IJBPAS, December, 2023, 12(12): 5732-5743

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

PHARMACOLOGICAL ACTIVITY OF *CARICA PAPAYA* ON GASTRIC ULCER: A COMPREHENSIVE OVERVIEW

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Received 19th Oct. 2022; Revised 16th Nov. 2022; Accepted 3rd April 2023; Available online 1st Dec. 2023

https://doi.org/10.31032/IJBPAS/2023/12.12.7640

ABSTRACT

Up to 10% of people worldwide may suffer from peptic ulcers, a chronic illness. The presence of gastric juice pH and the decline in mucosal defences both contribute to the development of peptic ulcers. The two main factors affecting the mucosal resistance to damage are non-steroidal anti-inflammatory medications (NSAIDs) and Helicobacter pylori (H. pylori) infection.

Large perennial herbaceous plant *Carica papaya* is known for its wide range of biological functions. In the past, it has purportedly been demonstrated that seeds, leaves, fruits, peels, roots, and stems have therapeutic and nutritional benefits. This plant has a high nutritional value that is low in calories and high in natural vitamins and minerals.

Keywords: Peptic ulcers, *Carica papaya,* Helicobacter pylori, NSAIDs, Gastric juice

INTRODUCTION

Ulcer is the term for any interior open wound. Peptic ulcers, also known as PUD or peptic ulcer disease, are ulcers that are classified as mucosal erosions of the digestive system that are at least 0.5 cm long and often quite painful due to the fact that they are acidic. Stomach mucosal sores caused by gastric ulcers, a common digestive condition, are thought to affect 4 million individuals annually worldwide. They are typically brought on by an imbalance between the digestive tract's defensive components, such are the mucus bicarbonate barrier and the surface epithelial cells, and its aggressive components, such as

consumed medications, pepsin, refluxed bile salts, and acid.

Since it was learned in the early 1980s that Helicobacter pylori is a significant contributor to peptic ulcers, care of the condition has been significantly impacted. As a result, there has been a recent decline in H pylori infection rates **[1]**. The occurrence of stomach ulcers has diverse causes however, increased as a result of other variables like stress, smoking, drinking, and other behaviour associated to these substances. In individuals older than 45–50 years old with greater than two weeks of the aforementioned symptoms, the likelihood the need for urgent treatment for peptic ulceration EGD's quick investigation. It is also known as a fruit of the "berry family" or an "ordinary man's fruit" and is a large perennial herbaceous plant that is also called as the papaya melon tree, Papua, or pawpaw **[2]**. The large perennial herbaceous plant *Carica papaya* is known for its wide range of biological functions. Different plant components, including the leaves, roots, fruits, peels, seeds, and stems, have reportedly been shown to offer nutritional and therapeutic benefits in the past. The plant has a high nutritional value that is low in calories and high in vitamins and natural minerals.

ETHIOLOGY

Helicobacter pylori: Chronic inflammation brought on by Helicobacter pylori colonising the antral mucosa is a major contributing factor about 90% of duodenal ulcers and to 60% of gastric ulcers. Despite the presence of antibodies, the immune system cannot eradicate the infection. Therefore, the bacterium can induce type B chronic active gastritis, which results there in a problem with how the portion of the stomach controls the creation of gastrin either increased or decreased gastrin secretion, which in the majority of instances leads to hypo- or achlorhydria.

NSAIDs: The usage of NSAIDs is a significant contributing factor. A coating of mucous that the gastric mucosa secretes to shield itself from gastric acid is triggered by specific prostaglandins. These prostaglandins must be produced by the enzyme cyclooxygenase 1 (COX-1), that is inhibited by NSAIDs. The risk of gastric ulcers associated with NSAIDs is roughly cut in half which the stomach mucosa does not require as much of the COX-2 specific anti-inflammatories like celecoxib or the recently discontinued rafecoxib, which predominantly inhibit this enzyme.

Alcohol & Smoking: Alcohol use has not been connected to peptic ulcers, although cirrhosis of the liver, a condition frequently brought on by daily heavy alcohol consumption, is associated with a higher prevalence of ulcers. When the lining of your stomach gets irritated, a peptic ulcer develops. Your stomach begins to absorb

acid when the lining starts to itch. You might have a peptic ulcer sooner if you smoke than you otherwise would. If you quit smoking, your peptic ulcers are more likely to heal.

