

# Natural Products Research in Peptic Ulcer Disease

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## ABSTRACT

This chapter discusses the recent research carried out in last fifteen years in the natural products research exclusively in peptic ulcer disease. Health and medicine importance has been realized from evolution. From ancient times natural products have been utilized by our family tree. The recent research focuses on the scientific validation of our traditional natural source. The ancient medical practice in traditional alternative medical system includes Ayurveda, Unani, and Siddha, Homeopathy, Naturopathy, Acupuncture, Chinese traditional medicines, Native American medicine and African traditional medicine. The rate of curing diseases without adverse effect is the significance of natural products research. The common vegetables, fruits, medicinal plants and its phytochemicals have been reviewed in this chapter.

**Keywords:** Peptic ulcer disease; Natural products; Medicinal plants; Phytochemicals

## INTRODUCTION

Natural products are pure compounds or mixtures that are derived from primary and secondary metabolites of cells, tissues, and secretions from microorganisms, plants, and animals. They are found in marine and terrestrial environments. Two-thirds of the population of the world uses alternative therapies, including botanical medicines, as their primary source of health care Pal [1]. Natural products are evolutionarily designed and chemically differentiated from the majority of synthesized molecules. Besides, they are capable of regulating biological systems because they are able to interact with various macromolecules Schmitt et al. [2]. Natural products have played an important role in the process of development and discovery of new drugs Newman, Cragg [3]; they have specific and selective biological activities Cragg, Newman [4]. A significant portion (28%) of the new drugs approved between 1981 and 2010 were of natural product origin Newman, Cragg [3]. According to an estimation of the WHO, almost 80% of people globally are treated by traditional medicine [5].

### Natural Products as Traditional Medicine

Traditional medicine has a long history. It is the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses. The terms complementary/alternative/non-conventional medicine are used interchangeably with traditional medicine in some countries [6].

## PEPTIC ULCER DISEASE

Peptic ulcer disease is a multifactor and complex disease involving gastric and duodenal ulcers. A peptic ulcer occurs in areas exposed to acid and pepsin and is defined as a break in the mucosa lining the stomach or proximal intestine extending through the muscularis mucosae. Classic peptic ulcer disease is a chronic recurring disease that represented defective wound healing [7]. Peptic ulcer disease is typically a non-fatal disease that primarily presents with symptoms of epigastric pain typically relieved by food or alkali. Despite medical advances, the management of peptic ulcer and its complications remains a challenge, with high morbidity and death rates for the disease. Non-steroidal anti-inflammatory drugs like, aspirin, indomethacin etc. are known to induce ulcers during the anti-inflammatory therapy [8]. The acid secretion amount is increased by westernization of foods and *Helicobacter pylori* (*H. pylori*) infected patient's decrease in Japanese. Therefore, the recent tendencies are decrease of peptic ulcer diseases by *H. pylori* infection and increase of non-steroidal anti-inflammatory drugs (NSAIDs) ulcers [9]. Short-term (7-28 days) exposure to glucocorticoids is significantly associated with peptic ulcer bleeding; this risk seems dose-dependent and is higher when nonselective NSAIDs or aspirin are used concurrently [10]. In age greater than 60 years, NSAID consumption and *H. pylori* infection are associated with the occurrence of gastroduodenal lesions [11].

Sustainable efforts and constant research in the area lead to the development of several drugs that can act at multi steps during ulcer pathogenicity such as proton pump blockers (Lansoprasole, Omeprazole), histamine receptor blockers (Ranitidine, cimetidine, famotidine) and *H.pylori* inhibitors (amoxicillin, erythromycin, metronidazole), however, majority of them have been documented with the pose of adverse effects. NSAID (Non Steroidal Anti-inflammatory Drugs) can be classified based on their level of risk such as lower, medium and high order risk. Drugs which come under lower risk are Nabumetone (Relafen), Etodolac (Lodine), Salsalate, Sulindac (Clinoril). Medium risk drugs such as Aspirin, even low dose aspirin (81 mg) used to protect the heart may pose some risk (although lower than standard doses), Ibuprofen (Motrin, Advil, Nuprin, Rufen), Naproxen (Aleve, Naprosyn, Naprelan, Anaprox), Diclofenac (Voltaren) Tolmetin (Tolectin). High order risk causing drugs are Fluriprofen (Ansaid), Piroxicam (Feldene), Fenoprofen, Indomethacin (Indocin) meclofenamate (meclomen), Ketoprofen (Actron, Oridis KT) Siddaraju, Ph.d thesis [12]. About 20 million people take the prescription of NSAID regularly and over 25 billion tablets of over the counter brands are sold each year in America [13].

