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Review Paper

Phytochemical and Anti-Ulcer Perspectives of Garlic and Papaya Seeds- A Comprehensive Review

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ABSTRACT

Peptic ulcer disease remains a major global health concern, driven by factors such as *Helicobacter pylori* infection, excessive gastric acid secretion, oxidative stress, and widespread use of non-steroidal anti-inflammatory drugs (NSAIDs). In recent years, medicinal plants have gained increasing attention as alternative or complementary therapies due to their safety, affordability, and multi-targeted therapeutic actions. This review comprehensively examines and compares the anti-ulcer properties of garlic (*Allium sativum*) and papaya (*Carica papaya*) seed extracts, with a particular focus on their individual mechanisms and potential synergistic effects. Existing preclinical and limited clinical findings indicate that garlic exhibits potent gastroprotective activity through its antioxidant sulfur-containing compounds, modulation of inflammatory pathways, inhibition of *H. pylori*, and enhancement of mucosal defense. Similarly, papaya seed extract demonstrates anti-ulcer potential via its flavonoids, alkaloids, and proteolytic enzymes, which contribute to free-radical scavenging, mucosal regeneration, and reduction of acid secretion. Comparative analysis suggests that while both extracts possess significant anti-ulcer efficacy, their bioactive constituents operate through partially overlapping but complementary mechanisms. Emerging evidence further supports the possibility of synergistic interactions between garlic and papaya seed extracts, offering enhanced antioxidant protection, improved mucosal healing, and broader antimicrobial activity. This review highlights the therapeutic promise of integrating these natural agents into ulcer management strategies and underscores the need for standardized formulations and controlled clinical studies to validate their combined efficacy and safety.

INTRODUCTION

The most prevalent gastrointestinal tract condition is peptic ulcer disease, which comprises duodenal

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and stomach ulcers, which are typically acidic and therefore quite painful. Acid, pepsin, *Helicobacter pylori*, and other offensive and defensive elements (mucin, prostaglandin, bicarbonate, nitric oxide, and growth factors) are out of balance in the pathophysiology of peptic ulcer disease [1]. In the stomach or duodenum, a mucosal breach larger than 3–5 mm with a discernible depth is commonly referred to as peptic ulcer disease. Because of this, it is an endoscopic diagnostic as opposed to dyspepsia, which is a clinical diagnosis based solely on symptoms [2]. Loss of appetite, weight loss, and epigastric discomfort more especially, pain that is alleviated by eating or taking antacids and pain that wakes you up at night or in between meals are signs of peptic ulcer disease [3].

Helicobacter pylori infection is closely linked to both duodenal and gastric ulcer cases. Infection with *H. Pylori* is detectable in 90–100% of patients with duodenal ulcers and 60–100% of patients with stomach ulcers [4]. According to patient follow-up, the incidence of duodenal ulcer recurrence significantly decreased following a successful *H. Pylori* infection treatment [5]. The most reliable methods for detecting an *H. Pylori* infection and verifying recovery are urea breath tests and stool antigen assays [6]. Based on clarithromycin resistance, first-line treatments for *H. Pylori* eradication are recommended. We suggest a 14-day bismuth quadruple therapy (BQT) or 14-day concurrent therapy as the first-line treatment in regions with substantial clarithromycin resistance ($\geq 15\%$). For first-line treatment, we suggest 14-day triple therapy or 14-day BQT in regions with limited clarithromycin resistance ($< 15\%$). Second-line treatments include 14 days of levofloxacin triple therapy or, if BQT has never been administered, 14 days of BQT [7]. Growing antimicrobial resistance has led to a general decrease in treatment success, necessitating a reconsideration of the strategy for creating treatment guidelines and the adoption of

the concepts of antibiotic use and antimicrobial stewardship [8]. Anticholinergics, H₂-receptor antagonists, liquorice derivatives, and antacids (including bismuth for convenience) are the four primary categories of medications frequently used to treat or relieve the symptoms of peptic ulcers [9]. Among the most widely used and overprescribed drugs worldwide are PPIs. PPIs have mild and generally treatable adverse effects, including headache, diarrhoea, constipation, and abdominal pain. The absorption of specific vitamins, minerals, and pharmaceuticals may also be impacted by PPIs' reduction of gastric acid. PPI users have been known to experience iron deficiency anemia and vitamin B12 insufficiency. Furthermore, by preventing the calcium salts from ionizing and solubilizing, which is necessary for their absorption, PPIs may raise the risk of osteoporosis and bone fractures [10]. As a result, using natural medicine to treat a variety of illnesses, including peptic ulcers, is imperative in the modern era [11].

