REVIEW PAPER

Phytochemicals in the Management of Peptic Ulcers: A Review of Plant-Based Substitutions

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ABSTRACT

Peptic ulcer infection (PUD) is a common gastrointestinal disorder influencing around 10% of the worldwide populace. It is essentially caused by Helicobacter pylori disease and the incessant utilisation of non-steroidal anti-inflammatory drugs (NSAIDs). Routine medicines, such as proton pump inhibitors (PPIs), H2 receptor blockers, and stomach settling agents, offer symptomatic help but are related to side impacts and frequent backslides. Later studies have appeared that phytochemicals—naturally occurring compounds found in plants—hold critical potential in the administration of PUD. These incorporate alkaloids, flavonoids, glycosides, and terpenoids, which have anti-ulcerogenic, anti-inflammatory, and antioxidant properties. This audit examines the pathogenesis of peptic ulcers, centering on the part of H. pylori and NSAIDs, and highlights the helpful guarantee of plant-based medications. Particular phytochemicals like berberine, quercetin, and beta-myrcene have appeared viable in preclinical models by lessening gastric corrosive discharge, upgrading mucosal obstruction, and relieving oxidative stress. Conventional plants, utilized in different societies for ulcer treatment, moreover display cost-effective and available options to present-day pharmaceuticals. Future investigations are required to investigate the clinical viability of these phytochemicals, particularly in large-scale trials. Also, the improvement of novel phytomedicines and personalized treatment approaches may lead to more successful and more secure administration of PUD. With anti-microbial resistance on the rise, elective treatments focusing on H. pylori contamination may also be pivotal in the coming years.

Keywords: Peptic ulcer disease, Diagnosis, Treatment, Beta-myrcene, Monoterpenes.

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1. Introduction

A persistent and recurring ailment, ulcers are identified by the sporadic development of lesions in the stomach mucosal membrane (Malfertheiner P et al 2023). Gastric ulcers, which are characterised by the development of open sores in the stomach lining, have long been acknowledged as a major global wellness risk (Narayanan M et al 2018). Stress is a complicated phenomenon that has a significant impact on many physiological processes in the human body, including the digestive system. Stress can cause modifications to the physiology of the stomach, including increased secretion of gastric acid, and decreased blood flow through the mucosa. These factors all have participated in the development of duodenum pustule. The complicated interaction of variable highlights how difficult it is to treat stomach ulcers brought on by stress (Prevalence C et al 2016). Phytochemicals are naturally occurring molecules found in plants that show great promise in the treatment of stomach ulcers brought on by various factors. The bioactive chemicals having potential therapeutic roles of large amount of phytoconstituents, such as, alkaloid, glycoside, flavonoid, tannins, terpenoids, polysaccharides, and saponins are important for managing ulcers since they have shown remarkable anti- ulcerogenic activities in preclinical and clinical investigation (Kumar A et al 2023). 'Alkaloids' anti-ulcerogenic qualities have made them appear as viable treatments for stomach ulcers. *Berberine* is a naturally occurring chemical found in many plants, including those in Berberis species. It has been shown to have a significant ulcer-prevention property. The lowering of stomach acid output and strengthening of the mucosal barrier are the main outcomes of these effects (Kapitonova M et al 2022). 'Glycosides' have a broad class of compounds with a variety of biological functions. Studies have revealed that certain glycosides, such as saponins, have the ability to prevent ulcers by regulating stomach acid secretion, encouraging the formation of mucus, and strengthening antioxidant defences (Arunachalam K et al 2023). `Flavonoids' have anti-inflammatory and antioxidant qualities, that have attracted attention for their ability to have anti-ulcerogenic effects. Certain fruits and vegetables include compounds called *quercetin* and *catechins* that have been shown to reduce inflammation and oxidase stress in the stomach mucosa (Serafim C et al 2020).

PEPTIC ULCER:

Peptic ulcer (shown in fig 1) disease is a prevalent abdominal condition which impacts around 10% of the global population (Belaynesh YM et al 2021). Esophageal,

gastric, and duodenal ulcers are the components of Peptic Ulcer Disease. The higher symptoms continuously occurring of peptic ulcer is epigastrium which is accompanied by gastroesophageal reflux disease (GERD) and heartburn. The occurring pain may be dyspepsia, bloating, or nausea. Peptic ulcer disease can caused by some factors, the one is persistent *Helicobacter pylori* infection and other one is unusual use of Non-Steroidal Anti-Inflammatory Drugs also known as NSAIDs (Kavitt RT et al 2019). Worldwide, a large number of herbal medications have been utilised to treat Peptic ulcer disease (PUD). Approximately 279 plants from 89 families were found in an evaluation by Ardalani and his associates to be potentially useful in the treatment of peptic ulcer (Boakye- Yiadom et al 2021). In addition, Boakye-Yiadom et al. have presently documented the use of 13 plants from ten distinct families to treat peptic ulcers in Ghana. The possibilities for the usage of herbal material and medication in illness from ulcers stems from their relative safety, availability and affordability when compared to most traditional herbal drugs (Ardalani H et al 2020). The conventional drugs currently used to treat PUD include antacids, PPIs, H2 antagonists, anticholinergics, mucosal protective agents, and antimicrobials for PUD caused by *H. pylori*. However, none of these drugs have long-term curative effects, and relapse is common even after extensive treatment. Furthermore, there is a chance that these conventional drugs will have detrimental side effects (Kumar R et al 2011).

