapeutic Effects of Pomegranate (Punica granatum) on Gastric Ulcers: A Comprehensive Review on Antioxidant, Anti-inflammatory Properties and Molecular Mechanisms

Mohammad Yasin Zamanian¹, Ahmad Jahdari², yasir Qasim almajidi³, Zhanna Gardanova⁴, Ahmed Hjazi⁵, Furqan M. Abdulelah⁶, Sarmad Dheyaa Noori⁷, Munther Abosaooda⁸, Fattaneh Khalaj⁹, Maryam Golmohammadi¹⁰, and Niloofer Taheri¹¹

¹Hamadan University of Medical Sciences Medical School
²Hamadan University of Medical Sciences
³Baghdad College of Medical Sciences
⁴Ernst & Young Russia
⁵Prince Sattam bin Abdulaziz University College of Applied Medical Sciences
⁶Al-Bayan University
⁷Al-Ayen University
⁸Islamic University
⁹Shariati Hospital
¹⁰Shahid Beheshti University of Medical Sciences School of Medicine
¹¹Shahroud University of Medical Sciences and Health Services

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Abstract

Peptic ulcer disease is a common gastrointestinal disorder. The current treatment for gastric ulcers (GUs) is pharmacological interventions including antacids, mucosal defensive agents, H2-receptor blockers, proton pump inhibitors (PPIs) as well as antibiotics targeting H. pylori infections. Additionally, there has been an increasing focus on the application of natural treatments, such as pomegranate extracts, which have significant potential in the prevention and management of GUs. The therapeutic effects of pomegranate (Punica granatum) on GUs include its ability to inhibit ulcer formation, reduce gastric acidity, and promote the healing of gastric mucosal lesions. This is attributed to the antioxidant, anti-inflammatory, and antimicrobial properties of the active constituents in pomegranate such as polyphenols, flavonoids, tannins, and anthocyanins. The results of this study showed that pomegranate extracts could significantly suppress gastric ulceration, reduce tissue lipid peroxidation, and enhance the levels of antioxidative enzymes. Pomegranate exerts its anti-inflammatory effects through the suppression of pro-inflammatory cytokine synthesis, including TNF-α, IL-1β, and IL-6. Additionally, pomegranate extracts increase the production of gastric mucosal protective factors such as PGE2 and NO, and have antimicrobial activity against H. pylori. Overall, while pomegranate showed promise as a natural remedy for the prevention and management of GUs, further research is needed to optimize its therapeutic efficacy.
Mohammad Yasin Zamanian1,2*, Ahmad Jahdari3, Yasir Qasim Almajidi 4, Zhanna R. Gardanova5,6, Ahmed Hjazi7, Furqan M. Abdulelah 8, Sarmad Dheyaa Noor9, Munther Abosaooda10, Fattaneh Khalaj11, Maryam Golmohammadi12*, Niloofar Taheri 13

1Department of Physiology, School of Medicine, Hamadan University of Medical Sciences, Hamadan 6718773654, Iran

2Department of Pharmacology and Toxicology, School of Pharmacy, Hamadan University of Medical Sciences, Hamadan 6718773654, Iran

3 Department of Internal Medicine, School of Medicine, Hamadan University of Medical, Hamadan 6718773654, Iran

4 Department of Pharmacy (pharmaceutics), College of Medical Sciences, Baghdad, Iraq.

5 Pirogov Russian National Research Medical University, Moscow, Russia.

6 Medical University MGIMO-MED, Moscow, Russia

7 Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Prince Sattam bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia.

8College of Pharmacy, Al-Bayan University, Baghdad, Iraq.

9 Pharmaceutical Chemistry Department, College of Pharmacy, Al-Ayen University, Thi-Qar, Iraq.

10College of pharmacy, the Islamic University, 54001 Najaf, Iraq.

11Digestive Diseases Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.

12 School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran 1988873554, Iran.

13 School of Medicine, Shahroud University of Medical Sciences, Shahroud, Iran.

* Corresponding Authors:

Mohammad Yasin Zamanian (mzamanian52@yahoo.com & mzamaniyan66@yahoo.com)

Tel: +989187018850

Dr. Maryam Golmohammadi , Email: maryam.golmohammadi.sbm@gmail.com

Abstract

Peptic ulcer disease is a common gastrointestinal disorder. The current treatment for gastric ulcers (GUs) is pharmacological interventions including antacids, mucosal defensive agents, H2-receptor blockers, proton pump inhibitors (PPIs) as well as antibiotics targeting H. pylori infections. Additionally, there has been an increasing focus on the application of natural treatments, such as pomegranate extracts, which have significant potential in the prevention and management of GUs. The therapeutic effects of pomegranate (Punica granatum) on GUs include its ability to inhibit ulcer formation, reduce gastric acidity, and promote the healing of gastric mucosal lesions. This is attributed to the antioxidant, anti-inflammatory, and antimicrobial properties of the active constituents in pomegranate such as polyphenols, flavonoids, tannins, and anthocyanins. The results of this study showed that pomegranate extracts could significantly suppress gastric ulceration, reduce tissue lipid peroxidation, and enhance the levels of antioxidative enzymes. Pomegranate exerts its anti-inflammatory effects through the suppression of pro-inflammatory cytokine synthesis, including TNF-α, IL-1β, and IL-6. Additionally, pomegranate extracts increase the production of gastric mucosal protective factors such as PGE2 and NO, and have antimicrobial activity against H. pylori. Overall, while pomegranate showed promise as a natural remedy for the prevention and management of GUs, further research is needed to optimize its therapeutic efficacy.
Significance statement:
This study presents experimental models of gastric ulcers, including the pylorus ligation model and the cold-restraint stress (CRS) model, which are used to investigate the effects of substances on gastric acid production, gastric pH, gastric volume, and the development of gastric ulcers. These models aid in understanding the pathophysiology of gastric ulcers and developing potential treatments or preventive strategies.

Studies on the antimicrobial, antioxidant, and anti-inflammatory activities of *Punica granatum* (pomegranate) extracts have shown promising results in protecting gastric epithelial cells, inhibiting oxidative stress and acid production, stimulating mucus production, and inhibiting inflammation, suggesting its potential as a natural remedy for managing gastric ulcers.

Research on the effects of *Punica granatum* peel extracts on experimentally-induced gastric ulcers in rodent models demonstrated anti-ulcer properties, anti-inflammatory effects, and promotion of the healing process by increasing PDGF concentrations.