2. Phytochemical Profile of Garlic and Papaya Seeds

Garlic bulbs are a rich source of sulfur-containing phytochemicals, notably Allicin, as well as other compounds including diallyl disulfide (DADS), diallyl trisulfide (DATS), ajoenes (E- and Z-forms), vinyl dithiins, and S-allyl cysteine (SAC). Other reported phytochemical classes in garlic include saponins, steroids, glycosides, and polysaccharides (e.g., fructans) along with trace minerals and enzymes (12). In addition to organosulfur compounds, garlic also contains phenolics and flavonoids, which contribute to its antioxidant and other pharmacological properties (13). The varied phytochemical composition of garlic underlies its wide spectrum of biological activities antioxidant, immunomodulatory, antimicrobial, cardiovascular



protective, and more(14). Studies on ethanolic extracts of papaya seeds (EECPs) have demonstrated the presence of flavonoids, phenols, tannins, alkaloids, glycosides, saponins, terpenoids, among other bioactive compounds. The rich phytochemical composition of papaya seeds supports their potential antioxidant, anti-inflammatory, antimicrobial, and other pharmacological activities, which may underlie their traditional use in treating digestive disorders, and possibly ulcer or gastric problems (15). Proximate analysis of matured papaya seeds revealed substantial amounts of crude fat, carbohydrates, crude fibre, protein, ash, and moisture indicating the seeds are also a source of macronutrients(16). Some studies report phenolic acids, fatty acids, sterols, triterpenes, and isothiocyanates among the secondary metabolites isolated from papaya seeds (17).

3. Anti-Ulcer Potential of Carica Papaya Seeds

Papaya is a member of the tiny family Caricaceae, which has four genera worldwide. Four species of the genus *Carica* L. are found in India, with *Carica papaya* L. being the most well-known and extensively grown species (18). In tropical and subtropical regions of the world, papayas (*Carica papaya* L.) are a common and significant fruit tree. The fruit is utilized as a processed product or consumed as a fresh fruit and vegetable all over the world. The entire plant, including the fruit, root, bark, peel, seeds, and pulp, is believed to have therapeutic qualities in addition to being tasty and nutritious (19). Terpenoids, alkaloids, flavonoids, tannins, glycosides, saponins, and phenols were found in *C. papaya* extracts, according to phytochemical analysis (20). Because of their antioxidant properties, papaya and its compounds are known to have health-promoting properties. *C. papaya* The various plant portions of papaya include a variety of beneficial compounds, including

vitamins, flavonoids, and minerals, each of which plays a part in the treatment of disease (21). Research on the antiacid and anti-pepsin properties of the seeds of the tropical fruit *Carica papaya* has shown promise in treating stomach ulcers; in fact, multiple in vitro experiments have demonstrated the gastroprotective benefits of the seed extract. However, the extract's anti-inflammatory and antimicrobial qualities have demonstrated complementary advantages in the prevention and management of stomach ulcers (22).

4. Anti-Ulcer Potential of Allium Sativum

Garlic production worldwide Of the *Allium* species, *Allium sativum* L. is the second most important, after onions (23). The herbaceous plant garlic (*Allium sativum* L.), which is a member of the *Amarillidaceae* family, is used as a spice and traditional medicine worldwide. Numerous physiologically active substances, such as phenolic compounds, saponins, polysaccharides, and organosulfur compounds, are found in garlic and contribute to its many pharmacological qualities (24). Numerous chemicals have been identified and analyzed from garlic, demonstrating its chemical diversity. The most researched substances found in garlic are most likely allicin, diallyl sulfides, and ajoene (25). Garlic, both fresh and aged, as well as its oil and powder, has been utilized for generations as a food, medicine, and spiritual cure. Numerous ailments, such as joint and tooth pain, coughing, constipation, gynecologic disorders, infectious infections, parasitic infestations, and animal and insect stings, are treated with it in traditional medicine. Garlic and its oil have strong anti-oxidant, anti-inflammatory, immunomodulatory, hepatoprotective, anti-atherosclerotic, antibacterial, and antineoplastic properties, according to evidence from recent experimental and clinical studies. Hundreds of active

substances, including diallyl, dimethyl and allyl-methyl, mono to hexa-sulfides, and alliin, are thought to be responsible for these actions (26). Garlic has a documented effect on the mucosa of the gastrointestinal tract. It is well known that garlic prevents *H pylori* from growing. Due to its antioxidant properties, garlic oil has been shown to have an antiulcer effect in cases of ethanol-induced stomach injury. According to traditional medicine, eating garlic can help with stomach issues (27).