Spicy & Alkaline food: Spice-enriched food releases more gastric juice for digestion. Oversecreting acid destroys mucosal cell walls and results in peptic ulcers. Due to an increase in bicarbonate ions, peptic ulcers also arise when eating more alkaline foods.

Stress: Additionally, stress is still being investigated as a potential factor, or at the very least a consequence, in the development of ulcers. Whether or not psychological stress might affect how peptic ulcers develop is up for discussion.

Gastrinomas: It is a rare gastrin-secreting tumour that also causes many ulcers that are challenging to repair (Zollinger Ellison syndrome).

Regulation of Acid secretion: The pathophysiology of peptic ulcers depends heavily on the control of acid secretion, which makes it a prime target for therapeutic action. The hydrogen ion concentration in the parietal cells' secretion is more than a million times higher than that in plasma, and it is an isotonic solution of HCl (150 mmol/l) with a pH below 1. The Cl is actively carried into the cells' canaliculi, which connect to the gastric glands' lumen and, consequently, to the stomach itself. K+ is released together with the Cl2 secretion, and a K+-H+ ATPase then converts the K+ to H+ from within the cell **[3]**. Carbon dioxide and water are combined by carbonic anhydrase to create carbonic acid, which then dissociates into H+ and bicarbonate ions. The latter trades for Cl across the parietal cell's basal membrane **[4]**.

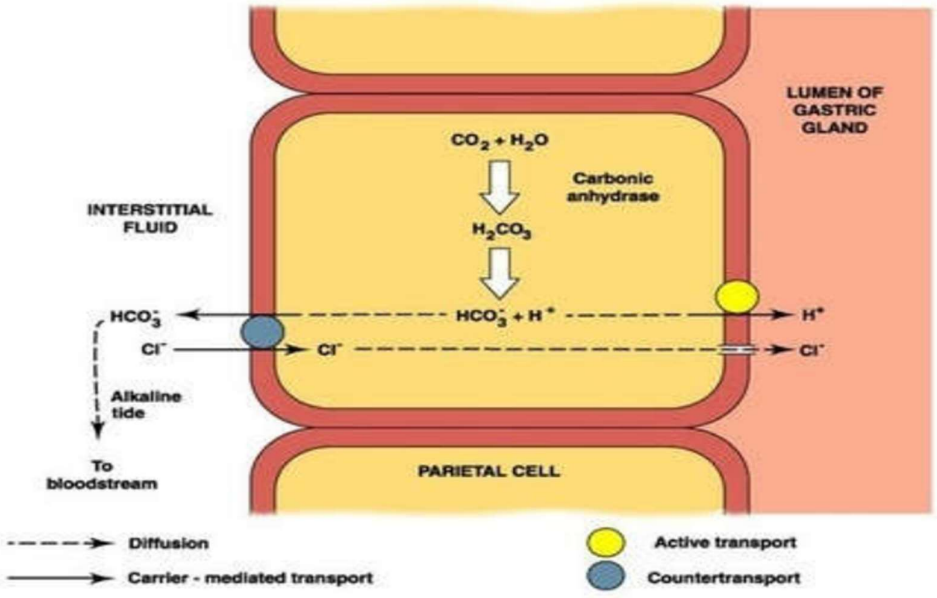

Figure 1: HCL Production

Peptic Ulcer Pathogenesis

The most common causes of peptic ulcer illness, H. pylori colonisation affects more than half of the global population **[6]**. Particularly in Central America, Eastern Europe, Central Asia, and Africa developing nations have higher rates of H. pylori prevalence **[7]**. It is not fully understood how H. pylori causes the various lesions could develop in the gastroduodenal mucosa. The kind of peptic ulcer is determined by the hypo- or hyperchlorhydria caused by H. pylori infection. Parietal cell-inhibiting cytokines secretion are the principal mediators of H. pylori infection **[8]**. Despite the fact that hyposecretion is associated with the occurrence of gastric ulcers, increased gastric secretion brought on by hypergastrinemia and decreased antral somatostatin levels are present in 10–15% of patients with H. pylori infection **[9]**. This causes a rise in histamine release, which in turn causes the parietal and stomach cells to secrete more acid or pepsin.