Abbreviations
GUs: Gastric ulcers
H. pylori: Helicobacter pylori
NSAIDs: Non-steroidal anti-inflammatory drugs
ROS: Reactive oxygen species
PPIs: Proton pump inhibitors
TNF-α: Tumor necrosis factor-alpha
IL-1β: Interleukin-1 beta
PGE2: Prostaglandin E2
NO: Nitric oxide
COX: Cyclooxygenase
CRS: Cold-restraint stress
SOD: Superoxide dismutase
CAT: Catalase
GPx: Glutathione peroxidase
HPA: hypothalamic-pituitary-adrenal
GSH: Glutathione
MDA: Malondialdehyde
H2O2: Hydrogen peroxide
PPEE: Pomegranate peel ethanol extract
MPO: Myeloperoxidase
VEGF: Vascular endothelial growth factor
EtOH: Ethanol
UI: Ulcer index
Introduction

Peptic ulcer disease represents an inflammatory condition of the stomach lining and is primarily caused by infectious agents or immune-related processes leading to epigastric discomfort and nausea. These ulcers typically arise along the lesser curvature of the stomach and penetrate deeper than the mucosal layer (1, 2). The development of gastric ulcers (GUs) can be attributed to various factors including infection with Helicobacter pylori (H. pylori) bacteria, prolonged use of non-steroidal anti-inflammatory drugs (NSAIDs), excessive alcohol consumption, and stress (3, 4). H. pylori infects the stomach lining and is a major cause of GUs (5, 6). H. pylori infection is very common, with an estimated 50-80% of people worldwide being infected (7). When H. pylori infects the stomach, it can cause inflammation and damage to the protective mucous layer of the stomach lining (8). This allows stomach acid to come into direct contact with the lining, leading to the formation of ulcers (9). The physiological response to gastric ulceration involves an intricate reparative mechanism encompassing cellular migration, multiplication, formation of new blood vessels, and deposition of the extracellular matrix. These concerted actions facilitate the restoration of the tissue’s structure and design within the ulcerative scar region (10). This dynamic process is regulated by an array of elements such as cytokines, growth factors, and hormonal agents (11). To treat GUs, the primary pharmacological interventions include antacids, mucosal defensive agents (sucralfate), H2-receptor blockers (ranitidine), proton pump inhibitors (PPIs) (omeprazole, esomeprazole, lansoprazole, and pantoprazole), and antibiotics targeting H. pylori infections (12).

Recently, there has been an increasing focus on the application of natural treatments for the prevention and treatment of GUs. One such natural remedy is Punica granatum, commonly known as pomegranate (13, 14). Punica granatum is a fruit-bearing shrub indigenous to the Mediterranean basin and utilized for generations in folk medicine due to its myriad therapeutic advantages (14). Pomegranate contains a plethora of active constituents such as polyphenols, flavonoids, tannins, and anthocyanins, which exhibit antioxidant, anti-inflammatory, and antimicrobial characteristics (15). These compounds are believed to contribute to the protective effects of pomegranate against GUs (16). Punica granatum extracts inhibit ulcer formation, reduce gastric acidity, and promote the healing of gastric mucosal lesions (13, 17, 18). The underlying processes of these effects are the antioxidant and anti-inflammatory properties of Punica granatum compounds (19).

Oxidative stress is responsible for the development and progression of GUs (20). In this regard, pomegranate extracts scavenge free radicals, reduce oxidative stress, and inhibit lipid peroxidation, which is the process by which ROS damage cell membranes (21, 22). These effects have been observed in both in vitro and in vivo
studies. So, by reducing oxidative stress, *Punica granatum* extracts protect the gastric mucosa from damage and promote its healing (23). In addition to their antioxidant effects, *Punica granatum* extracts exhibit anti-inflammatory properties (24). Pomegranate exerts its anti-inflammatory effects through the suppression of pro-inflammatory cytokine synthesis, including TNF-α, IL-1β, and IL-6, which are acknowledged contributors to inflammation and gastric tissue injury (25). Furthermore, pomegranate enhances the production of gastric mucosal protective factors, such as PGE2 and NO (26). PGE2 maintains the integrity of the gastric mucosa and promotes tissue repair, while NO regulates blood flow and maintains gastric mucosal defense mechanisms (27). In addition, extracts from *Punica granatum* have antimicrobial activity against H. pylori (17). H. pylori stands as a principal risk factor for GU genesis, and the ability of *Punica granatum* extracts to curb the proliferation and colonization of H. pylori may contribute to their gastro-protective effects (28).

Overall, the available evidence suggests that *Punica granatum* or pomegranate has significant promise in the prophylaxis and management of GUs (29). Its antioxidant, anti-inflammatory, and antimicrobial properties, along with its ability to enhance gastric mucosal defense mechanisms, make it a promising natural remedy for GU management (18). Additional investigation is needed to elucidate the specific mechanisms of action and optimize the dosage and formulation of pomegranate for maximum therapeutic efficacy (14).

In this review, the focus lies on exploring the fundamental mechanisms through which oxidative stress and inflammation play a role in the development of GUs (gastric ulcers). Additionally, the review investigates the effects of pomegranate supplementation on these factors. The ultimate objective is to identify potential targets that can pave the way for novel treatments for this condition.

2. Experimental models of gastric ulcer to evaluate the anti-ulcer activity of *Punica granatum*

There are various experimental models of gastric ulcer which are described below (Figure 1).

2.1. Indomethacin-induced gastric ulcer

Indomethacin, as a NSAID, is frequently used for its analgesic, anti-inflammatory, and antipyretic properties. It is categorized as a non-selective cyclooxygenase (COX) inhibitor (30). Indomethacin inhibits the activity of the COX enzyme, which is pivotal in synthesizing prostaglandins (31). Prostaglandins are hormone-like substances that play a role in inflammation, discomfort, and fever (32). By inhibiting the production of prostaglandins, indomethacin reduces inflammation and alleviates pain (33).

Indomethacin-induced GU is a model used in research to study the impacts of NSAIDS on the stomach lining (31). Indomethacin is a commonly used NSAID that can cause GU by inhibiting the production of prostaglandins, which serve a protective function in the stomach (31). In this model, indomethacin is administered orally to the rats, and it leads to the development of GUs (34). The severity of the ulcers can be assessed by measuring the ulcer index, which is a measure of the length and depth of the ulcers (35). The indomethacin-induced GU model is often used to evaluate the efficacy of potential anti-ulcer agents in preventing or reducing the formation of ulcers caused by NSAIDs (36). It allows researchers to investigate the mechanisms involved in NSAID-induced gastric damage and to test the protective effects of various compounds or interventions (37).

2.2. Aspirin-induced gastric ulcer

Aspirin, known as acetylsalicylic acid, is a common over-the-counter medication that belongs to the class of drugs called NSAIDs. It is extensively used for its analgesic, antipyretic, and anti-inflammatory properties (38). It suppresses the synthesis of specific compounds known as prostaglandins in the body, which play a role in pain, inflammation, and fever processes. By reducing the levels of prostaglandins, aspirin alleviates pain, reduces fever, and inflammation (39).