## Phytochemicals in Peptic ulcer Disease

Polyphenols are one of the largest secondary plant metabolites ubiquitously present in fruits and vegetables considered an integral part of the human diet. Administration of dietary polyphenols in the human diet or as part of dietary supplementation along with conventional treatment can result in perfect security and treatment of peptic ulcer [14].

Allylpyrocatechol is a phenolic compound elicited from the leaves of *Piper betel* (*P. betel*) act as antioxidant agent and also possesses anti-inflammatory, antibacterial, and anti-arthritic effects. Yadav et al. [15] showed the significant protection of allylpyrocatechol against indomethacin-induced gastric ulcer in an animal model in comparison with that of misoprostol and omeprazole.

Gallic acid (3, 4, 5-trihydroxybenzoic acid) is a polyhydroxy phenolic compound commonly used as a dietary herbal supplement. Gallic acid is naturally found in various vegetables and fruits, such as gallnuts, *Tragopogon* species, sumach, grapes, pineapple, *Phyllanthus* species and *Zinger* Roberts et al. [16], Madlener et al. [17], Farzaei et al. [18]. It is a strong antioxidant and possesses various therapeutic effects, including anti-cancer, anti-obesity, hepatoprotective, and anti-asthmatic effects [19].

Gallic acid was the active principle of the gallic acid enriched ethanol amla extract (GAE) that promoted healing of indomethacin induced gastric ulcers in mice. The beneficial effect of GAE was due to its ability to reduce neutrophils infiltration and increase mucosal (Prostaglandin) PGE<sub>2</sub> as well as (Nitric Oxide) NO levels that were down regulated by indomethacin. GAE increased the mucosal NO by augmenting the e-NOS/i-NOS ratio. All these factors, especially the modulation of the NOS-pathway helped in up regulating mucosal VEGF and HGF levels to promote angiogenesis and accelerate ulcer healing [20].

## Fruits in Peptic Ulcer Disease

### Apple - *Malus domestica*

Apple Polyphenol Extract (APE) reduced aspirin-induced mRNA and protein over-expression of Cyclo-oxygenase-2 (COX-2) and heparin-binding epidermal-growth-factor-like growth factor (HB-EGF) and decreased the gastric Malondialdehyde (MDA). APE did not significantly affect gastric acid secretion [21].

In rats given Chinese quince extract or apple juice, ulcer induction was strongly suppressed, and the effect was stronger for Chinese quince extract than for apple juice. Phenolic compounds are responsible for antiulcerative activity of Chinese quince extract and apple juice [22].

### Grapes - *Vitis vinifera*

The grape, a fruiting berry of the woody vines (*Vitis* species) from the family Vitaceae, is an essential source of nutritional phytochemicals such as flavonoids and anthocyanins. Saito et al. [23] showed grape seed extract and its proanthocyanidin constituents possess a preventive effect on ethanol/hydrochloride-induced gastric injury.

Grape seed proanthocyanidin extract mitigates gastrointestinal mucosal injury induced by acute or chronic stress via the prevention of superoxide anion production, DNA fragmentation, lipid peroxidation, and membrane microviscosity [24]. It diminishes aspirin-induced gastric injury and peroxidation of mucosal lipid in a similar manner to antioxidants agents and Vitamins E and C [25]. Dietary supplementation of grape seed proanthocyanidin (89.3%) for 2 wk protected against gastric ulcer induced by stress (water immersion restraint) and reduced the secretion of somatostatin, gastrin, and histamine. Iwasaki et al. [26] reported that inhibition of neutrophil infiltration to gastric mucosal tissue (reduction of gastric MPO) and enhancement of enzymatic antioxidant defense (e.g., SOD) are among the main contributors of dietary grape proanthocyanidin in the prevention of peptic ulcer. Grape extract (seed and skin) showed antibacterial effect on cagA-negative and cagA-positive *H. pylori* clinical strains, *in vitro* [27].

