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Review Article

Guava Leaf (*Psidium guajava*): A Potential Natural Remedy for Ulcer Treatment

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Abstract

Mucosal injury triggered by disequilibrium between noxious factors like gastric acid and impaired mucosal defence mechanisms is a characteristic of peptic ulcers that are gastric, duodenal, and stress ulcers. Helicobacter pylori infection, chronic NSAID therapy, mental stress, cigarette smoking, and dietary habits are common etiologic causes. Proton pump inhibitors (PPIs), H2 receptor antagonists, and antibiotics are some of the conventional ulcer medications that have worked well but are frequently linked to problems of recurrence, expense of therapy, adverse side effects, and drug resistance. Owing to these drawbacks, natural medicines like guava (Psidium guajava) leaves have gained interest due to their multi-target activity, easy availability, and good safety profiles. Guava leaf has long been traditionally utilized for the control of gastrointestinal disorders in various cultures. Its gastro protective effect is attributed to a multifaceted mixture of bioactive constituents, including alkaloids, tannins, terpenoids, saponins, and flavonoids (quercetin, kaempferol). Through the neutralization of oxidative stress, suppression of inflammation, reinforcement and repair of the gastric mucosal barrier, inhibition of H. pylori, and possibly stomach acid secretion modulation, these compounds operate in various mechanisms. Guava leaf provides a natural, plant-based solution with fewer side effects reported and additional benefits to health over traditional medicine. The argument for guava leaf as a natural cure for ulcers is further supported in this review, together with the benefits of this over traditional medicine treatments in terms of cost, safety, and broad-spectrum activity.

Keywords: Guava leaf, anti-ulcer activity, Phytochemicals, Gastroprotective effect, Herbal remedy.

Introduction:

The conventional definition of an ulcer is a slow disruption of tissues brought on by an internal pathology or etiology. Wounds, on the other hand, are usually caused by outside factors, such trauma. The distinction is significant because it affects our comprehension of their physiology, pathophysiology, anatomical locations, appearance, and demographics[1, 2]. According to histology, an ulcer is characterized by a rupture in the mucosal layer that penetrates deeper tissues or the sub mucosa. Because it distinguishes ulcers from erosions-which are superficial fractures limited to the mucosa-this depth is essential[3-5]. Lesions called ulcers, which are defined by the loss of surface tissue, can develop on the skin or mucous membranes. They may be brought on by an infection, poor blood circulation, or underlying medical issues, among other things[6]. Instead of using an objective measurement of the ulcer's depth, the diagnosis of an ulcer is frequently made based on the endoscopist's judgment during an endoscopic examination. This indicates that at the time of diagnosis, visual evaluation rather than histological confirmation is used to evaluate whether an ulcer is present[7]. The identification of ulcers is critical in the context of upper gastrointestinal bleeding (UGIB), as they are the most common cause of hospitalization for this condition. Understanding the characteristics of ulcers, including their depth and potential for bleeding, is essential for effective management and treatment[8]. A rupture in the mucosal surface's integrity is a hallmark of a peptic ulcer. The extent and depth of this split might vary, which is important for clinical classifications employed in research. 'Unambiguous', 'identifiable', or 'excavated' were used to characterize ulcers in order. This emphasizes how crucial the mucosal lesion's depth and size are in identifying an ulcer[9]. A pressure ulcer is described as "an area of localized damage to the skin and underlying tissue caused by pressure, shear, friction, and/or a combination of these" by the European Pressure Ulcer Advisory Panel (EPUAP). According to this concept, pressure ulcers can form as a result of many forces, highlighting the multifactorial nature of the damage[10].