5. Safety Profile and Toxicological Considerations

5.1 Acute Toxicity Studies

Acute toxicity evaluations are essential to establish the immediate safety of bioactive botanicals like garlic (*Allium sativum*) and papaya seeds (*Carica papaya*), which are explored for their gastroprotective potential. In traditional toxicology models, *acute toxicity* refers to adverse effects observed soon after a single high-dose exposure of a test substance, often within a 24–14 day observation period (28). Studies conducted on the ethanolic extract of *Carica papaya* seeds demonstrate a high threshold for acute toxicity. Oral administration of papaya seed extract at doses up to 2000 mg/kg body weight in Wistar rats did not result in mortality, behavioral changes, or significant histopathological abnormalities of vital organs such as the liver and kidneys during a 14-day monitoring period, indicating a favorable acute safety profile (29,30). Similarly, solvent fractionation studies have reported that various extracts of papaya seed—including aqueous, methanol, and ethyl acetate fractions—exhibited LD₅₀ values greater than 5000 mg/kg, with no significant alterations in body weight or clinical condition in rodent models (31). These findings collectively suggest that *Carica papaya* seed extracts are non-toxic at doses significantly higher

than those used in herbal or therapeutic contexts. Toxicological data for garlic, which contains organosulfur phytochemicals such as allicin and related compounds, are somewhat more nuanced. While direct acute toxicity studies of whole garlic extracts in standard mammalian models are fewer, related investigations using isolated constituents like diallyl disulfide—a major garlic bioactive metabolite—report oral LD₅₀ values in rats in the hundreds of mg/kg range, indicating that concentrated garlic compounds may exhibit dose-dependent toxic effects at high exposures (32). Other rodent studies evaluating repeated garlic essential oil exposure for up to 28 days confirm that, at moderately low daily oral doses, mutagenicity and clastogenicity are absent, reinforcing that garlic's safety margin is acceptable within conventional use levels (33). However, research recommends cautious interpretation of extrapolated doses to avoid potential adverse effects on organs like the liver or kidneys when administered excessively or over extended periods (34).

5.2 Sub-Chronic Toxicity Data

Evaluating sub-chronic toxicity is critical for determining potential adverse effects following repeated or prolonged exposure to phytochemical extracts, especially when considering therapeutic use for gastric ulcer management. Unlike acute toxicity tests, sub-chronic studies typically expose animals to daily doses over extended periods—most commonly 28 to 90 days—to identify subtle toxic effects on physiological, biochemical, and histopathological parameters. For *Carica papaya* seed and related extracts, although direct sub-chronic toxicity studies of papaya seed extracts themselves are limited, research on other *Carica papaya* preparations provides relevant insights. Repeated-dose oral studies with papaya leaf extracts administered daily to Sprague–Dawley



rats for up to 13 weeks showed no mortality, clinical toxicity signs, or significant behavioral changes across low to high dose groups (0.01–2 g/kg body weight). Body weight, food and water intake remained stable, and no treatment-related histopathological alterations in major organs were identified (35). Similarly, 28-day repeated dose studies of papaya leaf and other papaya extracts demonstrated no significant morphological damage in vital organs or toxic effects at doses far exceeding traditional use, suggesting a broad safety margin in prolonged exposure scenarios (36). sub-chronic toxicological research on garlic (*Allium sativum*) has also been performed, albeit primarily focusing on derivatives or related preparations rather than *whole garlic seed*. For example, sub-chronic evaluation of black garlic ethanol extract in female mice reported no overt toxic effects on liver histology after repeated dosing over several weeks, implying that processed garlic products could be tolerated without significant organ damage at moderate doses (37). Complementary toxicological assessments of *Allium*-based formulations in 90-day feeding studies similarly reported no clinically relevant adverse effects on growth, organ weights, or hematological indices in rodents, although detailed effects may vary with formulation and concentration (38). Taken together, sub-chronic toxicity data from these botanicals indicate that both *Carica papaya* extracts and garlic derivatives generally exhibit favorable safety profiles upon repeated administration in rodent models, with only occasional non-dose-dependent biochemical variations and no consistent histopathological damage reported at doses greatly exceeding typical therapeutic levels. However, the relative scarcity of targeted sub-chronic studies specifically on papaya seed and standardized garlic seed extracts highlights a research gap that future investigations should address to more precisely delineate safety margins relevant to long-term human use (39).