### Gooseberry- *Phyllanthus emblica*

Pretreatment with the butanol extract of the water fraction of *Phyllanthus emblica* fruits at the dose of 100 mg/kg body-weight, orally administered to rats for 10 consecutive days, was found to enhance secretion of gastric mucus, hexosamine and it hardly affected the Malondialdehyde (MDA) or Superoxide Dismutase (SOD) level in gastric tissue of the pretreated animal. An antioxidant property appears to be predominantly responsible for this cytoprotective action of the drug [28].

### Korean Blackberry - *Rubus coreanus*

Anthocyanins extracted from the fruits of *Rubus coreanus* exhibit possible antiulcer activity against naproxen induced acute ulcer in a rat model, by preventing lipid peroxidation and a significant increase in the activities of antioxidant enzymes such as catalase, superoxide dismutase,

and glutathione peroxidase. Anthocyanins induce activation of Matrix Metalloproteinase-2 and attenuate the activity of the proinflammatory molecules, such as tumor necrosis factor- $\alpha$  and interleukin-1 $\beta$  [29].

### **Papaya - *Carica papaya***

Indomethacin-mediated decrease in reduced glutathione level and indomethacin-mediated increase in malondialdehyde were reversed by **Carica papaya** extract. Pretreatment with aqueous extract of **Carica papaya** seed exhibited anti-ulcerogenic and antioxidant effects, which may be due to the enhanced antioxidant enzymes increased gastric pH and percentage of ulcer inhibition relative to indomethacin-induced ulcer rats [30].

### **Ripe banana - *Musa sapientum***

Gastric acid values were higher following banana as compared to porridge and the difference was statistically significant. Ripe banana is not a bland food. It should not be recommended as a part of bland diet for patients of acid peptic disease [31].

The Extract of *Musa sapientum* fruit showed antidiabetic and better ulcer healing effects compared with OMZ (antiulcer) or INS (antidiabetic) in diabetic rat and could be more effective in diabetes with concurrent gastric ulcer [32].

The anti-ulcer effect of methanolic extract of the peels on *Musa sapientum* may be due to its anti-secretory and cyto-protective activity. The healing of the ulcer base might not be unconnected with basic fibroblast growth factors responsible for epithelial regeneration [33].

### **Watermelon - *Citrullus lanatus***

The aqueous fruit pulp concentrate of *Citrullus lanatus citroides* showed significant gastro protective potential against pyloric ligation and indomethacin-induced ulceration in rats. The presence of the flavonoids and polyphenols may be responsible for the gastroprotective effect of *Citrullus lanatus citroides* [34].

### **Brindleberry - *Garcinia cambogia***

Oral pretreatment of rats with *Garcinia cambogia* fruit extract protected gastric mucosa against HCl-ethanol induced damage by decreasing the volume and acidity of gastric juice. Increased lipid peroxidation, decreased activity of antioxidant enzymes, altered levels of protein and glycoproteins in the ulcerated mucosa, and gastric juice were maintained at near normal levels in *Garcinia cambogia* pretreated rats. The anti-ulcer activity of *Garcinia cambogia* is by virtue of its ability to decrease acidity and increase mucosal defense [35].

### **Winter melon - *Benincasa hispida***

*Benincasa hispida* (Thunb.) Petroleum ether and methanol extracts mechanism of gastroprotective activity may be attributed to reduction in vascular permeability, free radical

generation, and lipid peroxidation along with strengthening of mucosal barrier. Besides, presence of phytoconstituents in this plant like flavone and sterols might be responsible for these actions. Petroleum ether and methanol extracts of *Benincasa hispida* (Thunb.) Cogn. fruit possess significant antiulcer as well as antioxidant property [36].

### **Pumpkin - *Curcubita pepo***

*Curcubita pepo* fruit pulp extract showed increase in AP activity and mucosal thickness along with decrease in UI, suggesting gastro duodenal protective and anti-ulcerogenic properties of *Curcubita pepo* pretreatment against aspirin induced stomach and duodenum of albino rats. The mechanism by which the extract works is still unknown [37].

### **Manila tamarind- *Pithecellobium dulce***

Ulcer score was significantly minimized in hydroalcoholic fruit extract of *Pithecellobium dulce* (HAEPD) administered animals. pH and acidity of gastric fluid were significantly minimized and the mucin, PGE2 levels were significantly maintained in drug pre administered animals. The activities of H<sup>(+)</sup>, K<sup>(+)</sup> ATPase and myeloperoxidase were found to be significantly elevated in ulcer control animals and found to be decreased in drug pretreated animals. The cell proliferation was found to be enhanced in drug received animals. The total protein bound carbohydrate to total protein ratio was found to be significantly maintained by HAEPD. The effects were found to be comparable with that of standard drug omeprazole. The Hydroalcoholic fruit extract of *Pithecellobium dulce* possess a potent antiulcer activity probably by acting as cytoprotective and anti-acid secretory agent [38].