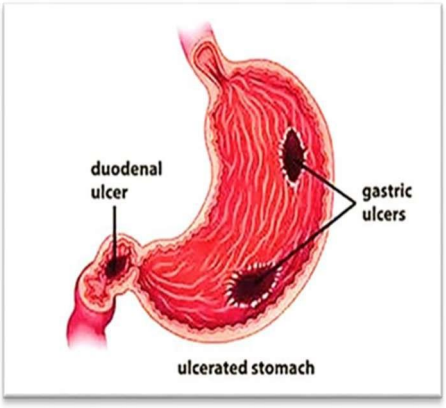

Figure 1: peptic ulcer

PATHOGENESIS OF PEPTIC ULCER

Helicobacter pylori, still one of the most common causes of peptic ulcer illness, is present in about half of the world's population (Siddique O et al 2018). Developing countries, mainly in Eastern Europe, Africa have higher rates of *H. pylori* prevalence (Hoai J.K.Y et al 2017). Most often in nations with lower socioeconomic positions, the creature is obtained during lower ages in a milieu of unhygienic circumstances and crowding. The inflammatory reaction that *H. pylori* sets off in the antrum ends in injury and degeneration of the epithelium cells. Neutrophils, lymphocytes, plasma cells, and macrophages are all involved in this reaction.

The exact method by which *H. pylori* causes various lesions to develop in the gastroduodenal mucosa remains unclear. The infection can be identified by the presence of either hyperchlorhydria or hypochlorhydria. The principal mediators of H. pylori infection are cytokines that inhibit parietal cell secretion; nevertheless, *H. pylori* can also directly affect the H+/K+ ATPase α-subunits, activate sensory neurones linked to somatostatin-related calcitonin gene-related peptide (CGRP), or stop gastrin from forming (Zaki M et al 2013). While hyposecretion has direct link in occurring of stomach ulcers, about 10-15% of patients infected with *H. pylori* contain hypergastrinemia, which results in increased gastric secretions, and lowered antral somatostatin range (El Omar EM et al 1997). This causes the parental and stomach cells to secrete more histamine, which in turn causes them to secrete more acid or pepsin. Furthermore, eliminating *H. pylori* causes an increase in somatostatin mRNA expression and a decrease in gastrin mRNA expression (Moss S.F et al 1992).

The systemic suppression of constitutively produced cyclooxygenase-1 (COX-1) is the main mechanism by which NSAIDs cause damage to the gastroduodenal mucosa. This mechanism is associated with mucus and bicarbonate

secretion, decreased mucosal blood flow, and suppressed cell proliferation. COX-1 is liable for prostaglandin fusion. The enzymes are reversibly and concentration-dependently inhibited by NSAIDs. When exogenous prostaglandin and COX-2 selective NSAIDs a used together, mucosal damage and ulcer risk are decreased (Bhala N et al 2013).

NSAIDs induce the oxidative phosphorylation in the mitochondria to become uncoupled and disturb mucus phospholipids, which starts the damage to mucosa. NSAIDs become protonated when they are exposed to acidic digestive fluid (ph 2), where they penetrate epithelial cells (pH 7.4) after crossing the lipid membrane, ionise, and release H±. The uncoupling of oxidative phosphorylation, a decrease in mitochondrial energy production, an increase in cellular permeability, and a reduction in cellular integrity result from NSAID's inability to crosses the membrane (lipid) and their subsequent entrapment in epithelium cells. NSAIDs induced ulcers are more common in patients over 65, who take high doses or a mix of NSAIDs, have a history of bleeding or peptic ulcers, and utilise steroids or anticoagulants concurrently (Narayanan M et al 2018).

1. DIAGNOSIS AND TREATMENT

Up until the early 1900s, the majority of diagnosis for peptic ulcers were made based on clinical indication and symptoms. A range of flexible endoscopies revolutionized shows a proper visualization of ulcers present in the 1950s. A complete clinical history and physical examination are necessary to create an exhaustive list of all clues and indications for the treatment. It is imperative to record all previous medical history, encompassing the duration of alcohol consumption, NSAID usage, smoking habits, and any potential incidence of peptic ulcer. The first is to rule out functional dyspepsia as the cause of the symptoms being described, and the second is to identify the precise source of the ulcer (Graham DY et al 2021).

- **Esophagogastroduodenoscopy**

In this novel method, gastroenterologists observe the stomach and small intestine by inserting a thin pipe consisting camera via oral route to gastric area. During this examination, the doctor could biopsy the stomach wall to check for *H. pylori* (NCBI NBK 310264 2015).

An investigation of *H. pylori* infection should be performed on each patient who has a gastric ulcers. After the detections in 1993, the administration has undergone with number of changes. It is commonly recognized that the infection's prevalence increases with age and is gender- neutral. To verify this a variety of tests are carried out for both diagnosis and follow-up after the eradication treatment. To identify *H. pylori,* both direct and indirect tests are used, depending on whether an endoscopy is required (Garza González e et al 2014).

- **X-RAY**

This entails making the patient lie down on an inclined examination table and forcing them to consume barium, a white, chalky substance that appears on X-rays. By tilting, the upper digestive tract's barium is evenly disturbed, allowing the X-ray to take pictures from various perspectives. This makes it possible for the physician to find the ulcer and assess its kind and severity (Nawaz M et al 2008).

- **RADIOLOGY**

Although the endoscopic investigation has largely replaced barium gastroduodenal studies in standard diagnostic protocols, these studies can still be useful in the few individuals who refuse the surgery in circumstances where oesophagal constriction makes endoscopy impossible. The sensitivity and specificity of barium radiology investigations are influenced by the radiologist's experience, the technique employed, the depth of the ulcer, the size of the lesion (less than 0.5 cm in diameter can be difficult to identify), and other factors. A symmetrical mucosal fold with uniform boundaries, a smooth, translucent band collar, an ulcer crater surrounding it that suggests oedema, and an indentation of the opposing wall are radiologic signs that point to a benign nature. Conversely, extensive ulcers, uneven filling, lack of contrast, and irregular mucosal folds are signs of cancer (Ahlawat R et al 2023).

- **Computed Tomography**

This is an faster way to detect an suspected penetration and perforation diagnosis related to duodenal ulcers. The purpose of this retrospective study is to evaluate the abdominal computed tomography results in patients suffering from peptic ulcer disease and to correlate them with the patient's clinical history, the results of upper GT series and endoscopic procedures, and any surgery that may have been done (Møller MH et al 2009).

TREATMENT

There are several synthetic or conventional treatments for peptic ulcer disease (shown in Table 1) and plant-based medicines or traditional plans used for the treatment of peptic ulcer disease (shown in Table 2).