Furthermore, eradicating H. pylori results in a decrease in the expression of gastrin mRNA and an increase in the expression of somatostatin mRNA **[10]**.

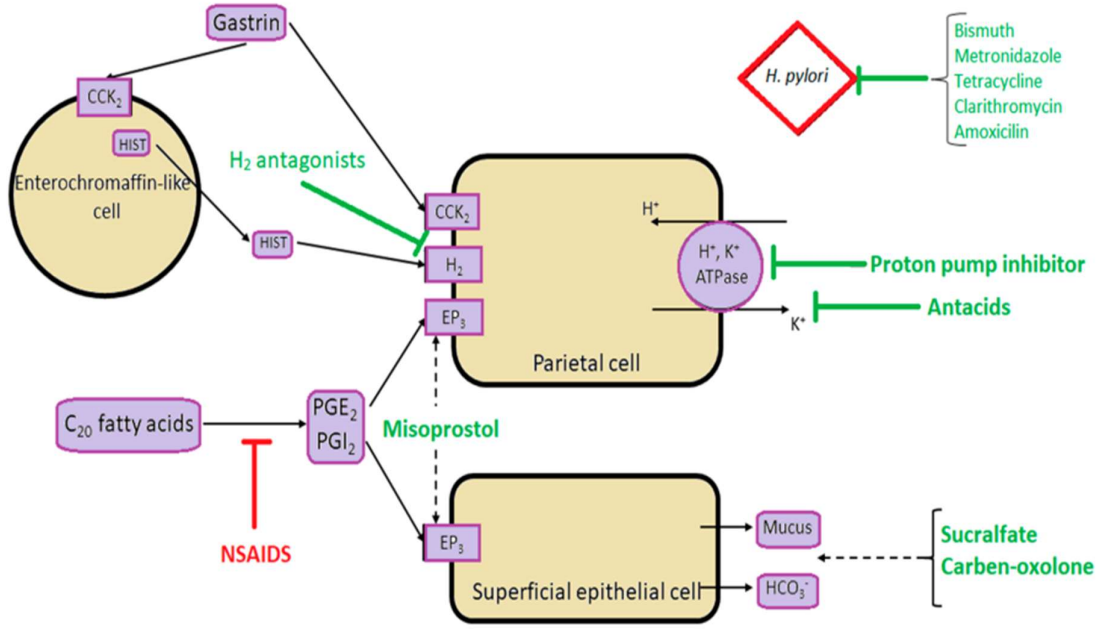

Figure 2: The main pharmacological treatments for the PUD and their sites of action. PGE2 = Prostaglandin E2; EP3 = Prostaglandin E receptor 3; PGI2 = Prostaglandin I2; CCK2 = Cholecystokinin Receptor; HIST = Histamine

CARICA PAPAYA

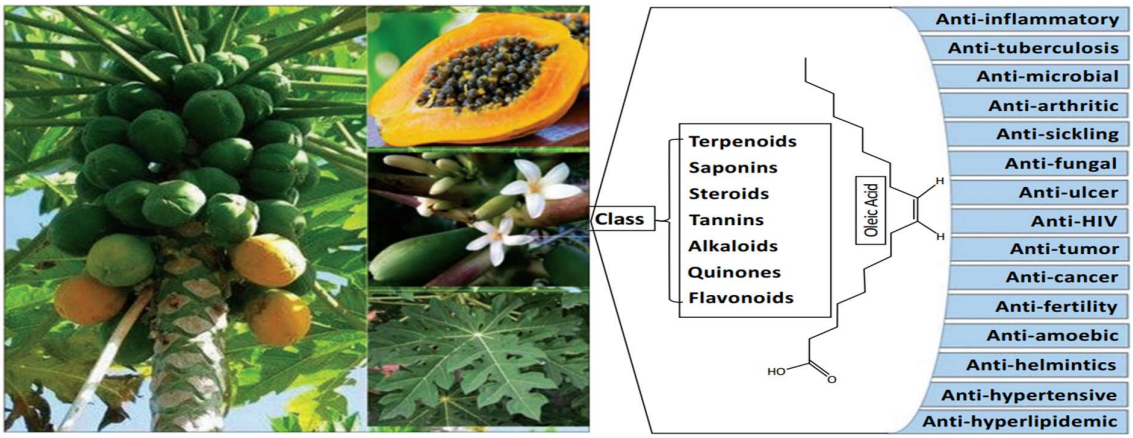

Figure 3: Chemical distinction and therapeutic qualities of papaya that are present in several plant sections

Morphology

Papaya trees can grow to a height of 8 to 10 metres in ideal conditions, but in cultivation, once they reach heights that make fruit gathering problematic, they are typically killed **[11]**. Analyse the morphological and fruiting traits of the triploid papaya generated from anthers to determine its applicability to commercial fruit production and breeding.