The aspirin-induced GU model is a frequently employed experimental paradigm in research to understand the effects of aspirin on the stomach lining and to evaluate potential treatments for aspirin-induced ulcers. In this model, aspirin is administered orally to animals, typically rodents, to induce GUs. The severity of the ulcers can be assessed by measuring the ulcer index, which considers the number, size, and depth of the
ulcers. Other parameters, such as gastric pH, gastric volume, and total acidity, may also be measured to evaluate the effects of aspirin on gastric acid production and mucosal integrity (40).

2.3. Pylorus ligation model

The pylorus ligation model serves as an experimental model used in research for examining the influence of various substances on the secretion of gastric acid and the development of GUs (41). It involves the surgical ligation of the pylorus, which is the opening between the stomach and the duodenum (42).

In this model, animals, typically rodents, undergo surgery to ligate or close off the pylorus, preventing the passage of gastric contents into the small intestine. This leads to the buildup of gastric acid and additional secretions within the stomach, leading to increased gastric volume and acidity (43). The pylorus ligation model provides researchers with a method to investigate the effects of substances on gastric acid production, gastric pH, gastric volume, and the development of GUs. It is often used to assess the anti-ulcer efficacy of pharmaceuticals or other interventions by measuring parameters such as ulcer index, gastric wall mucus, as well as total acidity (43). By using the pylorus ligation model, researchers can investigate the mechanisms involved in gastric acid secretion, mucosal protection, and ulcer genesis. It helps in understanding the pathophysiology of GUs and developing potential treatments or preventive strategies for gastric ulceration (44).

2.4. Alcohol-induced gastric ulcer

The alcohol-induced GU model is an experimental model used in research to study the effects of alcohol (ethanol) on the gastric mucosa and to evaluate potential treatments for alcohol-induced ulcers (45).

In this model, animals, typically rodents, are administered alcohol orally to induce GUs. Alcohol consumption exerts a deleterious impact on the stomach lining, resulting in deterioration and the formation of ulcers (46). It disrupts the protective barrier of the stomach, increases gastric acid secretion, and impairs the production of protective substances like mucus (47). The severity of the ulcers can be assessed by measuring the ulcer index, which takes into account the number, size, and depth of the ulcers (36). Other parameters, such as gastric pH, gastric volume, and total acidity, may also be measured to evaluate the impacts of alcohol on gastric acid production and mucosal integrity. The alcohol-induced GU model is often used to study the mechanisms underlying alcohol-induced gastric damage and to test the efficacy of potential gastroprotective agents. It helps researchers understand the pathogenesis of alcohol-induced ulcers and develop strategies to prevent or treat them (48).

2.5. Cold-restraint stress (CRS)

The CRS model is an experimental model used in research to induce stress-related GU in animals. It involves subjecting animals to a combination of cold temperature and physical restraint, which leads to the development of GUs (49).

In this model, animals, typically rodents, are placed in a cold environment, often at a temperature below their thermoneutral zone, and restrained to prevent movement. The combination of cold temperature and physical restraint induces stress responses in the animals, characterized by the stimulation of the HPA axis and the subsequent secretion of stress-related hormones, for instance, corticosterone (50). The stress response and release of stress hormones can lead to alterations in gastric mucosal integrity, increased gastric acid secretion, and reduced gastric blood flow, ultimately resulting in the development of GUs (51). The severity of the ulcers can be assessed by measuring the ulcer index, which takes into account the number, size, and depth of the ulcers (36). Other parameters, such as gastric pH, gastric volume, and total acidity, may also be measured to evaluate the impacts of CRS on gastric acid production and mucosal integrity. The CRS model is often used to study the mechanisms underlying stress-induced gastric damage and to test the efficacy of potential treatments or interventions for stress-related ulcers. It helps researchers understand the impact of stress on gastric health and develop strategies to prevent or mitigate stress-induced GUs (49).

Figure 1. Possible causes of gastric ulcer disease and their mechanisms.
3. Experimental Studies

3.1. Antioxidant activity of *Punica granatum*

Oxidative stress is a pivotal factor in the initiation and advancement of GU and *Punica granatum* has antioxidant activity against this process (Figure 2). This stress results from a disproportion between the generation of ROS and the organism’s capacity to counteract their harmful effects. ROS, including molecules like superoxide anion, hydrogen peroxide, and hydroxyl radicals, are highly reactive entities capable of inflicting cellular and tissue injury (52). In the context of GU, a surge in ROS levels is linked to the deterioration of the gastric lining. ROS are known to instigate lipid peroxidation, whereby free radicals target and degrade the lipids within cellular membranes, generating lipid peroxides that further injure the gastric lining and compromise its defensive barrier integrity (53). Furthermore, oxidative stress may lead to the depletion of intrinsic antioxidants such as SOD, CAT, and GPx, which are essential in mitigating ROS and shielding cellular structures from oxidative harm (20). In GU, decreased antioxidant defense mechanisms leave the gastric mucosa more vulnerable to oxidative stress (20). Ajaiikumar et al. demonstrated that administering methanolic extract from *Punica granatum* (pomegranate) significantly suppressed gastric ulceration caused by aspirin and ethanol. The extract’s effectiveness was observed as a dose-responsive reduction in ulcer index scores, reflecting its gastroprotective potential. Moreover, the extract increased the levels of antioxidative enzymes including SOD, CAT, GPx, and GSH which appeared diminished in the control group. It also reduced tissue lipid peroxidation, showcasing its antioxidative properties. Histological analysis revealed that the gastric tissue of the extract-treated subjects maintained a normal structure, contrasting with the severe mucosal erosion, submucosal swelling, and neutrophil infiltration seen in the control specimens. These results suggest that *Punica granatum* extract has gastroprotective activity through its antioxidant mechanism (54).

GSH is a tripeptide molecule composed of three amino acids: glutamate, cysteine, and glycine. It is a vital antioxidant that maintains cellular health and protects cells from oxidative damage (55). GSH is found in high concentrations within cells, particularly in the liver, where it is involved in various cellular processes. It acts as a powerful antioxidant, neutralizing harmful free radicals and ROS that cause DNA fragmentation (56). CAT is another antioxidant enzyme that protects cells from the harmful effects of H$_2$O$_2$ which is produced as a byproduct of various cellular processes (57). It is found in nearly all living organisms including plants, animals, and microorganisms (58). CAT catalyzes the decomposition of hydrogen peroxide into water and oxygen. This reaction prevents the accumulation of hydrogen peroxide, which can be toxic to cells and cause oxidative damage to cellular components such as DNA, proteins, and lipids (59, 60). Chauhan et al. indicated that the peel extract of *Punica granatum* L. (pomegranate) demonstrated gastric antiulcer and ulcer healing effects in rats. The extract exhibited significant protective activity against GUs by reducing offensive factors such as acid secretion and pepsin activity, while enhancing defensive factors like mucus secretion and mucosal glycoproteins. Additionally, the extract showed antioxidant properties by reducing oxidative stress in the gastric mucosa and increasing GSH and CAT activity. These findings suggested that *Punica granatum* L. peel extract may be beneficial in the prevention and treatment of GUs (61).