Skin ulcers are serious side effects of systemic sclerosis (SSc) that are mostly caused by vasculopathy, a disorder that affects the blood vessels. They may also be brought on by gangrene, calcinosis, or trauma. The quality of life for those who have these ulcers is significantly impacted because they are frequently painful and can significantly limit hand use[11]. Usually, ulcers appear on the toes, fingertips, and on bony protuberances like the elbows. The underlying vascular problems linked to SSc are linked to their frequent prevalence in certain places[12]. Both micro vascular and macro vascular problems are frequently involved in the multifactorial development of ulcers in SSc. The findings made clear that isolated SSc-related microvascular involvement was most likely the etiology of pure microvascular ulcers[6]. The causes of ulcers might differ. Venous stasis, for example, causes a venous leg ulcer, which alters the skin's physiology and anatomy. Similar to pressure ulcers, diabetic foot ulcers are caused by certain internal diseases that compromise the integrity of the skin. Effective treatment depends on knowing the underlying reasons[13]. A full-thickness lesion that pierces all of the skin's layers is called an ulcer. The fact that a foot ulcer is specifically located behind the ankle joint is essential to comprehending the different kinds of ulcers that diabetic people may develop[14].

Types of Ulcers:

Figure 1: Digestive tract ulcer

Figure 2: Skin and tissue ulcer

Other types of ulcer

a. mouth ulcer

b. genital ulcer

c. corneal ulcer

Causes of Ulcer:

One of the most frequent causes of peptic ulcer disease (PUD) is this bacteria. It is a major contributor to the formation of ulcers since its presence can cause inflammation and harm to the stomach lining. Smoking is linked to more severe ulcer illness because it damages the gastric mucosa, hinders healing, and increases the likelihood of ulcer formation [15]. One major factor in the formation of duodenal ulcers is H. pylori. Increased acid production and alterations in stomach physiology brought on by the infection may promote the development of ulcers[16, 17]. There is proof that hereditary variables affect a person's vulnerability to ulcer disease and H. pylori infection. According to twin studies, monozygotic twins have a higher concordance rate for ulcer illness than dizygotic twins, which may indicate a genetic component[18, 19].

Medications such as aspirin and other NSAIDs can induce direct injury to the stomach mucosa and impede the generation of protective mucus, increasing the risk of ulcers[20]. However, there is a higher chance of serious upper gastrointestinal issues, such as bleeding and perforation, while using NSAIDs[21, 22]. Antiplatelet therapy with low-dose aspirin (75-325 mg) lowers the risk of vascular events in patients with cardiovascular and cerebrovascular diseases, and the aging population appears to have contributed to their increased use of NSAIDs[23]. Ulcers can also develop as a result of exposure to specific chemicals, such as ethanol and hydrochloric acid. These chemicals have the potential to harm the stomach and intestinal mucosa, leading to ulcers. These drugs have the potential to irritate the stomach lining and decrease the formation of protective mucus, increasing the risk of gastric acid injury[24].

One of the most frequently mentioned causes of ulcer development is psychological stress. Although it might not be the direct cause of ulcers, it might worsen pre-existing diseases and raise the production of acid[15, 20]. The body may experience physiological changes as a result of stress, including elevated blood pressure and changed blood flow. Tissue perfusion may be impacted by these alterations, increasing the skin's vulnerability to harm from outside pressure. For example, stress reactions during surgery may result in hypotension, which raises the risk of developing pressure ulcers[25, 26].

Limitations of Conventional Ulcer Treatment:

It might be difficult to eradicate Helicobacter pylori (H. pylori), a primary cause of peptic ulcers. Treatment failure may result from elements like bacterial resistance, the stomach's acidic environment, and the low absorption of antibiotics[27-29]. Patient characteristics, such as food and lifestyle choices, can reduce the efficacy of traditional therapy. Treatment results may be considerably impacted by noncompliance with

recommended regimens[30]. Certain pharmaceutical drugs employed in traditional therapies have a number of negative side effects and are not always successful. Due to this restriction, interest in alternative therapies—especially those made from medicinal plants—has grown[31]. Alternative therapy must be investigated because the development of resistant strains of H. pylori can reduce the efficacy of traditional antibiotic treatments[32].

Numerous studies focus mostly on healing rates or full healing, ignoring other significant outcomes including pain, quality of life, and cost-effectiveness. This limited focus may result in an inadequate comprehension of the treatment's overall effects on patients determining which populations benefit most from particular treatments is made more difficult by the large range of medicines available for diabetic foot ulcers. Clear inclusion and exclusion criteria must be established in future research in order to more accurately identify patient groups that are appropriate for each therapy[33]. Although they have shown potential, certain alternative therapies—like some herbal preparations—are backed by research with flaws in their methodology. This calls into doubt the validity of the data underlying these therapies[34]. A more varied patient sample, including individuals with wounds that are difficult to heal, is frequently included in conventional trials. Because the effectiveness of treatment may vary depending on the patients' underlying problems, this variability may result in variable healing outcomes Studies employing traditional dressings may have less-than-ideal reporting, which can mask the actual efficacy of these therapies. Inadequate reporting may make it difficult to evaluate the true advantages and drawbacks of traditional ulcer therapies[35].