Roots

Young papaya plant roots display well-differentiated epidermis, endodermis, cortex, and are often thick and nonaxis in colour **[12]**.

Stem

The cylindrical, soft, hollow trunk of the stem has a diameter that varies from 30 cm at the base to roughly 5 cm at the crown. Papaya trees typically have a single stem and a crown of enormous palmate leaves that extend from the top of the trunk, but damage can cause trees to develop many stems **[13, 14]**.

Leaves

The leaves are substantial at 50 to 70 cm in width. The plant has broad, spirally arranged leaves with 5–9 pinnated lobes that range in width from 40–60 cm, and it clusters in the upper section of fully developed trees.

Seeds

Papaya plants typically start out as seeds. Plant seeds have an oblong, flattened cotyledon, a straight embryo, meaty endosperm, and a blackish to brownish hue **[15]**.

The fruit's interior cavity is filled with many black seeds that are mucin-coated. The seeds are edible and have a pungent, spicy flavour. They also have antibacterial characteristics that help prevent renal failure brought on by toxins **[16, 17]**.

Flowers

The term "trioecious" refers to the fact that various plants can support either female, male, or bisexual blooms, and this describes the flowers of C. papaya. When closed, the blooms of the male papaya are small and held by long stalks, whereas the flowers of the bisexual papaya are tubular. Bisexual plants are typically preferable and superior to plants that are either male or female **[12]**. Actinomorphic, bracteolate, and stationary in the cluster, the blooms are positioned along a single central axis.

Table 1: Different papaya components and their therapeutic uses

Parts	Usages
Leaves	• **In curing dengue fever** • **Treating injuries and wounds** • **In treating malaria** • **Stop cancer cell proliferation and increase Thi-type cytokine production.** • **Reduce blood sugar** • **Increased in platelet count** • **Treating ulcer** • **Treating high blood pressure**
Seeds	• **Treating gastric ulcer** • **Prevent prostate cancer cells** • **Prevent toxicity and bacteriostatic effect** • **Employ as a contraception**
Roots	• **In the management of malaria** • **Healing wounds**
Stems	• **Healing wounds**
Fruits	• **To treat sickle cell disease** • **Treatment of sinus problems, ulcers of the tongue, mouth, and throat, epithelioma, corns, warts, and other skin conditions** • **Reduce rheumatic issues and the formation of elephantoids**

PHARMACOLOGICAL ACTIVITIES

Anti-Ulcer Activity

It was determined that the ethanolic extract of papaya plant leaves, which was proved to be efficient against ulcers, has gastroprotective and healing properties **[18]**. Aqueous and methanol extracts of whole, immature papaya fruit were tested for their antiulcer properties using ethanol and indomethacin **[19]**. The produced extracts significantly ($P< 0.05$) decreased the ulcer index in both experimental models compared to the control group, with methanolic extract showing superior protection against indomethacin-induced ulcers and aqueous extract showing superior protection against ethanol-induced ulcers. It was determined that the papaya fruit seed oil contains benzyl isothiocyanate and that the proteolytic enzyme papain from the unripe fruit latex had potent antiulcer properties **[20]**.

Antifungal Activity

Numerous body organs, including the skin, nails, reproductive system, gastrointestinal tract, heart, and nervous system, are susceptible to damage by fungi. Essential oil of papaya seeds exhibits promising anti

scandida action. The filter paper disc diffusion method and the broth dilution method were used **[21]**. Drug-resistant infectious fungi have been on the rise for decades due to the extensive use of broad-spectrum antifungal drugs including itraconazole, ketoconazole, and fluconazole **[22]**. In order to combat the fungal resistance strains in the fight against infection, this had prompted the researchers to revisit the natural and secure alternatives that are readily accessible locally **[23]**. Mitochondrial membrane potential degradation and decreased activity of the mitochondria respiratory chain enzymes, as well as the antifungal effects of PSE, could all be attributed to the production of oxygen radicals **[24]**.