The gastric H$^+$, K$^+$-ATPase enzyme, often referred to as the proton pump, is an essential component located in the stomach’s parietal cells (62). It is integral to the secretion of gastric acid, serving a vital function in food digestion (63). This enzyme facilitates the active exchange of H$^+$ into the gastric lumen while concurrently transporting K$^+$ out of the parietal cells (64). This activity is essential for creating the highly acidic environment in the stomach. This environment is critical for breaking down food and activating different digestive enzymes (64). Targeting the gastric H$^+$, K$^+$-ATPase enzyme to inhibit its function is a common strategy for pharmaceutical interventions aimed at diminishing gastric acid production and managing GUs and other acid-related conditions (65, 66). Alimi and colleagues discovered that the extract from the root bark of *Punica granatum* has antioxidant and protective effects on the gastric mucosa, guarding against ulcers induced by ethanol in Wistar rats. In vitro analyses showed that *Punica granatum* has a greater ability to neutralize hydroxyl radicals compared to quercetin, but a lower ferric reduction potential than catechin. On the other hand, in vivo analyses demonstrated that oral administration of *Punica granatum* at doses of 100, 200, and 400 mg/kg effectively prevented ulceration caused by ethanol. *Punica granatum* usage prevented the development of severe ulcerative lesions, reduced the volume and acidity of gastric secretions,
promoted gastric mucus production, increased the levels of natural antioxidant enzymes, and decreased the concentrations of MDA and MPO. As part of this study, a liquid chromatography-mass spectrometry analysis of *Punica granatum* identified five phenolic acids and four flavonoids, all of which exhibited strong binding properties and inhibitory effects on the gastric H+, K+-ATPase enzyme. The research suggests that *Punica granatum* has a synergistic effect in enhancing antioxidant and anti-inflammatory activities, as well as inhibiting H+, K+-ATPase, which collectively support its therapeutic effectiveness in the management of GUs (18). Alam et al. further revealed that the aqueous methanolic extract of *Punica granatum* exerted a significant protective influence against experimentally-induced GUs in rodent models. The preparation mitigated the severity of ulcerative lesions prompted by alcohol, indomethacin, and aspirin. Additionally, it diminished gastric acid output and total acidity while enhancing the pH and mucus production in pylorus-ligated rodents, indicating the anti-ulcerative capability of *Punica granatum* (67).

**Figure 2.** The protective effects of *Punica granatum* on gastric epithelial cells by inhibiting oxidative stress and acid production.

### 3.2. Anti-inflammatory activity of *Punica granatum*

In addition to oxidative stress, inflammation is pivotal in the development and progression of GUs which is hindered by *Punica granatum* (Figure 3). When the lining of the stomach is damaged, either due to infection, medication, or other factors, the body’s immune response is triggered, leading to inflammation. This inflammation further damages the gastric mucosa and exacerbates the ulcer (68). Inflammatory markers such as MPO and cytokines (TNF-α, and IL-1β) are closely associated with the development and progression of GUs (69). MPO is an enzyme released by neutrophils during inflammation. Its activity is increased in GUs, indicating the presence of neutrophil-dependent inflammatory response and invasion of gastric tissues by neutrophils. This contributes to gastric mucosal damage and ulceration (70). Cytokines such as TNF-α and IL-1β are critical proinflammatory agents implicated in the development of GUs. These molecules contribute to the promotion of inflammation and damage within the gastric mucosal layer. Specifically, TNF-α is known to activate caspase-3 in both epithelial and endothelial cells within the gastric lining, initiating apoptosis and consequent tissue injury (71, 72). The increased levels of these inflammatory markers in GUs suggest the presence of inflammation and tissue damage. Inhibition or reduction of these markers helps in the healing and repair of GUs (73). Neutrophil infiltration refers to the migration and accumulation of neutrophils, a type of white blood cell, into a specific tissue or area of the body. This process occurs in response to inflammation or infection. Neutrophils are an important component of the immune system and play a crucial role in fighting off pathogens and clearing damaged tissue (74). Moghaddam et al.’s research identified that the methanol extract derived from pomegranate peel exerted a marked defensive effect against ethanol-triggered GUs in rodent models. Administering the extract at 50 mg/kg yielded the most substantial reduction in ulcer formation, exhibiting a prophylactic index of 65.87%. Varied dosages of the extract also manifested significant GU protection. Histological analysis of gastric tissue from ulcer-afflicted rats treated with the extract at 50 mg/kg disclosed extensive mucosal damage, characterized by pronounced erosion, edema in the submucosal stratum, and neutrophil infiltration. The findings underscore the methanol extracts of pomegranate peel as potential anti-ulcer agents, with their efficacy likely linked to their potent antioxidant capabilities (75).

VEGF serves as a pivotal protein in angiogenesis, the process of new blood vessel formation from existing vascular structures. It acts as a fundamental modulator of vascular development and functionality (76). Various cell types, such as endothelial cells that constitute the inner lining of blood vessels, synthesize VEGF. This protein functions as a signaling molecule, attaching to particular receptors on the surface of endothelial cells, triggering a series of events that enhance the proliferation and permeability of blood vessels (77). In the context of GUs, VEGF facilitates the formation of new vascular channels within the afflicted zone, delivering essential oxygen and nutrients to the damaged tissues, a process vital for the restoration and mending of GUs (78). VEGF increases vascular permeability, allowing fluids and immune cells to enter the affected area. This leads to a quicker influx of immune cells like neutrophils and macrophages, which play a key role in the inflammatory response and tissue healing process (79). Furthermore, VEGF stimulates
The growth and movement of endothelial cells. These cells play a crucial role in the formation of new blood vessels, helping to foster the development and healing of the damaged tissue. This process is essential for the overall recovery progress (80). In this regard, Chauhan et al. showed that treatment with Punica granatum L. peel extract reduced gastric ulceration in rats induced by CRS and ethanol (EtOH). In CRS-induced ulceration, the extract decreased the ulcer index (UI) and MPO levels compared to CRS alone. In EtOH-induced ulceration, the extract also reduced the UI and concentrations of proinflammatory cytokines (TNF-α and IL-1β), although the decrease in VEGF was not statistically significant. Overall, the study suggested that the extract had protective effects against gastric ulceration and contributed to the healing of such ulcers (81).