Overview of guava leaf as a traditional medicinal plant:

Guava leaves are round, elliptical, dark green, and distinguished by their obtuse-shaped apex. The pulp and seeds of guava leaves are used to treat gastrointestinal and respiratory conditions as well as to boost platelets in dengue fever patients[36]. Guava leaves have been used in traditional medicine in many different countries. They are known for treating a wide range of diseases, including diarrhoea, diabetes, cough, cold, and skin disorders. Their historical relevance emphasizes how crucial they are to traditional medicine[37]. On a dry weight basis, 9.73% of guava leaves have protein[38]. The nutritional value of guava leaves, which comprises important vitamins and minerals, is also well known. This supports their usage in traditional medicine and adds to their overall health advantages[39]. Guava's main components, ascorbic acid and citric acid, are crucial for their anti-mutagenic properties[40]. Leaves that include α-pinene, limonene, β-pinene, isopropyl alcohol, menthol, terphenyl acetate, caryophyllene, longicyclene, and β-bisabolene are said to possess essential oil. The guava leaves also contain oleanolic acid[41]. Analgesic, anti-inflammatory, antibacterial, hepatoprotective, and antioxidant qualities are among the many therapeutic qualities of guava leaves. The presence of phenolic chemicals in the leaves is primarily responsible for these advantages[42]. Bioactive substances such as polyphenols, flavonoids, saponins, tannins, terpenoids, and glycosides are abundant in the leaves. Among the important components found are rutin, Gallic acid, quercetin, and catechin. These substances give the leaves their antibacterial and antioxidant qualities and aid in their medicinal benefits[43].

Compounds with anti-inflammatory qualities found in the leaves can help with pain relief and inflammation reduction in a number of illnesses, including liver damage[44, 45]. Antioxidants such as quercetin, which has spasmolytic properties, are abundant in guava leaves. By halting cellular damage, these antioxidants aid in the fight against oxidative stress and may improve general health[46, 47]. Certain chemicals found in guava leaves have been demonstrated in studies to block pancreatic cholesterol esterase, which lowers cholesterol levels. The ability of catechins to prevent type 2 diabetes and obesity is especially well-known[48, 49]. Extracts from guava leaves have the ability to stop the growth of a variety of bacteria, including both gram-positive and gram-negative types. Extracts, for example, have shown promise as natural antibacterial agents by being efficient against Bacillus cereus and Staphylococcus aureus. Because of their significant antibacterial activity against strains of bacteria that are resistant to several drugs, guava leaves have been shown to have anti-cough properties and have been assessed for their ability to reduce cholera epidemics[50, 51].

Guava leaf's potential as an anti-ulcer agent:

Aspergillus aureus and Candida albicans, two common infections associated with mouth ulcers, were strongly inhibited by the gauva leaf gel formulations produced. Since these microbes have been implicated in the causation of mouth ulcers, guava leaves can be employed to treat infections related to these conditions[52]. In comparison to synthetic alternatives, which tend to possess deleterious side effects such as burning and irritation because of their alcoholic composition, guava leaf's herbal preparation was found to be safer yet more effective. Guava leaves are hence emerged as a viable natural cure for mouth ulcers[53]. Anti-inflammatory and oral mucosal healing effect of guava leaves has been suggested to be responsible for their anti-ulcer activity. For aphthous ulcers, which occur with bitter-tasting mouth ulcers, this is particularly so[54]. According to the study, guava leaf extract significantly promotes wound healing. Studies conducted in vivo showed that rats given guava leaf extract healed more quickly than rats given corticosteroids. This implies that by hastening the healing process, guava leaf extract may help treat ulcers. The antibacterial qualities of the guava leaf extract are essential when it comes to ulcers, which are frequently prone to infection. According to the study, the extract decreased the number of cells that came into contact with it, demonstrating its capacity to inhibit bacterial growth, which is crucial for averting difficulties in ulcerative lesions[55].