Reno-protective Hepato- and activities

Because cytotoxic agent overdoses are a frequent cause of severe liver damage, papaya seeds' ameliorative and therapeutic properties have been researched and compared to other hepatic protectants. Oxidative stress in the liver was significantly reduced by papaya seeds [25, 26]. Another study found that papaya significantly increased glutathione peroxidase activity while significantly decreasing liver hydroxyproline and malondialdehyde levels, hence inhibiting the mice with hepatic fibrosis brought on by CCl4 **[27]**.

Wound healing effects

Animal studies have looked closely at papaya's capacity to repair wounds when it comes to treating skin disorders. In comparison to ripe fruit peel extract, mature green fruit (unripe) peel extract has demonstrated in rats and mice, epidermal wound recovery is more rapid. In mouse burn models, latex from the skin was also used to assess how well wounds healed **[28]**. The latter view, however, suggested that latex was in fact what gave latex its healing properties. The latex of unripe papaya fruits contains chymopapain A and B, papain, papaya endopeptidase II, caricain, papaya endopeptidase IV, glutaminyl cyclase, omega, protease inhibitors, endopeptidase chitinase II and additional proteins with unknown functions. According to traditional beliefs, papaya has a high capability for mending wounds **[29]**.

Anti-sickling characteristics

Sickle cell disease, also known as genetic illnesses can impact Hb of red blood cells, is caused by a rapid shift in the red blood cells haemoglobin structure, in which valine amino acid was swapped for glutamine at six locations **[30]**. There are two types of sickle cell anaemia: - α-thalassemia and β-thalassemia. The black race is the one with the highest prevalence of this disease, yet it is still present among the races in the Mediterranean regions **[31]**. Papaya fruits that aren't ripe and dried leaves may have anti-sickling properties that can help treat

sickle cell anaemia, according to several research **[32]**.

Antioxidant and immunomodulatory property

Any chemical that prevents the substrates from oxidising is considered an antioxidant **[33]**. Because of the harm caused by free radicals in our bodies, the human body naturally produces free radicals that promote the creation of oxidation in cells and cause diseases like arthritis, cardiovascular and chronic diseases like cancers of the colon, skin, and trauma as well as atherosclerosis **[34]**. Recently, an extract from C. papaya seeds has been marketed as a nutritional supplement to boost vitality and improve overall health **[35]**.

Additionally, oxidative stress developed as a result of the development of ROS in the cells, specifically hydroxyl (HO2+) and superoxide free radical (O2). Antioxidants and pro-oxidants are not balanced out in the body leads to oxidative stress. The ROS obliterate essential DNA, protein, cell, enzyme, and plasma membrane apoptosis **[36]**. The in vivo redox homeostasis enzyme systems involved in preserving a low amount of ROS. In the enzyme system, superoxide dismutase, catalase, and glutathione peroxidase are the primary antioxidant enzymes **[37]**.

Polyunsaturated fatty acid membranes in the kidney, liver, and stomach of rats experience oxidative damage as a result of acrylamide, a study found that it increases MDA but decreases catalase activity of GSH and SOD **[38]**. Human eosinophils have been known to be stimulated by C. papaya papain by eliminating granules to create superoxide anion. The protein G receptor served as a mediator for the activity of human eosinophils **[39]**. The antioxidant action of C. papaya a study was conducted on superoxide radicals and hydroxyl, which are part of the metabolism of intestinal microbes at the cellular level, has been reported to be associated to the fruit's antimicrobial effect **[40]**.

CONCLUSION

According to this review paper, C. papaya is still one of the most significant in the tropical and subtropical zone as a nourishing fruit. The plant chemicals and enzymes it contains, which are supported by scientific and clinical investigations, are what give it its medicinal and nutritional benefits. To fully understand the potential of *Carica papaya* L. leaves, more research is required. The pharmacological benefits of papaya, which include anti-inflammatory, antioxidant, antibacterial, and immunomodulatory activity, have been shown to be effective in treating a variety of diseases.

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