Table 1 Mechanism of action and ADR of conventional treatment.

Target Areas	Drugs	Mechanism of Action	Adverse Effects	References
Proton Pump Inhibitors (PPIs)	➢ Pantoprazole ➢ Lansoprazole ➢ Rabeprazole ➢ Omeprazole	To pronounced and long lasting reduction of gastric acid production.	• Diarrhoea • Nausea • Constipation • Abdominal pain • Vomiting	(Mossner J et al 2016 / Maes ML et al 2017).
H2 Receptor Blockers	➢ Cimetidine ➢ Famotidine ➢ Nizatidine ➢ Ranitidine	Preventing histamine from binding to H2 receptor on gastric parietal cells.	• Fatigue • Muscle aches • Drowsiness • Thrombocytopenia • Anxiety	(Pension J et al 1986).
Antacids **Cytoprotective Agents**	➢ Aluminium hydroxide ➢ Misoprostol	Raises the ph of the stomach to more than four and stops pepsin's proteolytic action. Increase blood flow and stimulate formation of mucus in git	• Nausea • Vomiting • Chalky taste • Hypophosphatemia • Abdominal cramping • Diarrhoea • Abdominal pain • Headache • Constipation	(Maton P.N et al 1999). (Marks I.N and Aubert J et al 1991/2014).

Table 2 . Overview of plants used in treatment of peptic ulcer disease.

S. No	Binomial Name	Family	Part Used	Condition of Plant Used	Method of Preparation	Reference
1.	*Aloe gilbertii-Shrub*	Asphodelaceae	Leaf	Fresh	Young leaves are pulverized and filtrate taken orally.	(Belayneh A et al 2020).
2.	*Aloe pubescens -Shrub*	Aloaceae	Gel	Fresh	Fresh gel is eaten .	(Belayneh A et al 2020).

3.	*Calpurnia aurea-Shrub*	Fabaceae	Leaf	Fresh	Chewing	(Tefera et al 2019).
4.	*Carica papaya-Tree*	Caricaceae	Seed	Fresh	Oral	(Amsalu N et al 2018).
5.	*Casimiroa edulis- Tree*	Rutaceae	Fruit	Fresh	Eating	(Tefera et al 2019).
6.	*Dichrostachys cinerea-Tree*	Fabaceae	Steam	Dry	Burns stem, make solution from the ash and take it orally.	(Bussa NF et al 2020).
7.	*Lippia adoensis-Herb*	Verbenaceae	Leaf	Fresh	Chewing	(Amsalu N et al 2018).
8.	*Thymus schimperi-Herb*	Lamiaceae	Seed	Dry	Crushed seeds are boiled in water and served as a drink	(Atnafu H et al 2018).

2. Monoterpenes used in peptic ulcer disease

Monoterpenes are compounds containing two isoprene units (Zwenger, s. Basu). Monoterpenes can be found as a major compound in plants such as Origanum vulgare L (Silva et al, 2012), Citrus lemon (Rozza et al 2011), Citrus aurenticum (Rahimi A. et al 2014), Humulus lupulus L. (Aberl A., Coelhan M. 2012), etc. other monoterpenes are listed in table 3.

Table 3: list of monoterpenes used in peptic ulcer disease

Compound	**Effect**	**Mechanism**	**Reference**
Linalool	Gastroprotective and healing effect	reduce level of Myeloperoxidase and lipoperoxidase	(Shi et al 2016).
Menthol	Gastroprotective effect	reduce acid secretion, myeloperoxidase, tumour necrosis factor and increase mucus, GSH	(Rozza A.L, et al 2013).
α-pinene	Gastroprotective effect	decrease acid secretion and increase mucus secretion	(Pinheiro et al 2015).

Thymoquinone		increase superoxide dismutase & nitric oxide and reduce total oxidation status	(Zeren S, et al 2016).
Carvacrol	Gastroprotective and bactericidal effect	increase mucus secretion, sulfhydryl compounds and catalase	(Oliveira, et al 2012).
Limonene	Gastroprotective and bactericidal effect	increase mucus secretion, GPx and decrease myeloperoxidase & tumour necrosis factor	(De Souza et al 2019).
β-myrcene	Gastroprotective and bactericidal against *H.pylori*	increase mucus & glutathione reductase and decrease malondialdehyde	(Bonamin F, et al 2014).

- **Beta-myrcene**

Chemically known as 7-methyl-3-methylene-1,6-octadiene, it is a vital flavouring compound frequently utilized in the food and beverages sector. Additionally, often utilized in products like cosmetics & detergents. It is commercially used as a key ingredient for producing flavours such as geraniol, and linalool (Behr A, et al 2009).

- **Sources and method of extraction**

β-myrcene can be obtained from various sources like hop-essential oil, cannabis plant, orange, lemongrass and mangoes. Some of the sources and methods of extraction of beta-myrcene are listed in Table 4.

Table 4: - sources and method of extraction of β-myrcene.

PPlant lant	**Family**	**Parts used**	**Extraction method**	**Assay**	**Reference**
Citrus aurantium L.	Rutaceae	Flower	Hydrodistillation	GC-MS	(Rahimi A. et al 2014).
Citrus aurantium L.	Rutaceae	Fruit	SPME	GC-O	(Miyazaki T. et al 2012).
Humulus lupulus	Cannabaceae	Cones & pellets	HS trap	GC-MS	Albert A, et al (2012).
Humulus lupulus	Cannabaceae	Essential oil	SPME	GC-qMS	(Goncalves J et al 2012).
Humulus lupulus	Cannabaceae	Cones	HS-SPME	GC	(Vazquez- Araujo L, et al 2013).
Cannabis sativa L.	Cannabaceae	Female flowering tops	Solvent extraction	GC-FID-NMR	(Romano LL, et al 2013).
Cannabis sativa L.	Cannabaceae	Flowers	Exhaustive SE	GC-MS	(Ibrahim EA, et al 2019).
Pistacia lentiscus	Anacardiaceae	Essential oil	HS-SPME	GC-MS	(Zachariadis GA, et al 2012).