The alkaline property of guava leaves provide a strong barrier against gastric acidity. The majority of communities currently create guava tea by boiling 10 to 15 young guava leaves in 3 to 4 cups of water, then drinking the warm mixture to eliminate the acidity. In vitro, the methanolic extract exhibited the strongest antacid and ulcer-healing properties of all the extract solvents[56]. Helicobacter pylori, a bacterium linked to peptic ulcers, have been demonstrated to be inhibited in its growth by quercetin, a significant flavonoid present in guava leaves. Its anti-inflammatory properties are further enhanced by its ability to scavenge free radicals and inhibit inflammatory enzymes. Guava leaves may be useful in treating stomach ulcers, according to the data, which revealed a substantial drop in ulcer indices between the test and control groups. The control group's ulcer index was noticeably greater than that of the guava extract-treated group[57, 58].

Phytochemical Composition of Guava Leaf:

1. Essential Oils

Essential oils are abundant in GLs (Table 2). Trans-caryophyllene and 1,8-cineole are the main components of GL essential oil[59]. Using gas chromatography (GC) and gas chromatography/mass spectrometry (GC–MS), Chen et al[60]. Identified 50 chemicals in GL essential oil and discovered that the main ones were 1,8-cineole, β-caryophyllene, and α-pinene. A distinct profile was discovered in GL essential oil from the Philippines, with the main constituents being limonene, α-pinene, β-caryophyllene, and longicyclene[61]. The monoterpenes limonene and α-pinene were more abundant in Ecuadorian GL essential oil, whereas veridiflorol and trans-caryophyllene were more abundant in Tunisian guava leaf oil[62, 63]. In contrast to other research that found sesquiterpenes to be the main constituent in GL essential oil, Soliman et al[64]. Discovered a higher proportion of monoterpenes. Four α-selin-7(11)-enol, α-selinene, β-caryophyllene, and β-caryophyllene oxide were identified by El-Ahmady et al[65]. as the main components of GL essential oil. Another study used gas chromatography–mass spectrometry (GC–MS) to identify sixty-four distinct components in essential oil extracted from GLs. Caryophyllene, an antioxidant, anticancer, anti-inflammatory, and antibacterial compound, was found to be the most prevalent of them at 24.97%[66]. According to this study, the concentrations of monoterpenes, oxygenated sesquiterpenes, and non-oxygenated sesquiterpenes were 8.55%, 12.94, and 73.67 percent, respectively.

Table 1: Essential oil components of guava leaves.

Compounds	Content/Composition	References
Essential oil components		
α-Pinene	1.53%	
Benzaldehyde	0.83%	
p-cymene	0.52%	
Limonene	54.7%	
1,8-Cineole	32.14%	64
β-cis-Ocimene	0.28%	
γ-Terpinene	0.38%	
α-Terpineol	1.79%	
β-Caryophyllene	2.91%	
α-Humulene	0.77%	
Total identified constituents	95.85%	
Caryophyllene, copaene,nerolidol, caryophyllene oxide, humulene, limonene, eucalyptol, beta-bisabolene, cadin-4-en-10-ol, trans-cadina-1,4-diene, sesquiterpenes, eugenol, isoeugenol, cevadine, emetine (extracted from guava leaves, Ludhiana, India using hydro-distillation by Clevenger-type apparatus)	-	66

2. Phenolic Compound

GLs' antihyperglycemic properties have made them a popular traditional medicine in Asian nations. They contain high-quality bioactive polysaccharides, proteins, lipids, essential oils, vitamins, and minerals, as was indicated in the preceding sections.