COX-2 is an enzyme implicated in the biosynthesis of prostaglandins. It is an isoform within the cyclooxygenase enzyme family, with COX-1 as its counterpart isofrm (82). COX-2 predominantly facilitates the synthesis of prostaglandins that play a critical role in the mediation of inflammation and discomfort. This enzyme is upregulated following an inflammatory trigger, such as tissue injury or microbial invasion. In the context of tissue damage or inflammation, there is an enhanced expression of COX-2, which is pivotal in the transformation of arachidonic acid to prostaglandins, thereby amplifying the inflammatory cascade (83). Mohamed and Mabrok showed that pomegranate peel powder (10%) had a protective effect against GUs in rats induced by aspirin. Administration of pomegranate peel powder was associated with a decrease in GU dimensions and ulcer index, along with a reduction in both the volume and acidity of gastric juice. Moreover, it facilitated the restoration of gastric mucus content and promoted the recovery of gastric tissue as observed histologically. Concurrently, there was an increase in plasma NO production and a decrease in plasma TNF-α levels following treatment with the pomegranate peel powder. The gene expression of COX-2 and TNF-α in the gastric mucosa was significantly downregulated by pomegranate peel powder. Overall, the study suggested that pomegranate peel powder could be used as a natural food supplement to protect against gastric (16). IL-1β is another pivotal pro-inflammatory cytokine in orchestrating immune responses and inflammatory processes. It is synthesized by a spectrum of cells such as macrophages, monocytes, and dendritic cells following infection, trauma, or inflammation. Its involvement is critical for the activation of immune cells, induction of fever, and enhancement of inflammation through the stimulation of further pro-inflammatory cytokines and chemokines. Additionally, IL-1β contributes to the modulation of cellular proliferation, differentiation, and apoptosis (84, 85). Interferon gamma (IFNγ) acts as a key cytokine in mounting immune defenses against viral and bacterial challenges. It is chiefly secreted by activated T cells and natural killer (NK) cells. IFNγ participates in the orchestration of both the innate and adaptive branches of the immune system and enhances the activity of macrophages, promoting their ability to kill intracellular pathogens (86). It also stimulates the production of antibodies by B cells and promotes the cytotoxic activity of NK cells. Additionally, IFNγ modulates the expression of major histocompatibility complex (MHC) molecules, which are important for antigen presentation to T cells (87). IFNγ is known for its anti-viral and anti-tumor properties. It inhibits viral replication and promotes the destruction of infected cells. It also has immunomodulatory effects, regulating the balance between pro-inflammatory and anti-inflammatory responses (88). IL-10 is an anti-inflammatory cytokine that modulates immune reactions and preserves equilibrium within the immune system. This cytokine is synthesized by a diverse array of immune cells, encompassing T cells, B cells, macrophages, and dendritic cells (89). IL-10 has potent immunosuppressive effects and dampens immune responses. It inhibits the production of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6. It also suppresses the activation and function of immune cells, including T cells, NK cells, and macrophages (90). IL-10 primarily restricts rampant inflammatory responses and safeguards tissues from harm resulting from immune hyperactivity. It is instrumental in preserving immune homeostasis and averting autoimmunity. Additionally, IL-10 contributes to the restoration of tissues and the healing process of wounds (91, 92). NFκB functions as a pivotal regulatory transcription factor for gene expression pertinent to immunological responses, inflammation, cellular longevity, and growth. NFκB responds to a spectrum of triggers, encompassing pro-inflammatory cytokines, microbial elements, oxidative stress, and viral infections (93, 94). In its inactive state, NFκB resides in the cytoplasm, associated with inhibitory proteins known as IxBs (95). Activation prompts the phosphorylation and subsequent degradation of IxBs, facilitating the translocation of NFκB into the nucleus. NFκB targets specific DNA sequences,
the xB sites, enhancing the transcription of genes integral to immune and inflammatory pathways (95). The engagement of NFkB triggers the synthesis of pro-inflammatory cytokines, chemokines, cell adhesion molecules, and enzymes that are crucial in producing inflammatory mediators. Furthermore, it modulates gene expressions pivotal to cell viability and multiplication, thus playing an essential role in an array of both normal and pathological conditions including immune reactions, inflammation, oncogenesis, and autoimmunity (96). Besides, apoptosis is vital for sustaining equilibrium between cell division and cell demise within the gastric mucosal layer (97). It removes damaged or injured cells, allowing for the regeneration of healthy cells and tissue repair. This process is important for the healing of GUs. Apoptosis regulates the inflammatory response in GUs. It eliminates inflammatory cells, such as neutrophils and macrophages that are recruited to the site of injury. Excessive inflammation exacerbates tissue damage and delays ulcer healing, so apoptosis controls and resolve the inflammatory process (98). Apoptosis maintains the integrity of the gastric epithelial barrier and removes damaged or compromised epithelial cells (99). Disruption of the epithelial barrier leads to further damage and delayed ulcer healing. Excessive or prolonged apoptosis has detrimental effects on GU healing. If there is an imbalance between cell death and cell proliferation, it can lead to excessive tissue damage and delayed healing. In some cases, increased apoptosis contributes to the persistence or chronicity of GUs (100, 101). On the other hand, Bcl-2 functions as an anti-apoptotic molecule, thereby fostering cellular survival and impeding apoptosis. It achieves this by hindering the discharge of cytochrome c from mitochondria, an essential phase in triggering the apoptotic cascade (102). Bcl-2 obstructs the liberation of cytochrome c, which helps to preserve the integrity of the mitochondrial membrane and prevents the activation of caspases. Caspases are proteolytic enzymes that catalyze the initiation of apoptosis (102). The equilibrium between pro-apoptotic and anti-apoptotic proteins within the Bcl-2 family is integral in deciding a cell’s fate—whether it will succumb to apoptosis or persist. A disturbance in this delicate balance can profoundly affect cellular viability and the maintenance of tissue equilibrium. For instance, heightened expression of Bcl-2 results in augmented cellular endurance and a formidable resistance to apoptotic signals, correlating with the emergence and advancement of oncogenic processes (103). On the other hand, downregulation or inhibition of Bcl-2 can promote apoptosis and cell death. This has been explored as a therapeutic strategy in cancer treatment, as targeting Bcl-2 can sensitize cancer cells to chemotherapy-induced apoptosis (104). In this process, caspase 9 is a critical enzyme within the intrinsic or mitochondrial apoptosis pathway, which stands as one of the primary conduits for programmed cell eradication. Apoptosis is a meticulously orchestrated mechanism designed to dispose of superfluous or compromised cells, with caspase 9 playing an essential role as a facilitator of this process (105, 106). Within the intrinsic apoptosis pathway, a variety of cellular stressors such as genotoxic stress or intracellular distress signals, instigate the migration of cytochrome c from the mitochondria into the cytosol. Following this, cytochrome c associates with Apaf-1, assembling into a structure known as the apoptosome. This configuration then proceeds to recruit and activate caspase 9, which in turn spearheads the cascade of events that constitute the apoptotic process (107, 108). Upon its activation, caspase 9 proceeds to cleave and catalyze the activation of subsequent effector caspases like caspase 3. These effectors carry out the apoptotic program by specifically cleaving cellular substrates. The targets encompass structural proteins, enzymes involved in DNA repair, and suppressors of DNA fragmentation, culminating in the demise of the cell (109, 110). The activation of caspase 9 is tightly regulated by the balance of pro-apoptotic and anti-apoptotic factors in the cell. For example, the Bcl-2 family of proteins, including anti-apoptotic members like Bcl-2, inhibits the release of cytochrome c and prevents the activation of caspase 9. On the other hand, pro-apoptotic members of the Bcl-2 family, such as Bax and Bak, promote cytochrome c release and caspase 9 activation (102, 111, 112). PGE2 is a lipid molecule that plays a critical role in maintaining the integrity of the gastric mucosa and promoting gastric mucosal defense. It is produced by the COX enzyme from arachidonic acid, which is released from cell membranes during inflammation or injury (113, 114). PGE2 inhibits the secretion of gastric acid by reducing the activity of the proton pump in the parietal cells of the stomach. This prevents excessive acid production, which contributes to the development of GUs. PGE2 has anti-inflammatory properties and reduces inflammation in the gastric mucosa. It inhibits the production of pro-inflammatory cytokines and chemokines, and it can also suppress the activation of immune cells involved in the inflammatory response (115, 116). Katary and Salahuddin’s research demonstrated that administering
punicalagin (PCG) prior to ethanol exposure mitigated gastric ulceration and attendant histological deteriorations associated with ethanol-induced GU. Moreover, PCG curtailed the oxidative distress instigated by ethanol while amplifying antioxidative mechanisms. It moderated the transcriptional activity of TNF-α and attenuated the mucosal concentrations of pro-inflammatory cytokines, including TNF-α, IL-1β, and IFNγ, and concurrently augmented the mucosal levels of the anti-inflammatory cytokine IL-10. Additionally, PCG decreased the expression of NFκB within the gastric mucosa, the activity of MPO and caspase 3, as well as the transcription of caspase 9. In contrast, it enhanced the expression of the anti-apoptotic gene Bcl-2, along with elevating mucosal nitric oxide and mucin quantities. Contrarily, PCG exhibited an inhibitory influence on PGE2 and gastric acid secretions. Based on these findings, it can be concluded that PCG possesses gastroprotective properties against ethanol-induced gastric ulcers. These properties are achieved by reducing oxidative stress and inflammation in the gastric mucosa through the NFκB signaling pathway. Additionally, PCG strengthens the protective mechanisms of the gastric cells, independent of PGE2 and acid secretion activities (117).