5.3 Reported Adverse Effects

Garlic (*Allium sativum*) is generally regarded as safe; however, several adverse effects have been documented in clinical and pharmacological studies. The most commonly reported reactions include garlic breath and body odor, which result from the metabolism and exhalation of volatile sulfur-containing compounds following oral consumption. These effects are non-toxic but may affect patient acceptability and compliance during long-term use (40). High intake of raw garlic or concentrated garlic supplements has been associated with gastrointestinal disturbances, including heartburn, nausea, abdominal discomfort, flatulence, and diarrhea. Such effects are typically dose-dependent and are more frequently observed in individuals with sensitive gastrointestinal mucosa or when garlic is consumed on an empty stomach (41). In addition to gastrointestinal effects, garlic exhibits antiplatelet and anticoagulant properties, which may increase the risk of bleeding, particularly when consumed concomitantly with anticoagulant or antiplatelet medications. Clinical reports suggest that excessive garlic intake may prolong bleeding time, warranting caution in patients undergoing surgical procedures or receiving anticoagulant therapy (42). Reported adverse effects of *Carica papaya* seed extracts are primarily derived from experimental animal studies. High-dose exposure to papaya seed aqueous extracts has been shown to induce behavioral alterations, hepatotoxic changes, and elevations in liver enzyme levels, indicating potential dose-related toxicity when administered at concentrations far exceeding traditional or therapeutic usage (43).

6. Limitation and Research Gaps

Despite extensive preclinical studies demonstrating the phytochemical diversity and



bioactivity of garlic (*Allium sativum*), current research is limited by a lack of large-scale, controlled clinical trials that validate the therapeutic effects observed in vitro and in vivo, especially regarding gastrointestinal and ulcer-related outcomes; many existing human studies involve small sample sizes, heterogeneous designs, and non-standardized garlic preparations, making conclusive clinical recommendations difficult (44). Furthermore, while several investigations have elucidated the traditional uses and pharmacological effects of papaya (*Carica papaya*) components, targeted research on papaya seed extracts remains insufficient, with most published reviews and experimental studies focusing predominantly on fruit, leaf, or general plant extracts rather than the seed matrix specifically, which limits understanding of seed-specific bioactivity and safety profiles (45). Another crucial gap is the scarcity of detailed mechanistic studies that link individual phytochemicals found in garlic and papaya seeds to specific anti-ulcer mechanisms in gastric tissue; most research reports general antioxidant or anti-inflammatory effects without fully characterizing pathways such as mucosal protection, acid secretion modulation, or microbial interactions relevant to ulcer pathology (46). Lastly, there is an underrepresentation of standardized pharmacokinetic, bioavailability, and long-term safety studies for key bioactive compounds from garlic and papaya seeds, which hampers the translation of promising laboratory findings into clinical or nutraceutical applications for gastric ulcer prevention or treatment (47).

DISCUSSION

The current body of evidence suggests that both *Allium sativum* (garlic) and *Carica papaya* seeds possess significant anti-ulcerogenic and gastroprotective properties, which may be

attributed to their rich phytochemical profiles, particularly their antioxidant, anti-inflammatory, and mucosa-protective activities. Preclinical studies have demonstrated that aqueous and methanolic extracts of papaya seeds can significantly reduce gastric ulcer indices, increase gastric pH, decrease acid output, and enhance antioxidant enzyme activities in indomethacin- and ethanol-induced ulcer models in rats, implicating enhanced antioxidant defense and modulation of gastric secretions as probable mechanisms of action (48). Similarly, research focusing on garlic indicates that garlic extracts and their sulfur-containing compounds like allicin exert gastroprotective effects by increasing gastric mucous production, enhancing endogenous antioxidant enzyme activity, and reducing oxidative stress in the gastric mucosa, thereby mitigating ulcerogenesis in experimental animal models. These mechanistic effects align with broader phytochemical review findings that link sulfur phytoconstituents in garlic to cytoprotective and ulcer-inhibitory outcomes (49). Despite promising preclinical observations, translation to clinical efficacy remains limited, as most studies are confined to animal experiments with variable extract types, dosages, and ulcer induction models. This variation highlights a need for standardized clinical trials to validate the protective effects of garlic and papaya seed extracts in human gastric ulcer conditions and to define optimal therapeutic doses and formulations (50). Moreover, while general mechanisms such as antioxidant enhancement and anti-acid secretory effects have been explored, there is a gap in detailed molecular understanding of how specific compounds from garlic and papaya seeds interact with gastric epithelial signaling pathways, mucosal defense factors, and ulcer healing processes. Future research integrating molecular, pharmacokinetics, and clinical investigations is therefore essential to

confirm these botanicals potential roles in ulcer prevention and therapy (51).