Spondias mombin L.	Anacardiaceae	Fruit	SPME	GC-MS	(Ceva-Antunes PMN, et al 2003).

GC-ms= Gas chromatography and mass spectrometry, GC-O= Gas chromatography olfactometry, GC-FID-NMR= gas chromatography/flame ionization detection- nuclear magnetic resonance, HS-SPME= Headspace solid-phase microextraction, SE= solvent extraction, GC-Qms=gas chromatography-quadrupole mass spectrometry.

- **Synthesis of Beta-myrcene**

1. Isoprene bromide and Geranyl bromide react with Ethyl acetoacetate to produce β-keto esters via Wetting reaction they can be transformed to beta-myrcene (M.B. Kolicheski et al 2007).
2. It can be obtained from β-pinene (99.2 mol%) by pyrolysis. At a temperature extending from 573K-873K, the inhabitant time was 0.2s. By the end of pyrolysis, it formed β-myrcene, ψ-limonene and limonene by joint biradical reaction intermediates. The medium of adaptation of β-myrcene from β-pinene was closely resembling to the accretive fracture of the cyclobutane ring. Whereas others were formed from biradicals (Zheng et al 2017). The synthesis is shown in fig 2.

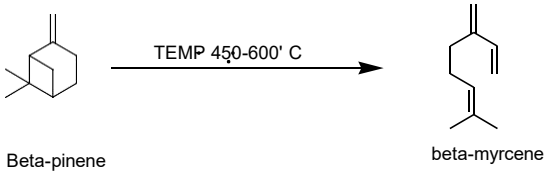

Fig 2: - Pyrolysis of pinene to form myrcene

- **Physical and Chemical properties**

Table 5 Physical and Chemical properties of beta myrcene.

Parameter	Description	References
Appearance	Yellow oily liq./ colourless liq.	(NCBI 2020).
Boiling point (◦C)	167	(Veith SR et al 2004).
Melting point (◦C)	<10	(Chemicals Inspection and Testing Institute Japan 1992).
Odour	Woody, herbaceous and balsamic	(Stenhaus M, et al 2000).
Solubility	Water Insoluble, Soluble in alcohol, ether, glacial acetic acid	(Merk Index 2013).
Stability	Polymerises at room temp.	(Behr A, et al 2009).

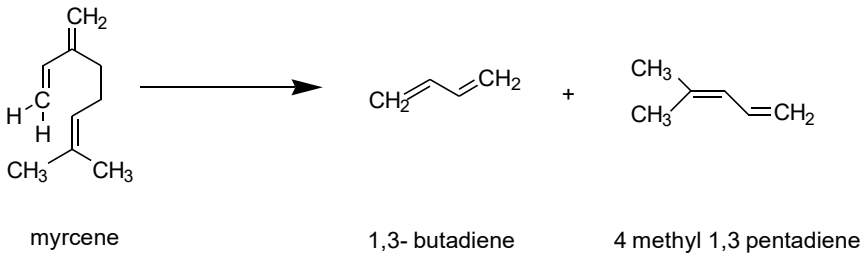

Fig 3 Route of decomposion (M.B. Kolicheski et al 2007).

Myrcene exhibit 2 isomeric forms α & β. B-myrcene is a naturally occurring isomer that has an isopropylidene group. While α-myrcene is not found naturally has an isopropenyl group. Ruziuka et al demonstrated that the naturally occurring form is β-myrcene by ozonolysis experiments. Later confirmed by infrared and NMR (Behr A, et al 2009).

Decomposition of myrcene forms 1,3-butadiene and 4 methyl-1,3-pentadiene via free radical. This agrees with the universal pyrolysis model by Gwyn (M.B. Kolicheski et al 2007) the route is shown in Figure 3.

4. Pharmacological Properties of β-myrcene

β-myrcene has a wide range of pharmacological properties. It has sedative and anticonvulsant properties in the neurological system. It also has antioxidant and anti-inflammatory properties. It can also be applied to the control of pain and the treatment of peptic ulcer disease.

- **Nervous system (CNS/ANS)**

Cannabis saliva's essential oil (beta-myrcene 22.9%), showed great activity on ANS in healthy humans. They inhaled essential oil for 5 minutes which improved their nerve activity and got relief from stress & anxiety. To the control group, they administered sweet almond oil. This study revealed that those subjects were more energetic and their mood was elevated. Their electroencephalogram reports were similar to those who were doing meditation (Gulluni N. et al 2018). Essential oil from Cinnamosma madgascariensis (content 8.9%) showed anticonvulsant activity caused by PTZ in Wistar rats. The GABA & glutamate neurotransmission were responsible for the sedative effect due to that beta-myrcene shows anticonvulsant activity (Rakotosaona R. et al 2017).

- **Anti-inflammatory Activity**

Beta-myrcene is a powerful anti-inflammatory agent that reduces inflammation via PEG-2 (Lorenzetti BB. Et al 1991). In the model of isoproterenol-induced, it prevented cardiac failure via a decrease in MMP-2, TGF-β, and iNOs (Tian J, et al 2020). In models of osteoarthritis, it showed anti-inflammatory activity in a dose of 20-50μg/ml. It acts by decreasing the levels of IL-1β, NF-$_k$B, and jun terminal kinase. And promote the maintenance of the differentiated chondrocyte phenotype (Rufino AT, et al 2015).