PDGF is recognized as a crucial element within the human growth factor cohort, orchestrating cellular proliferation and differentiation. Initially identified within the serum component of whole blood, it is notably absent in the serum derived from plasma devoid of cells. PDGF is integral to the wound healing cascade, promoting cellular proliferation, motility, and the formation of new blood vessels (118). Talaat et al. conducted a study to examine how methanolic pomegranate peel extracts affect the healing of experimentally-induced GUs in rodent models. The results showed that the extracts had anti-ulcer properties and also acted as anti-inflammatory agents. This was demonstrated by a significant reduction in the expression of COX-2 in the gastric mucosa and a decrease in plasma TNF-α levels. Additionally, the extracts facilitated the healing process by increasing PDGF concentrations. The most noticeable regenerative effect was observed when the epicarp extract was given at a dose of 500 mg/kg. The study suggests that pomegranate peel extracts could be a promising therapeutic option for managing GUs due to their combined anti-inflammatory and healing properties (119).

NO, synthesized by eNOS, serves as a potent vasodilatory agent, facilitating the relaxation of blood vessels and subsequently augmenting blood flow to the gastric mucosa (120). This increased perfusion is vital for maintaining an adequate supply of oxygen and nutrients, crucial for the structural integrity and reparative processes of the gastric lining. Furthermore, NO exerts antioxidative properties, enabling the neutralization of ROS that are implicated in oxidative stress. Through the mitigation of oxidative stress, NO contributes to the protection and recuperation of the gastric mucosa (121). In addition to its role in oxidative stress, NO modulates the inflammatory cascade within the gastric mucosa. It has the capacity to impede the adhesion and activation of inflammatory cells, such as neutrophils, and curtail the synthesis of pro-inflammatory cytokines. This anti-inflammatory action of NO is essential in attenuating inflammation and subsequent tissue damage that characterizes GUs (122). Additionally, MDA is a marker of oxidative stress and lipid peroxidation. In the context of GUs, MDA levels can be used to assess the extent of oxidative damage to the gastric mucosa. GUs are often associated with an imbalance between the production of ROS and the antioxidant defense mechanisms in the stomach. This imbalance leads to increased oxidative stress and the generation of MDA (53, 123). The presence of GUs can result in the disruption of the gastric mucosal barrier, allowing ROS to attack the lipid membranes of cells. This attack leads to the peroxidation of lipids, resulting in the production of MDA as a byproduct. Elevated levels of MDA in the gastric mucosa or in the blood can indicate the presence of oxidative stress and the severity of the ulcer (124). Also, IL-2 functions as a cytokine, a category of signaling proteins used for intercellular communication within the immune system. It is predominantly synthesized by activated T lymphocytes, including both CD4+ helper T cells and CD8+ cytotoxic T cells. The pivotal function of IL-2 lies in its capacity to orchestrate immune responses, earning its designation as a T cell growth factor due to its critical role in the proliferation and differentiation of these cells (125, 126). An increase in IL-2 concentrations within the gastric mucosa or systemic circulation is indicative of immune system engagement and inflammation, which are commonly associated with the pathogenesis of GUs. The increased synthesis of IL-2 can drive the mobilization and activation of various immune cells, precipitating tissue injury and the development of ulcerative lesions (127). IL-6 is a multifunctional cytokine
that is integral to the immune response and inflammatory processes. It is synthesized by a diverse array of
cells, including those within the immune system such as T cells, B cells, and macrophages, as well as cells
outside the immune system, including fibroblasts and endothelial cells. IL-6 plays a complex role in host
defense mechanisms, aiding in the stimulation of acute phase responses, hematopoiesis, and inflammation.
It also assists in the regulation of metabolic, regenerative, and neural processes (128). Elevated levels of IL-6
have been consistently detected within the gastric mucosa and the circulatory system of individuals afflicted
with GUs. The prevailing hypothesis is that IL-6 contributes significantly to the inflammatory pathway
and subsequent tissue damage that characterize ulcer development. Its influence includes the stimulation
of additional pro-inflammatory cytokines and chemokines, the attraction and recruitment of immune cells
to the site of inflammation, and the further activation of these cells, all of which converge to promote the
inflammatory environment associated with gastric ulceration (129, 130). IL-6 is pivotal in maintaining the
equilibrium between pro-inflammatory and anti-inflammatory agents within the gastric mucosa. Disruptions
in this delicate cytokine equilibrium can interfere with the natural reparative processes and may lead to
the chronicity or recurrence of GUs (131). Research conducted by Abd el-Rady et al. illustrated that
the administration of pomegranate extract and pomegranate-loaded nanoparticles (PLN) yielded a notable
decrease in indomethacin-induced GUs in rat models. Observations of the gastric mucosa in subjects treated
with PLN and pomegranate peel extract revealed an absence of noticeable lesions. Furthermore, there
was a significant reduction in both the ulcer scores and the ulcer index for the groups receiving PLN and
extract treatments in comparison to the cohort treated with indomethacin alone. Notably, PLN was found
to possess a superior gastroprotective effect, with a net inhibition index of 97.06%, whereas PPE exhibited a
net inhibition index of 76.48%. In the experimental group, the incidence of multiple GUs was notably higher
in rats administered indomethacin when juxtaposed with the control counterparts. There was an increment
in the ulcer index as well as a rise in serum concentrations of MDA, IL-2, and IL-6. Conversely, there was
a substantial decline in the concentrations of IL-10, PGE2, and NO, alongside a decrease in eNOS mRNA
expression. Histological examination revealed considerable damage to the gastric surface epithelium, with
glandular structure disruption and pronounced immune cell infiltration within the lamina propria. Enhanced
TNF-α expression and reduced eNOS presence were detected in the gastric mucosa via immunohistochemical
analysis. Nonetheless, oral administration of PLN and extract markedly ameliorated the morphological
appearance of the gastric mucosa and reinstated the homeostasis of biochemical parameters, histopathological
integrity, and immunohistochemical profiles. Overall, the study demonstrated that pomegranate extract and
PLN have significant gastroprotective effects against GUs induced by indomethacin in rats. They reduce
ulcer formation, restore the balance between oxidants and antioxidants, increase gastric protective factors,
and exhibit anti-inflammatory effects (132).