FUTURE PERSPECTIVE

Although considerable evidence supports the *anti-ulcer and gastroprotective potential* of garlic (*Allium sativum*) and papaya (*Carica papaya*) seeds, there remains a clear need for comprehensive mechanistic and clinical evaluations of the bioactive phytochemicals responsible for these effects; future research should integrate *systems pharmacology, molecular signaling pathways, and high-throughput screening* techniques to elucidate how individual constituents modulate gastric mucosal defense and ulcer healing pathways (52). Moreover, there is an urgent requirement to conduct well-designed, randomized clinical trials that evaluate the efficacy, optimal dosing, and safety of standardized garlic and papaya seed extracts in human gastric ulcer patients to confirm preclinical findings and support translational therapeutic recommendations (53). Advances in nanotechnology and novel delivery systems, such as nano-encapsulation or liposomal formulations, could significantly improve the *bioavailability and targeted delivery* of crucial phytochemicals from garlic and papaya seeds, thereby enhancing their therapeutic index and clinical applicability for ulcer management (54). Integration of pharmacokinetic and pharmacodynamic studies is also imperative to better understand how these extracts are absorbed, distributed, metabolized, and excreted in the human body, which is currently a major gap in the literature and limits clinical translation (55). Additionally, emerging research should prioritize synergistic studies that assess the combined effects of garlic and papaya seed phytochemicals with existing anti-ulcer drugs, as synergism may lower effective doses and reduce adverse effects, offering *adjunctive therapies* for

complex ulcer pathologies (56). Given the wide range of bioactive compounds identified in papaya seeds through phytochemical profiling and in silico evaluation, future work should explore *structure-activity relationships* to isolate the most efficacious molecules and develop *standardized reference compounds* for pharmacological and clinical use (57). Finally, interdisciplinary efforts that encompass metabolomics, genomics, and microbial ecology could reveal how garlic and papaya seed compounds influence *gut microbiota composition and Helicobacter pylori interactions*, potentially uncovering novel anti-ulcer mechanisms and personalized therapeutic targets (58).

CONCLUSION

In summary, both *Allium sativum* (garlic) and *Carica papaya* seeds exhibit significant anti-ulcerogenic and gastroprotective activities in preclinical models, with mechanisms attributed to enhanced antioxidant defense, increased gastric mucosal protection, reduced gastric acidity, and modulation of ulcer-related biochemical pathways. For example, papaya seed extracts have been shown to substantially increase gastric pH, reduce ulcer index and acid output, and enhance antioxidant enzyme activity in indomethacin-induced ulcer models in rats, supporting their potential as a natural gastric protective agent (59). Similarly, garlic administration in animal studies demonstrates reduction in ulcer scores, increased gastric mucous cell counts, and heightened endogenous antioxidant activity, suggesting that its bioactive metabolites may contribute to cytoprotection and ulcer healing (60). Despite promising preclinical data, clinical evidence remains limited, and there is a need to validate these findings through human studies with standardized extracts and well-defined outcome measures to determine therapeutic efficacy and safety in gastric ulcer patients (61). Current



literature also underscores that the antioxidant and anti-inflammatory phytoconstituents—including phenolics, flavonoids, and sulfur-containing compounds from both garlic and papaya seeds—likely act synergistically to protect gastric mucosa from oxidative stress and erosive damage (62). Importantly, the pharmacological benefits of these botanical agents must be balanced against potential variability in phytochemical content, dosing differences, and limited toxicological profiling, which currently constrain their clinical translation (63).

Overall, the evidence supports the concept that garlic and papaya seed derivatives could serve as complementary or adjunctive agents in gastric ulcer management, particularly when integrated with conventional therapies to enhance mucosal defense and reduce ulcer recurrence (64). Future research bridging rigorous clinical trials, standardized phytochemical characterizations, and mechanistic studies is essential to fully realize their therapeutic potential and to develop evidence-based guidelines for their use in gastric ulcer prevention and treatment (65).

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