- Treatment of peptic ulcer disease

β-myrcene has ulcer healing and antioxidant properties it can be used to manage oxidative stress-induced disease conditions. In the Ethanol-induced ulcer model, β-myrcene inhibited ulcer formation by 60% (dose 7.5 mg/kg) via an increase in glutathione, glutathione reductase and glutathione peroxidase. It also reduced the levels of superoxide dismutase. Also, in the indomethacin-induced model, β-myrcene reduced ulcers by 74% via a decrease in myeloperoxidase in gastric mucosa. In the ischaemia-reperfusion model, β-myrcene reduced ulcers by 86% through the increase in glutathione level and limiting myeloperoxidase. Pretreating animals with L-NAME reversed the ulcer protective effect shown by β-myrcene. It uncovered that the nitric oxide pathway is vital for the component of activity for ulcer protection by β-myrcene. It also increased the level of adhered mucosa by 50% in pylorus- ligated rats. The minimum inhibitory concentration for causing hindrance in the growth of H. pylori was found to be 500 μg/ml via serial dilution (Bonamin F. et al 2014).

- **Antinociceptive activity**

β-myrcene possesses central and peripheral palliative effects (Paula-Freire LI et el 2016). 10mg/kg dose was effective in producing a strong antinociceptive effect in mice suffering from acute pain.

The effect was antagonized by yohimbine and naloxone which showed that the mechanism of action was through α-2 adrenoceptors (Rao VS et al 1990). Lemongrass essential oil (15-20% myrcene) showed sturdy palliative effects in the experimental pain models. After repetitive administration for 5 days, no tolerance was seen as compared to morphine (Lorenzetti BB et al 1991).

5. Conclusion:

Helicobacter pylori infection and long-term use of non-steroidal anti-inflammatory medicines (NSAIDs) are the main causes of peptic ulcer disease (PUD), a serious worldwide health issue that weakens the stomach mucosal defenses and causes ulcers. Proton pump inhibitors (PPIs), H_2 receptor antagonists, and antacids are examples of standard treatments that work well but can also cause relapse, side effects, and antibiotic resistance.

Plant-based treatments have drawn interest as safer, more affordable substitutes for or supplements to traditional medications. Significant anti-ulcerogenic activity is exhibited by medicinal plants belonging to families including Asphodelaceae, Aloaceae, and Fabaceae. Bioactive phytochemicals such as alkaloids, flavonoids, glycosides, tannins, and saponins—which offer cytoprotective, anti-inflammatory, and antioxidant properties—are primarily responsible for their therapeutic effects.

By blocking inflammatory mediators and oxidative stress, beta-myrcene, one of these substances, exhibits strong anti-inflammatory and antioxidant qualities that improve

mucosal defense and encourage ulcer healing.

Overall, plant-derived drugs exhibit encouraging promise, even though traditional pharmacotherapy is still essential for managing PUD. To elucidate their mechanisms and facilitate their incorporation into contemporary therapeutic approaches, more investigation is required.

6. Future Aspects:

It is anticipated that multidisciplinary research aiming at increasing efficacy and decreasing recurrence would progress the therapy of peptic ulcer disease (PUD) in the future. Large-scale clinical trials should be given top priority in future research to confirm the efficacy and safety of phytochemicals including terpenoids, alkaloids, flavonoids, and glycosides. It may be possible to improve plant-based treatment approaches by comprehending their processes, especially how they interact with Helicobacter pylori and NSAID-induced stomach damage.

By standardizing and transforming bioactive plant chemicals into clinically appropriate dose forms, phytomedicine presents a significant opportunity for the creation of new drugs. To incorporate these treatments into routine practice, cooperation between researchers and the pharmaceutical sector will be crucial.
Relapse rates could be decreased by tailoring treatment according to lifestyle factors, gut microbiota composition, and genetic profile thanks to advancements in personalized medicine. The incidence of disease may be further decreased by preventive measures that emphasize microbiome manipulation through dietary changes, probiotics, and prebiotics.

Furthermore, biomarker-based techniques and innovative non-invasive diagnostic instruments may improve early detection and monitoring. Another crucial area is using alternative antimicrobial agents, such as phytochemicals, to treat H. pylori's drug resistance. The reduction of side effects linked to traditional treatments like proton pump inhibitors and H_2 blockers should also be a goal of research.

In order to provide more efficient and patient-centered treatment, the management of PUD in the future will likely involve the integration of phytotherapy, customized medicine, cutting-edge diagnostics, and safer medication combinations.

References:

1. Aberl A, Coelhan M. Determination of volatile compounds in different hop varieties by headspace-trap GC/MS–in comparison with conventional hop essential oil analysis. J Agric Food Chem. (2012) 60:2785–92. doi: 10.1021/jf205002p
2. Ahlawat R, Hoilat GJ, Ross AB. Esophagogastroduodenoscopy. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. Available:https://www.ncbi.nlm.nih.gov/books/NBK532268/. 2023;532268
3. Amsalu N, Bezie Y, Fentahun M, Alemayehu A, Amsalu G. Use and conservation of medicinal plants by indigenous people of Gozamin wereda, East Gojjam zone of Amhara region, Ethiopia: an ethnobotanical approach. Evid Based Complement Altern Med. 2018;2018:1–23. doi:10.1155/2018/2973513
4. Amsalu N, Bezie Y, Fentahun M, Alemayehu A, Amsalu G. Use and conservation of medicinal plants by indigenous people of Gozamin wereda, East Gojjam zone of Amhara region, Ethiopia: an ethnobotanical approach. Evid Based Complement Altern Med. 2018;2018:1–23. doi:10.1155/2018/2973513
5. Ardalani H., Hadipanah A., Sahebkar A. Medicinal plants in the treatment of peptic ulcer disease. Rev. Mini. Rev. Med. Chem. 2020;20(8):662–702.
6. Arunachalam K, Sreeja PS, Yang X (2023) Mechanisms and therapeutic actions of edible fruits in inflammatory bowel disease: a review of pre-clinical studies. Food Chem Adv 3:100498
7. Atnafu H, Awas T, Alemu S, Wube S. Ethnobotanical study of medicinal plants in Selale mountain ridges, North Shoa, Ethiopia. Biodiversity Int J. 2018;2(6):567–577. doi:10.15406/bij.2018.02.00114
8. Aubert J., Bejan-Angoulvant T., Jonville-Bera A.P. [pharmacology of misoprostol (pharmacokinetic data, adverse effects and teratogenic effects)] J. Gynecol. Obstet. Biol. Reprod. (Paris) 2014;43:114–122. doi: 10.1016/j.jgyn.2013.11.006
9. Behr A, Johnen L. Myrcene as a natural base chemical in sustainable chemistry: a critical review. ChemSusChem. (2009) 2:1072–95. doi: 10.1002/cssc.200900186.
10. Belayneh A, Demissew S, Bussa NF, Bisrat D. Ethno-medicinal and bio-cultural importance of aloes from South and East of the Great Rift Valley floristic regions of Ethiopia. Heliyon. 2020;6(6):e04344. doi:10.1016/j.heliyon.2020.e04344
11. Belayneh YM, et al. Evaluation of the antiulcerogenic activity of hydromethanol extracts of Solanum incanum L.(Solanaceae) leaves and roots in mice; single and repeated dose study. Metabolism Open. 2021;11:100119
12. Bhala N., Emberson J., Merhi A., Abramson S., Arber N., Baron J.A., Bombardier C., Cannon C., Farkouh M.E., FitzGerald G.A., et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: Meta-analyses of individual participant data from randomised trials. Lancet. 2013;382:769–779
13. Bhala N., Emberson J., Merhi A., Abramson S., Arber N., Baron J.A., Bombardier C., Cannon C., Farkouh M.E., FitzGerald G.A., et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: Meta-analyses of individual participant data from randomised trials. Lancet. 2013;382:769–779
14. Boakye-Yiadom M., Kumadoh D., Adase E., Woode E. Review article medicinal plants with prospective