Diclofenac is an NSAID widely recognized for its analgesic, anti-inflammatory, and antipyretic effects.
It is classified within the phenylacetic acid derivatives drug category and suppresses the synthesis of
prostaglandins in the body (133). By reducing the levels of prostaglandins, diclofenac helps to alleviate
pain, reduce inflammation, and lower fever. It is important to note that diclofenac, like other NSAIDs,
can have side effects, particularly on the gastrointestinal system, and should be used under the guidance
of a healthcare professional (134). Diclofenac can increase the risk of developing peptic ulcers through its
mechanism of action as a NSAID. NSAIDs, including diclofenac, work by inhibiting the production of an
enzyme called COX. This enzyme is responsible for the synthesis of prostaglandins, which are substances
that play a protective role in the gastrointestinal tract (135). Piracha et al. showed that the methanolic
extracts of *Punica granatum* (Pomegranate) peel and seed demonstrated significant gastroprotective activity
against diclofenac-induced peptic ulcers. The treatment groups that received the extracts showed a signif-
ificant reduction in gastric juice volume, an increase in pH of gastric juice, and a reduction in ulcer index
compared to the disease control group. The combination of pantoprazole (a standard antulcer drug) with
the peel and seed extracts showed the best results, exhibiting greater antulcer activity than pantoprazole
alone. Overall, the study concluded that *Punica granatum* peel and seeds could be used for the prevention
of peptic ulcers (136).

Indomethacin is a NSAID that is commonly used to reduce pain, inflammation, and fever. It belongs to the
class of medications known as COX inhibitors, which work by blocking the production of certain chemicals in the body that cause inflammation. Indomethacin is often prescribed for conditions such as rheumatoid arthritis, osteoarthritis, gout, and certain types of headaches. It is available in various forms, including oral capsules, suppositories, and injections (137). Al-badry and Aziz demonstrated that administering an aqueous extract of pomegranate peels at varying concentrations (25, 50, and 100 mg/kg body weight) resulted in a notable amelioration of gastric ulceration in the experimental rat models. In the group with induced gastric ulceration, there was a notable reduction in the body weight of the rats when contrasted with the control group. In contrast, those administered with pomegranate peel extract exhibited a significant elevation in body weight relative to the group with gastric ulceration. The weights of internal organs, including the heart, liver, kidneys, spleen, and ovaries, diminished markedly in the rats with gastric ulceration compared to controls. However, the administration of pomegranate peel extract across all tested concentrations led to an upturn in the weights of these organs when compared with the ulcerated group. In the gastric ulceration group, the level of luteinizing hormone (LH) decreased significantly compared to the control group. However, there was no significant change in the levels of follicle-stimulating hormone (FSH), estrogen, and progesterone. Treatment with pomegranate peel extract resulted in a decrease in hormone levels compared to the gastric ulceration group. The administration of indomethacin, which induced gastric ulceration, caused various histopathological changes in the stomach, including an affected muscularis layer, fibrosis, infiltration of inflammatory cells, changes in the epithelium layer, and congestion of blood vessels. However, treatment with pomegranate peel extract at all concentrations led to the reconstitution of the stomach with a normal mucosa layer, epithelial tissue, and no signs of GU. In summary, the study demonstrated that the aqueous extract of pomegranate peels has beneficial effects in the treatment of gastric ulceration in experimental rats. It improved body weight, organ weight, hormone levels, and histopathological changes associated with gastric ulceration (13). Moreover, Moghaddam and colleagues demonstrated the protective effects of pomegranate peel’s methanol extract against ulcer formation. When administered orally as a preemptive treatment, the extract safeguarded the gastric lining from indomethacin-triggered damage. Optimal outcomes were recorded at a dose of 50 mg/kg using the sour summer variety, which showed a significant reduction in peptic ulcer development in comparison with the group where GUs were induced by indomethacin. The extract also showed antioxidant activity, which may contribute to its anti-ulcer properties (29).