The edible fruits of *Pithecellobium dulce* (Roxb.) Benth are traditionally used for various gastric complications in India. The antiulcer activity of hydroalcoholic fruit extract of *Pithecellobium dulce* (HAEPD) by applying cysteamine is demonstrated by its antioxidant and cytoprotective nature [38].

### **Bael - *Aegle marmelos***

Oral administration of methanolic extract of *Aegle marmelos* fruit reduced the gastric ulcer compared to sucralfate. *A. marmelos* fruit extract shows good antioxidant activity. Hence, it exerts its antiulcer effect by inhibiting secretory parameters and activating antioxidant mechanism, thus protecting the gastric mucosa against HP-LPS induced ulceration [39].

Several compounds are present in the Bael leaves among which Cineole exhibits antioxidant property by restoring ethanol associated depletion of non-protein sulfhydryl level to normal in the stomach indicating that it can prevent the generation of reactive oxygen species (ROS) and prevent ethanol induced gastric injury in rats. At Higher doses, cineol also inhibited pylorus ligation induced gastric acid secretion [40].

The bioactive compounds present in beal among which Luvangetin a pyranocoumarin isolated

from the seeds of bael fruit protects against multiple models of gastric ulceration in rodents [41,42]

Marmin bioactive compound found in immature bark of the tree (*Bael Aegle marmelos*(L.) Corr.) also possess antiulcer activity in experimental ulcer. Oral administration of marmin and nobiletin inhibited both the appearance of ethanol- induced gastric hemorrhagic lesions dose-dependently. Intra-gastrical administration of marmin and nobiletin prevented the peptic disease induced by ethanol. Both marmin and nobiletin given intragastrically inhibited gastric motor activity measured as intraluminal pressure recordings. Marmin and nobiletin exhibited concentration-dependent relaxations of contractions induced by acetylcholine, transmural electrical stimulation and histamine in isolated guinea pig ileum, respectively. These findings suggest that the anti-ulcer effects of marmin and nobiletin are ascribed primarily to the maintenance of the mucosal barrier integrity and inhibition of gastric motor activity and secondarily due to the prevention of the effects of endogenous acetylcholine and histamine [43].

*Aegle marmelos* showed significant antibacterial activity and enhanced the antioxidants but decreased free radicals and myeloperoxidase activities thereby decreasing tissue damage and inflammation and thus, affording ulcer healing [44].

The protection by *Aegle marmelos* may be due to vitamin E, beta-carotene, flavonols, and flavonoids, which are present in its pulp extract. Phenolic compounds of the *Aegle marmelos* fruit extract provide a good source of antioxidants that could offer potential protective effects against aspirin- induced gastro-duodenal ulceration in albino rat model [45].

### **Marmalade orange - *Citrus aurantium***

The  $\beta$ -myrcene from *Citrus aurantium* was also endowed with marked enhancement of antioxidant enzyme activity from GR system as evidenced by the decreased activity of superoxide dismutase and increased levels of glutathione peroxidase, glutathione reductase, and total glutathione in gastric tissue [46].

### **Bolivian mangosteen - *Garcinia achachairu***

Methanolic extracts and guttiferone A obtained from *Garcinia achachairu* (Clusiaceae) and guttiferone A produce gastroprotective effects against ethanol/HCl, indomethacin/bethanechol induced ulcer in experimental rats [47].

### **Jujube date - *Ziziphus jujube***

*Ziziphus jujube* stem bark extract had a potential antiulcer activity which might be due to its protective activity, providing a direct, protective effect on the gastric mucosa. Anti-*H.pylori* activity was not among gastro protective mechanism of *Ziziphus jujube*. Further pre-clinical and clinical investigations for evaluating natural active agents and efficacy of this plant are recommended [48].