Phenolic acids, flavonoids, triterpenoids, sesquiterpenes, glycosides, alkaloids, and saponins are some of the several secondary metabolites found in GLs. Phenolic compounds (PCs) are important bioactive substances that give GLs their hypoglycemic and antioxidant qualities. In general, these PCs are crucial for controlling a range of physiological and metabolic

processes in the human body. Using high-performance liquid chromatography, a diode array detector, and quadrupole time-of-flight tandem mass spectrometry, about 72 distinct phenolic chemicals have been identified in GLs[67]. GLs typically include five quercetin glycosides. Guavinosides A and B, two novel benzophenone galloyl glycosides, and Guavinoside C, a quercetin galloyl glycoside, were also identified[68]. There have also been reports of 19 different kinds of sesquiterpenoids, 30 different kinds of flavonoids, and 17 different kinds of triterpenoids in GLs[69]. Additionally, GLs were found to include psiguanins A–D (1–4)[70], sesquiterpenoid-diphenylmethane meroterpenoids (psiguadials A and B)[71], and diphenylmethane[72]. The protective effects of polyphenolic chemicals against chronic illnesses like diabetes, cancer, and cardiovascular and neurological disorders have been demonstrated by epidemiological research[73]. In order to combat chronic diseases, phenolic chemicals alter a wide range of physiological functions, including signal transduction pathways, cellular redox potential, enzyme activity, and cell proliferation[74].

Table 2: Phenolic compounds of guava leaves

Origin of Guava Leaves	Extract/Fraction	Bioactive Compounds	References
Leaves from Guangzhou (China	Ethyl acetate-soluble fraction, n-butanol-soluble fraction, 75% ethanol extract, residual fraction, dichloromethane-soluble fraction	Quercetin, avicularin, apigenin, guaijaverin, kaempferol, hyperin, myricetin	75
Leaves from Jing-cin Farm (Tianzhong Township, Changhua County, Taiwan)	Aqueous extract	Gallic acid, catechin, epicatechin, quercetin, chlorogenic acid, epigallocatechin gallate, caffeic acid	76
Leaves from Motril (Spain)	Acetone, water, and acetic acid extract	Proanthocyanidins (PAs)	67
Leaves from Jiangmen (China)	Methanol extract	Gallic acid, chlorogenic acid, epicatechin, mono-3-hydroxyethyl-quercetinglucuronide, rutin, isoquercitrin, quercetin-3-O-α-L-arabinofuranoside, quercetin-3-O-β-D-xylopyranoside, avicularin, quercitrin, kaempferol-3-arabofuranoside, quercetin, kaempferol	77, 78

Quercetin is one of the main bioactive phenolic compounds found in GLs. In recent years, diets enhanced with bioactive chemicals have drawn a lot of attention because of their potential to reduce the risk of developing a number of chronic illnesses. The ethyl acetate (EtOAc)-soluble GL fraction was separated into seven pure components using Sephadex LH-20 column chromatography with reversed-phase thin layer chromatography (RP-TLC) to track separation: quercetin, avicularin, apigenin, guaijaverin, kaempferol, hyperin, and myricetin. The chemical structures were clarified using nuclear magnetic resonance spectroscopy and mass spectrometry[75]. Phenolic chemicals were extracted and examined from fermented guava leaves (FGLs) and non-fermented guava leaves (NFGLs) by Wang et al[79]. Using electrospray ionization quadropole–time-of-flight mass spectrometry in conjunction with high-performance liquid chromatography (HPLC–TOF–ESI/MS). Gallic acid, rutin, chlorogenic acid, avicularin, isoquercitrin, quercitrin, and kaempferol were all found in the NFGL and FGL samples, according to the scientists. Of these, approximately 65% of the chromatogram's peak area was filled by quercetin, rutin, gallic acid, avicularin, and isoquercitrin. While Gallic acid, chlorogenic acid, quercetin, caffeic acid, and epigallocatechin gallate were found in lesser concentrations in GL extract, another investigation found higher concentrations of epicatechin (1.45%) and catechin (2.25%)[76]. Alkaloids (cevadine and emetine) and phenolic compounds (eugenol and isoeugenol) were also found. Díaz-de-Cerio et al[80]. investigated the degree of polymerization of proanthocyanidins in various oxidation states and improved their extraction from GLs using an HPLC–fluorimetric detector (FLD)–ESI–MS as antidiabetic and antiobesity drugs[81]. Therefore, GL extract's phytochemical profile shows that it contains a wide variety of phytochemicals with unique therapeutic qualities, indicating that it may be used to treat human illnesses[82].