benefits in the management of peptic ulcer diseases in Ghana. BioMed Res. Int. 2021;2021

15. Bonamin F, Moraes TM, Dos Santos RC, Kushima H, Faria FM, Silva MA, et al. The effect of a minor constituent of essential oil from citrus aurantium: the role of b- myrcene in preventing peptic ulcer disease. Chem Biol Interact. (2014) 212:11–19. doi: 10.1016/j.cbi.2014.01.009
16. Bussa NF, Belayneh A. Long-standing herbal medicinal traditions from the prehistoric Harar town and the surroundings, Eastern Ethiopia. J Ayurvedic Herb Med. 2020;6(3):154–172. doi:10.31254/jahm.2020.6311
17. Ceva-Antunes PMN, Bizzo HR, Alves SM, Antunes OAC. Analysis of volatile compounds of taperebá (Spondias mombin L.) and cajá (Spondias mombin L.) by simultaneous distillation and extraction (SDE) and solid phase microextraction (SPME). J Agric Food Chem. (2003) 51:1387–92. doi: 10.1021/jf025873m
18. Chemicals Inspection and Testing Institute. Bioaccumulation Data of Existing Chemicals Based on the CSCL Japan. Japan Chemical Industry Ecology-Toxicology and Information Center (1992).
19. de Souza, M.C.; Vieira, A.J.; Beserra, F.P.; Pellizzon, C.H.; Nóbrega, R.H.; Rozza,

A.L. Gastroprotective effect of limonene in rats: Influence on oxidative stress, inflammation and gene expression. Phytomedicine 2019, 53,37–42. Doi: 10.1016/j.phymed.2018.09.027

20. Disease GBD, Injury I, Prevalence C (2016) Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the global burden of disease study 2015. Lancet 388(10053):1545–1602
21. El-Omar E.M., Oien K., El-Nujumi A., Gillen D., Wirz A., Dahill S., Williams C., Ardill J.E., McColl K.E. Helicobacter pylori infection and chronic gastric acid hyposecretion. Gastroenterology. 1997;113:15–24. doi: 10.1016/S0016- 5085(97)70075-1
22. Garza-González E, Perez-Perez GI, Maldonado-Garza HJ, Bosques-Padilla FJ. A review of helicobacter pylori diagnosis, treatment, and methods to detect eradication. World J Gastroenterol. 2014;20(6):1438–49
23. Gonçalves J, Figueira J, Rodrigues F, Camara JS. Headspace solid phase microextraction combined with mass spectrometry as a powerful analytical tool for profiling the terpenoid metabolomic pattern of hop essential oil derived from Saaz variety. J Sep Sci. (2012) 35:2282–96. doi: 10.1002/jssc.201200244
24. Graham DY, Khalaf N. Peptic Ulcer Disease. Geriatr Gastroenterol Second Ed. 2021;(March):1565–95
25. Gulluni N, Re T, Loiacono I, Lanzo G, Gori L, Macchi C, et al. Cannabis essential oil: a preliminary study for the evaluation of the brain effects. Evid Based Complement Altern Med. (2018). 2018:1709182. doi: 10.1155/2018/1709182
26. Hooi J.K.Y., Lai W.Y., Ng W.K., Suen M.M.Y., Underwood F.E., Tanyingoh D., Malfertheiner P., Graham D.Y., Wong V.W.S., Wu J.C.Y., et al. Global prevalence of Helicobacter pylori infection: Systematic review and meta-analysis. Gastroenterology. 2017;153:420–429. doi: 10.1053/j.gastro.2017.04.022
27. Ibrahim EA, Wang M, Radwan MM, Wanas AS, Majumdar CG, Avula B, et al. Analysis of terpenes in Cannabis sativa L. Using GC/MS: method development, validation, and application. Planta Med. (2019) 85:431–8. doi: 10.1055/a-0828-8387

28. InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. What happens during a gastroscopy? 2015 Jun 30 [Updated 30].Available:https://www.ncbi.nlm.nih.gov/books/NBK310264/. 0002.pdf%0Ahttp://dx.doi.org/10.1038/srep22311%0Ahttp://www.life.um
29. Kapitonova M, Gupalo S, Alyautdin R, Ibrahim IAA, Salim N, Ahmad A, Talip SB, Nwe TM, Morokhina S (2022) Gastroprotective effect of Berberis vulgaris on ethanol- induced gastric mucosal injury: histopathological evaluations. Avicenna J Phytomed 12(1):30–41
30. Kavitt R.T., Lipowska A.M., Anyane-Yeboa A., Gralnek I.M. Diagnosis and treatment of peptic ulcer disease. Am. J. Med. 2019;32(4):447–456.
31. Kumar A, Kumar M, Jose A, Tomer V, Oz E, Proestos C, Zeng M, Elobeid T, Oz F (2023) Major phytochemicals: recent advances in health benefits and extraction method. Molecules 28(2):887
32. Kumar R. Glacier pothole. In: Singh VP, Singh P, Haritashya UK, editors. Encyclopedia of snow, ice and glaciers. Netherlands: Dordrecht, Springer; 2011. p. 414–5] / [Toth-Manikowski SM, Grams ME. Proton pump inhibitors and kidney disease—GI upset for the nephrologist? Kidney Int Rep. 2017;2(3):297–30
33. Lorenzetti BB, Souza GE, Sarti SJ, Santos Filho D, Ferreira SH. Myrcene mimics the peripheral analgesic activity of lemongrass tea. J Ethnopharmacol. (1991) 34:43–8. doi: 10.1016/0378-8741(91)90187-I
34. Lorenzetti BB, Souza GE, Sarti SJ, Santos Filho D, Ferreira SH. Myrcene mimics the peripheral analgesic activity of lemongrass tea. J Ethnopharmacol. (1991) 34:43–8. doi: 10.1016/0378-8741(91)90187-I
35. Maes M.L., Fixen D.R., Linnebur S.A. Adverse effects of proton-pump inhibitor use in older adults: A review o2f 0t1h5e evidence. ThJeur.n Adv. Drug Saf. 2017;8:273–297. doi: 10.1177/20420986137(711)5:13–810. Available from:http://sc
36. Malfertheiner P, Camargo MC, El-Omar E, Liou J-M, Peek R, Schulz C, Smith SI, Suerbaum S (2023) Helicobacter pylori infection. Nat Rev Dis Primers 9(1):19 doi: 10.1016/j.bpg.2006.04.005
37. Marks I.N. Sucralfate-safety and side effects. Scand. J. Gastroenterol. Suppl. 1991;26:36–42. doi: 10.3109/00365529109093218
38. Maton P.N., Burton M.E. Antacids revisited: A review of their clinical pharmacology and recommended therapeutic use. Drugs. 1999;57:855–870. doi: 10.2165/00003495- 199957060-00003
39. Matura M, Sköld M, Börje A, Andersen KE, Bruze M, Frosch P, et al. Selected oxidized fragrance terpenes are common contact allergens. Contact Dermatitis. (2005) 52:320–
8. doi: 10.1111/j.0105-1873.2005.00605.x
40. Merck Index. The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals.Whitehouse Station, NJ: Merck & Co., Inc (2013).
41. Miyazaki T, Plotto A, Baldwin EA, Reyes-De-Corcuera JI, Gmitter FG Jr. Aroma characterization of tangerine hybrids by gas-chromatography-olfactometry and sensory evaluation. J Sci Food Agric. (2012) 92:727–35. doi: 10.1002/jsfa.4663
42. Møller MH, Adamsen S, Wøjdemann M, Møller AM. Perforated peptic ulcer: How to improve outcome? Scand J Gastroenterol. 2009;44(1):15–22.
43. Moreno OM. Acute Oral Toxicity Studies of Myrcene in Mice, Rats and Rabbits. Unpublished report

to the Research Institute of Fragrance Materials (1972).

44. Moss S.F., Legon S., Bishop A.E., Polak J.M., Calam J. Effect of helicobacter pylori on gastric somatostatin in duodenal ulcer disease. Lancet. 1992;340:930–932. doi: 10.1016/0140-6736(92)92816-X

45. Mössner J. The indications, applications, and risks of proton pump inhibitors. Dtsch. Arztebl. Int. 2016;113:477–483. doi: 10.3238/arztebl.2016.0477.

46. Narayanan M, Reddy KM, Marsicano E (2018) Peptic ulcer disease and helicobacter pylori infection. Mo Med 115(3):219–224 PMCID: PMC6140150PMID: 30228726

47. Narayanan M., Reddy K.M., Marsicano E. Peptic ulcer disease and Helicobacter pylori infection. Mo. Med. 2018;115:219–224

48. Nawaz M, Jehanzaib M, Khan K, Zari M. Role of barium meal examination in diagnosis of peptic ulcer. J Ayub Med Coll Abbottabad. 2008;20(4):59–61.

49. NCBI. PubChem Compound Summary for CID 31253, Myrcene. (2020). Available online at: https://pubchem.ncbi.nlm.nih.gov/compound/Myrcene (accesse July 15, 2020).

50. NTP. NTP Technical Report on the Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies). Research Triangle Park, NC, National Institutes of Health (2010).

51. Oliveira, I.S.; da Silva, F.V.; Viana, A.F.S.C.; dos Santos, M.R.V.; Quintans-Júnior, L.J.; Martins, M.C.C.; Nunes, P.H.M.; Oliveira, F.A.; Oliveira, R.C.M. Gastroprotective activity of carvacrol on experimentally induced gastric lesions in rodents. Naunyn. Schmiedebergs. Arch. Pharmacol. 2012, 385, 899–908. doi: 10.1007/s00210-012-0771-x

52. Paula-Freire LI, Molska GR, Andersen ML, Carlini EL. Ocimum gratissimum essential oil and its isolated compounds (Eugenol and Myrcene) reduce neuropathic pain in mice. Planta Med. (2016) 82:211–6. doi: 10.1055/s-0035-1558165

53. Paumgartten FJR, Delgado IF, Alves EN, Nogueira ACMDA, Presgrave RDF, Neubert

D. Single dose toxicity study of beta-myrcene, a natural analgesic substance. Braz J Med Biol Res. (1990) 23:873–7.

54. Pension J., Wormsley K.G. Adverse reactions and interactions with H2-receptor antagonists. Med. Toxicol. 1986;1:192–216. doi: 10.1007/BF03259837

55. Pinheiro, M.A.; Magalhães, R.; Torres, D.; Cavalcante, R.; Mota, F.X.; Oliveira Coelho, E.A.; Moreira, H.; Lima, G.; da Costa Araújo, P.; Cardoso, J.L.; et al. Gastroprotective effect of alpha-pinene and its correlation with antiulcerogenic activity of essential oils obtained from Hyptis species. Pharmacogn. Mag. 2015, 11, 123.