### 3.3. Antimicrobial activity of *Punica granatum*

Omeprazole, a drug classified as a proton pump inhibitor, is frequently prescribed for managing ailments associated with an overproduction of stomach acid, such as gastroesophageal reflux disease, peptic ulcer disease, and Zollinger-Ellison syndrome. Its therapeutic effect is achieved through the diminution of gastric acid secretion, thus aiding in symptom alleviation and the restoration of gastric mucosal integrity (138, 139). Muhialdin et al. showed that the aqueous extract of *Punica granatum* (pomegranate) peel had a significant inhibitory effect on the formation of stomach ulcers caused by *H. pylori*. The high dose of the extract (500mg/kg) resulted in an 84.60% inhibition of ulcer formation, while the low dose (250mg/kg) resulted in a 42.87% inhibition. In comparison, the standard drug omeprazole only achieved a 24.50% inhibition. The extract also showed a decrease in gastric acidity and a change in the color of the stomach, indicating its protective effects. Histopathological examination revealed that the extract prevented ulcer formation and reduced damage to the stomach mucosa. Overall, the study demonstrated the gastro-protective and therapeutic effects of *Punica granatum* against stomach ulcers caused by *H. pylori* (17). Alam et al. documented that the aqueous methanolic extract of *Punica granatum* possessed considerable anti-ulcer efficacy in a rat model. Administered at a dosage of 980 mg/kg, the extract yielded an ulcer index of 0.35±0.08, which translates to a substantial 87.5% diminution of ulcerative activity when juxtaposed with the toxic control group. In comparison, omeprazole, the reference medication utilized within the research, manifested an ulcer index of 1.41±0.08, correlating to a 49.64% reduction in ulcer formation. In summary, the study found that the aqueous methanolic extract of *Punica granatum* has potent anti-ulcer activity, while other extracts did not show significant anti-ulcer activity. Omeprazole, a commonly used drug for treating ulcers, also exhibited anti-ulcer activity in the study (140).

*In vivo* investigations conducted with female Wistar rats revealed that an 8-day oral regimen of PPEE
substantially diminished H. pylori-induced gastritis and lessened both lymphocytic presence and chronic inflammation indicators. The regimen proved to be devoid of acute toxic effects, even at comparatively substantial dosages. Given these results, the research implies the viability of pomegranate peel extract as an adjunctive or alternative therapeutic agent for the amelioration of H. pylori-related GUs (141). Faisal showed that the aqueous and ethanolic extracts of *Punica granatum* (pomegranate) peel had antibacterial activity against H. pylori. The ethanolic extract was found to be more potent than the aqueous extract, possibly due to the higher concentration of bioactive components. The extracts were effective in inhibiting the growth of H. pylori *in vitro*, with the ethanolic extract showing a higher degree of inhibition. The study also identified various bioactive components in the extracts, including alkaloids, flavonoids, glycosides, tannins, and saponins, which contributed to their antimicrobial activity. Overall, the study suggested that pomegranate peel extracts had the potential to be used as alternative therapeutic options for H. pylori infections (142). Furthermore, Mayyas et al. showed that pomegranate peel ethanol extract (PPEE) exhibited significant antibacterial activity against H. pylori *in vitro*, with a minimum inhibitory concentration of 0.156 mg/mL. The extract also demonstrated urease inhibitory activity against H. pylori. When PPEE was combined with metronidazole, a synergistic effect was observed. Infection with H. pylori is a considerable risk factor for the onset of GUs. The bacterium can disrupt the protective mucous layer of the stomach, allowing acid and other irritants to damage the underlying tissue. It also produces toxins that can directly damage the gastric epithelial cells (143). Overall, these studies suggested that *Punica granatum* extract could be a promising alternative or complementary therapy for the treatment of GUs associated with H. pylori infection. However, further research and clinical trials are needed to validate these findings and determine the optimal dosage and treatment duration for human patients. It is important to consult with a healthcare professional before using pomegranate or any other natural remedy for the treatment of GUs or H. pylori infections.

Al-Hussaini’s study indicated that rabbits administered with an ethanolic extract of *Punica granatum* peel at an oral dose of 200 mg/kg/day over a 15-day period exhibited a notable decrease in serum glucose, urea, creatinine, ALT, and gamma-glutamyl transferase (GGT) levels in contrast to the cohort treated with ethanol alone. Yet, the alteration in blood triglyceride concentrations was not statistically significant. Histological analysis of gastric tissues from the treated rabbits revealed a regenerative response in GUs and lesions, along with restoration of the superficial glandular structures within the mucosa, unlike the observations in the gastric tissues of the ethanol-only group. These outcomes imply that the extract of pomegranate peel confers a protective mechanism against the gastric mucosal damage prompted by ethanol in rabbit models used for experimentation (144).

Experimental studies have shown that *Punica granatum* extracts significantly suppressed gastric ulceration, reduced tissue lipid peroxidation, and exhibited antioxidant, anti-inflammatory, and anti-ulcer activities. The extracts elevated the levels of antioxidative enzymes, reduced tissue lipid peroxidation, and promoted tissue repair. Additionally, pomegranate extracts demonstrated antibacterial activity against H. pylori. Moreover, pomegranate peel extracts have been found to increase PGE2 and NO levels, decrease oxidative stress, and inhibit the production of pro-inflammatory cytokines. The extracts were also effective in reducing the activity of the gastric H⁺, K⁺-ATPase enzyme, which is essential in reducing gastric acid production and managing gastric ulcers.

**Figure 3. The protective effects of Punica granatum on gastric epithelial cells by stimulating mucus production and inhibiting inflammation.**

**Table 1** shows a summary of the results of the studies.

**Conclusion**

The study investigated the impacts of *Punica granatum* on GUs and found that *Punica granatum* extracts can inhibit ulcer formation, reduce gastric acidity, and promote the healing of gastric mucosal lesions. The underlying processes of these observed effects are thought to involve the antioxidant and anti-inflammatory properties of *Punica granatum* compounds. It was determined that pomegranate exerts its anti-inflammatory
effects through the suppression of pro-inflammatory cytokine synthesis, including TNF-α, IL-1β, and IL-6, which are acknowledged contributors to inflammation and gastric tissue injury. Additionally, *Punica granatum* enhanced the production of gastric mucosal protective factors, such as PGE2 and NO, which maintain the integrity of the gastric mucosa, regulate blood flow, and contribute to its antioxidant effects. However, further investigation is needed to elucidate the specific mechanisms of action and optimize the dosage and formulation of pomegranate for maximum therapeutic efficacy. Therefore, pomegranate shows potential for application in future clinical studies for the treatment of GUs, but additional research and clinical trials are necessary to validate its efficacy and determine the optimal treatment protocols.

**Authors’ contributions**

M.Y.Z, & M.G; investigation, Y.Q.A, Z.R.G & A.H; resources, F.M.A., & S.D.N.; data curation, M.A., F.K & N.T.; writing—original draft preparation, M.G., A.J & M.Y.Z.; writing—review and editing, M.G & M.Y.Z visualization and supervision, M.G. & M.Y.Z; project administration. All authors have read and agreed to the published version of the manuscript.

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