Figure 3: Structure of phenolic compound present in guava leaf

Mechanisms of Anti-Ulcer Action of Guava Leaf

1. Antioxidant Activity: Reducing oxidative stress in the gastric mucosa.

A reducing action, which entails giving electrons to oxidized intermediates, is another feature of the extracts. These intermediates are stabilized by this mechanism, which stops more oxidative damage. According to the study, the phenolic content of guava leaves plays a critical role in this lowering action and greatly enhances the antioxidant capacity overall. The leaves of the guava plant had the highest antioxidant activity among its numerous sections, with a TEAC value of 4.91 ± 0.050 mM trolox equivalents/mg extract. This suggests that guava leaves are very good at maintaining antioxidant defence, which may help lessen oxidative stress in the stomach mucosa[83]. The study found that the extraction solvent affects the antioxidant activity of guava leaves. Because the methanol fraction was able to extract more of the active chemicals that support both was reducing and free radical scavenging processes, it demonstrated the best antioxidant activity. This implies that guava leaf extracts' ability to effectively counteract oxidative stress can be improved by the solvent selection[77].

Psidium guajava leaf ethanolic extract (EEPG) and ethyl acetate fraction (EAFPG) were tested for free radical scavenging activity against DPPH and inhibition of nitric oxide radicals. The findings show that EAFPG and EEPG both scavenged stable nitric oxide radicals with efficacy, and EAFPG possessed notable free radical scavenging activity, which may be attributed to flavonoids like quercetin. The process of both acute and chronic ulceration in the stomach mucosa is linked to oxidative stress, which frequently involves free radicals created from oxygen. Psidium guajava leaf extracts' antiulcer activity and ulcer-healing capabilities are greatly enhanced by their antioxidant qualities, particularly their capacity to scavenge these free radicals[84].

2. Anti-Inflammatory Properties: Suppressing pro-inflammatory cytokines.

Levels of significant pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) have been significantly reduced by Psidium guajava L. The reduction of these cytokines indicates an overall anti-inflammatory effect, given the significant role they play in the inflammatory response[85]. Prostaglandin E2 (PGE2) and nitric oxide (NO), two inflammatory mediators, have been shown to be inhibited by Psidium guajava L. leaf extracts. These are synthesized by enzymes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), respectively, which are stimulated by lipopolysaccharide (LPS) and pro-inflammatory cytokines[45, 85, 86]. To regulate the inflammatory response and modulate the expression of a number of genes responsible for the production of inflammatory mediators, recent studies indicate that MAPK (Mitogen-Activated Protein Kinase) signalling pathways are critical. There are three main pathways of MAPK, namely p38, JNK, and ERK[87, 88].

It has been discovered that Psidium guajava leaf extracts significantly suppressed the production of NO. This was an effect observed in RAW264.7 macrophages stimulated by lipopolysaccharide (LPS), where the extract suppressed nitric oxide synthase (NOS). Our previous research has also shown that P. guajava leaf extract significantly suppresses the production of NO and prostaglandin E2 (PGE2). P. guajava leaf ethanol extracts inhibited TNF-αα, IL-1, and IL-6 at protein and mRNA levels. Through inhibiting the mRNA expression of inflammatory mediators such as iNOS, TNF-α, IL-6, and IL-1β, these leaf extracts inhibited inflammation, as indicated by quantitative real-time PCR (qPCR) experiments[89].

3. Cytoprotective Effects: Strengthening and regenerating the gastric lining.

The fact that healing was performed so earlier demonstrates that the extract facilitates tissue regeneration. The plant has a number of compounds, including flavonoids and tannins, which have astringent, antibacterial, antifungal, and anti-inflammatory activities. By managing infection and the inflammation that is normally destructive to healing, such activities may indirectly promote tissue regeneration. Guava extract reduced cell counts in the in vitro experiment, but in vivo data showed that the wounds healed quicker. This suggests a complex mechanism whereby its components are exerting their effects to cause tissue regeneration through mechanisms other than multiplication of cells per se in a culture system[55]. Through inhibiting the gastric lesions, reducing the volume of gastric secretion, and inhibiting acid output, guava leaves have been found to be able to prevent stomach ulcers. They also increase the pH level of the stomach. The anti-ulcer activity of guava leaves is largely attributed to their protective action on the stomach mucosa. The flavonoids present in the leaves are thought to be the causative agents for the protective action[90].