56. Rahimi A, Hashemi P, Talei G, Borzuei M, Ghiasvand A. Comparative analyses of the volatile components of Citrus aurantium L. flowers using ultrasonic-assisted headspace SPME and hydrodistillation Combined with GC-MS and evaluation of their antimicrobial activities. Anal Bioanal Chem Res. (2014) 1:83–91

57. Rakotosaona R, Randrianarivo E, Rasoanaivo P, Nicoletti M, Benelli G, Maggi F. Effect of the leaf essential oil from Cinnamosma madagascariensis Danguy on pentylenetetrazol-induced seizure in rats. Chem Biodivers. (2017) 14:e1700256. doi: 10.1002/cbdv.201700256

58. Rao VS,Menezes AM, Viana GS. Effect of myrcene on nociception in mice. J PharmPharmacol. (1990) 42:877–8. doi: 10.1111/j.2042-7158.1990.tb07046.x
59. Romano LL, Hazekamp A. Cannabis oil: chemical evaluation of an upcoming cannabis- based medicine. Cannabinoids. (2013) 1:1–11.
60. Rozza, A.L.; de Mello Moraes, T.; Kushima, H.; Tanimoto, A.; Marques, M.O.M.; Bauab, T.M.; Hiruma-Lima, C.A.; Pellizzon, C.H. Gastroprotective mechanisms of Citrus lemon (Rutaceae) essential oil and its majority compounds limonene and -
pinene: Involvement of heat-shock protein-70, vasoactive intestinal peptide, glutathione, sulfhydryl compounds, nitric oxide and prostaglandin E. Chem. Biol. Interact. 2011, 189, 82–89.
61. Rozza, A.L.; Hiruma-Lima, C.A.; Takahira, R.K.; Padovani, C.R.; Pellizzon, C.H. Effect of menthol in experimentally induced ulcers: Pathways of gastroprotection. Chem. Biol. Interact. 2013, 206, 272–278. doi: 10.1016/j.cbi.2013.10.003
62. Rufino AT, Ribeiro M, Sousa C, Judas F, Salgueiro L, Cavaleiro C, et al. Evaluation of the anti-inflammatory, anti-catabolic and pro-anabolic effects of E-caryophyllene, myrcene and limonene in a cell model of osteoarthritis. Eur J Pharmacol. (2015) 750:141–50. doi: 10.1016/j.ejphar.2015.01.018
63. Serafim C, Araruna ME, Júnior EA, Diniz M, Hiruma-Lima C, Batista L (2020) A review of the role of flavonoids in peptic ulcer (2010–2020). Molecules 25(22):5431
64. Shi, F.; Zhao, Y.; Firempong, C.K.; Xu, X. Preparation, characterization and pharmacokinetic studies of linalool-loaded nanostructured lipid carriers. Pharm. Biol. 2016, 54, 2320–2328. doi: 10.3109/13880209.2016.1155630
65. Siddique O., Ovalle A., Siddique A.S., Moss S.F. Helicobacter pylori infection: An update for the internist in the age of increasing global antibiotic resistance. Am. J. Med. 2018;131:473–479. doi: 10.1016/j.amjmed.2017.12.024.
66. Silva, F.V.; Guimarães, A.G.; Silva, E.R.S.; Sousa-Neto, B.P.; Machado, F.D.F.; Quintans-Júnior, L.J.; Arcanjo, D.D.R.; Oliveira, F.A.; Oliveira, R.C.M. Anti- Inflammatory and Anti-Ulcer Activities of Carvacrol, a Monoterpene Present in the Essential Oil of Oregano. J. Med. Food 2012, 15, 120814114042001.
67. Steinhaus M, Schieberle P. Comparison of the most odor-active compounds in fresh and dried hop cones (Humulus lupulus L. Variety Spalter Select) based on GC?Olfactometry and odour dilution techniques. J Agric Food Chem. (2000) 48:1776–83. doi: 10.1021/jf990514l.
68. Tefera, B.N., Kim, YD. Ethnobotanical study of medicinal plants in the Hawassa Zuria District, Sidama zone, Southern Ethiopia. J Ethnobiology Ethnomedicine 15, 25 (2019). https://doi.org/10.1186/s13002-019-0302-7
69. Tian J, Zhang R, Weng Y, Qin Q, Zhang X, Liu A, et al. Myrcene enhances the cardioprotective effect through matrix remodelling in an experimental model of heart failure. ArchMed Sci. (2020) 16:1–12. doi: 10.5114/aoms.2020.95875
70. Vázquez-Araújo L, Rodríguez-Solana R, Cortés-Diéguez SM, Domínguez JM. Use of hydrodistillation and headspace solid-phase microextraction to

characterize the volatile composition of different hop cultivars. J Sci Food Agric. (2013) 93:2568–74. doi: 10.1002/jsfa.6078

71. Veith SR, Pratsinis SE, Perren M. Aroma retention in sol? gel-made silica particles. J Agric Food Chem. (2004) 52:5964–71. doi: 10.1021/jf049356a.

72. Zachariadis GA, Langioli AV. Headspace solid phase microextraction for terpenes and volatile compounds determination in mastic gum extracts, mastic oil and human urine by GC- MS. Anal Lett. (2012) 45:993–1003. doi: 10.1080/00032719.2012.670787

73. Zaki M., Coudron P.E., McCuen R.W., Harrington L., Chu S., Schubert M.L. H. Pylori acutely inhibits gastric secretion by activating CGRP sensory neurons coupled to stimulation of somatostatin and inhibition of histamine secretion. Am. J. Physiol. Gastrointest. Liver Physiol. 2013;304:G715–G722. doi: 10.1152/ajpgi.00187.2012