Characterized cytoprotective substances possessing established anti-ulcer genic activity include flavonoids. These agents are thought to both counteract the aggressive factors in the gastrointestinal lumen and facilitate the release of protective agents such as mucus and bicarbonate. Psidium guajava's flavonoid content is largely responsible for the observed anti-ulcer activity[91].

4. Antimicrobial Action:

Methanol and ethanol extracts of guava leaves were inhibitory in efficacy, predominantly against gram-positive bacteria (S. aureus and B. cereus). In contrast, gram-negative bacteria exhibited resistance towards all solvent extracts. Gram-negative bacteria's cell wall organization, comprising a thin lipopolysaccharide outer membrane that can restrict plant extracts entry, is believed to be accountable for their resistance[51]. Among some of the several compounds found in guava leaves (Psidium guajava L.) are tannins that have very good antibacterial activity. Both bacterial and fungal infections are influenced by these activities depending on the concentration of tannin as well as the type of

microorganism. Natural preservatives or chemicals having antioxidant and antibacterial activity can be derived from guava leaves. Guava leaf tannin preparations have also exhibited inhibitory effects on a range of bacterial infections. They inhibit Pseudomonas aeruginosa and Escherichia coli. The Gram-negative bacteria, such as P. aeruginosa and E. coli, are more vulnerable to tannin's attack on cell wall proteins because their cell walls are thinner (10–15 nm) compared to Gram-positive bacteria. Denaturation of proteins and depressed bacterial metabolism can be triggered by the capacity of tannins to participate in hydrogen bonding with protein molecules of bacteria. Protein precipitation can be induced by denaturation. They can also disrupt the plasma membrane of bacteria, causing leakage of vital metabolites and deactivation of enzyme machinery, thereby inhibiting microbial growth or killing them[92].

It is widely recognized that flavonoids exhibit antimicrobial action. Although terpenoids are mostly recognized to be fragrant in nature, they are also antibacterial. Phenols are antifungal in nature by inhibiting glucosamine, a fungal growth indicator, and ergosterol, a cell membrane constituent of the fungus. Aqueous tannins are antibacterial by multiple mechanisms, such as extracellular enzyme inhibition, inhibition of oxidative phosphorylation, and deprivation of substratum. The wide range of polyphenolic compounds present in guava leaf extracts is thought most likely to be responsible for their antibacterial activities[93].

5. Acid-Neutralizing Properties:

Guava leaf extract's capacity to reduce the potency of acidic environments is one of many attributes that make it a effective corrosion inhibitor. Its combination with acid molecules, which minimizes the destruction capability of the acid, is the primary manner in which this effect is observed. Under acidic environments like 0.1, 0.3, and 0.5 M H2SO4, the inhibitor (guava leaf extract) is observed to restrain the corrosion of mild steel. This is because the strength of the acid is reduced due to the molecules of the inhibitors halting the molecules of the acid[94].

The guava leaves are activated chemically to form activated carbon (GL-HAC) using hydrochloric acid (HCl) in the ratio of 1:1 (wt%). After activation, the sample is washed with hot distilled water until the pH of the filtrate remains neutral. For the preparation of activated carbon for other characterisation and adsorption studies, this neutralisation step is very important. In the synthesis of acid-activated GL-HAC, there is a neutralisation step following acid activation. Its surface charge behaviour as indicated by its pHpzc of 4.3 is important to successful adsorption, especially for cationic dyes like methylene blue at a pH level higher than 4.3. Its ability to absorb substance is complemented by the existence of different functional groups[95].

Advantages:

- Preparation of a tea from guava leaves can lower stomach acidity. Among several regions, traditional use continues to dominate. Guava leaves and fruits bear flavonoids and saponins that are major determinants in their ability for lowering acidity and the consequent development of ulcers in the stomach[96].
- Guava leaf extracts have potent antimicrobial properties. This is crucial for the treatment of ulcers, particularly those that bacterial infections may exacerbate[97].
- Guava leaf extracts have analgesic and anti-inflammatory properties. These characteristics help control the discomfort and swelling brought on by ulcers[98].
- Guava leaves have historically been used to cure a variety of ailments, including diarrhoea, diabetes mellitus, wound healing, coughing, and sore throats. They also have a reputation for being calming[99].
- Psidium guajava has been used as a herbal remedy for a number of oral conditions, including ulcers, sore throats, swollen gums, and toothaches. Guava leaf decoction has also been used as mouthwash[50].
- The antioxidant lycopene, which is abundant in guava, is crucial for the prevention and treatment of cancer. Out of all of them, breast and prostate cancer respond the best. Aqueous extract from guava budding leaves possesses anti-prostate cancer qualities. activity in a cell line model and concluded that they are a promising medication for androgen-sensitive prostate cancer[100].
- The sufficient quantity of dietary fiber present in guava fruits and leaves serves as the cornerstone for the treatment of constipation. Younger tender leaves have a very high fiber and roughage content, which is crucial for treating and preventing constipation and haemorrhoids[101].

Comparison with Conventional Anti-Ulcer Drugs:

Synthetic and semi-synthetic pharmaceuticals, such as antibiotics, antiseptics, local anesthetics, local analgesics, and steroidal and non-steroidal anti-inflammatory drugs, are frequently used in conventional therapies for mouth ulcers. Even though topical steroids are commonly utilized, long-term usage of them can have major negative effects. Adrenal insufficiency, immunosuppression, osteoporosis, hyperglycaemias, and gastrointestinal disorders are some examples of these adverse consequences[53]. In comparison to synthetic pharmaceuticals, plant-based medications—such as those made from guava leaves—are becoming more and more popular since they improve patient compliance and have fewer negative effects. The goal of using herbal compounds like guava leaf extract is to offer a less dangerous substitute with a decreased chance of negative side effects[102]. Micro particle-loaded gels, which function as mucoadhesive formulations, can

be made with guava leaf extract. A sustained release of the active ingredients is made possible by this kind of formulation, which guarantees good dispersion, convenience of application, and the capacity to stick to the oral mucosa for an extended period of time[54].

Guava leaf extract exhibits encouraging anti-ulcer properties; in some cases, it even outperforms traditional anti-ulcer medications like omeprazole. Flavonoids and phenolic acids are two of the many healthy components found in guava leaves that support their anti-inflammatory, anti-microbial, and antioxidant qualities. At some concentrations, the extract exhibited a greater percentage of inhibition than the common medication omeprazole. Omeprazole exhibited 57.91% inhibition at 60 µg/ml, whereas the extract demonstrated 42.23%. Omeprazole, however, achieved 78.72% inhibition at 80 µg/ml, whereas the extract demonstrated 51.95%. Omeprazole showed 88.37% inhibition at 100 µg/ml, while the extract showed 57.38%. Omeprazole's half maximal inhibitory concentration (IC50) was 32.09 µg/ml, while the guava leaf extract's was 78.62 µg/ml. Guava leaf extract is a promising natural alternative for treating oral ulcers, especially when applied to mucoadhesive buccal patches, because of its longer action, higher bioavailability, and the localized treatment[103].

Conclusion:

Guava leaf (Psidium guajava) is an effective natural remedy for the prevention and treatment of peptic ulcers, owing to its rich phytochemical content and intricate pharmacological properties. Evidence from both traditional use and recent scientific research indicates that its gastroprotective properties may arise from antioxidant, anti-inflammatory, antibacterial, and mucosal-protective mechanisms. Flavonoids such as kaempferol and quercetin, tannins, and saponins are significant because they protect the gastric mucosa, combat Helicobacter pylori, and reduce oxidative stress. Common treatments for ulcers include proton pump inhibitors, H_2 receptor antagonists, and antibiotics. Guava leaf extracts are cheaper, have fewer side effects, and are less likely to cause resistance to medications. They also help with many different health problems, which may improve current treatment plans. Preclinical studies show promise, but we need more carefully planned clinical trials to make sure they work, set standard doses, and make sure they are safe in the long run. Guava leaf is a strong, safe, and easy-to-find natural medicine that may help with ulcers. It might also help people not need as many man-made drugs.

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Author's Contribution:

Kirti Patil: Conceptualisation, Methodology, Investigation, writing original draft preparation, Visualisation.

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