## Vegetables in Peptic Ulcer Disease

### Spiny Bitter Gourd - *Cochinchina momordica*

Major compounds of *Cochinchina momordica* seed extract include momordica saponins. The gastroprotective effect of *Cochinchina momordica* seed extract in an ethanol-induced gastric damage rat model is mediated by suppressing proinflammatory cytokines and downregulating cytosolic phospholipase A2, 5-lipoxygenase and the activation of calcitonin gene-related peptide. The *Cochinchina momordica* seed extract (SK-MS10) pretreatment group exhibited lower myeloperoxidase levels than the diclofenac group. The expression of cytosolic phospholipase A2 and 5-lipoxygenase was decreased by SK-MS10 pretreatment in each of the three NSAID treatment groups. *Cochinchina momordica* seed extract exhibited a gastroprotective effect against NSAID (aspirin, indomethacin, and diclofenac) induced acute gastric damage in rats. *Cochinchina momordica* seed extracts exerted significantly protective effect against cysteamine induced duodenal ulcer by either cPLA2 inhibition or glutathione preservation [49].

### Bitter gourd - *Momordica charantia*

*Momordica charantia* L. (Cucurbitaceae) commonly known as 'bitter gourd' is a multi purpose herb. The healing of acetic acid induced gastric ulcer was increased. The methanol extract of *Momordica charantia* L. fruit increases healing of gastric ulcer by increase in gastric mucosal content and also prevents development of gastric ulcers and duodenal ulcers in rats by decreasing ulcer index, total acidity, free acidity and pepsin content [50].

### Spiny gourd - *Momordica dioica*

*Momordica dioica* extract possess antiulcerogenic effect, that attributable to augmentation of gastric defense mechanisms [51].

### Atthalakai - *Momordica cymbalaria*

Pretreatment with aqueous extract of *Momordica cymbalaria* fruits showed significant decrease in the total acidity and ulcer index, a fact that supports the traditional use of the decoction of *Momordica cymbalaria* fruits for its antiulcer effect Dhasan et al. [52]. The polyphenols like quercetin reported from the plant may attribute to the antiulcer property of the extract. The antiulcer activity of *Momordica cymbalaria* may be attributed to its polyphenolic constituents, particularly quercetin, reported from it [53].

### Mango ginger (*Curcuma amada*) and Ginger (*Zingiber officinale*)

The presence of antioxidants such as the phenolic acids and pectic polysaccharides in Mango ginger (*Curcuma amada*) and Ginger (*Zingiber officinale*) play a key role in prevention and healing of ulcer at multi steps of ulcer pathogenicity. These compounds leads to inhibition of H<sup>+</sup>, K<sup>+</sup> -ATPase, inhibition of *Helicobacter pylori* growth, exhibiting antioxidant, antiproliferative and

DNA protective potentials. The compositional studies reported the presence of precise levels of various sugars in ginger pectic polysaccharide extract it is composed of Rhamnose (4%), Arabinose(24%), Xylose(8%), Mannose(3%), Galactose(>1%) and Glucose (54%) and in addition it contained 5.7% phenolic, particularly cinnamic acid and p-coumaric acid exhibiting antioxidant property. Cinnamic acid of polysaccharide shown to possess antiproliferative activity Siddaraju, Ph.d Thesis, [12].

### **Celery - *Apium graveolens***

A fully standardized celery preparation has been prepared known as an alcoholic extract of the seeds of a plant source derived from northern India. It has been shown to protect against and/or reduce gastric irritation caused by NSAIDs, as well as act synergistically with them to reduce inflammation [54].

### **Greater burdock - *Arctium lappa***

Leaves of **Arctium lappa** contain several mono- and dicaffeoylquinic acids<sup>1</sup>, 3-O-dicaffeoylquinic acid, which presented gastric protection [55].

### **Ridge gourd - *Luffa acutangula***

*Luffa acutangula* methanolic extract (LAM) and aqueous extract (LAW) were administered. LAM increased mucosal glycoprotein and antioxidant enzyme level in gastric mucosa of diabetic rats than LAW. LAM was efficient in reversing the delayed healing of gastric ulcer in diabetic rats close to the normal level. LAM exhibited better ulcer healing effect than glibenclamide and LAW, because of its both antihyperglycemic and mucosal defensive actions. LAM is proved to be a better alternative for treating gastric ulcers co-occurring with diabetes [56].

### **Paprika - *Capsicum annuum*:**

*Capsicum annuum* (Solanaceae), commonly known as chilli, is a medicinal spice used in various Indian traditional systems of medicine and it has been acknowledged to treat various health ailments. Therapeutic potential of chilli and capsaicin were well documented; however, they act as double-edged sword in many physiological circumstances. In traditional medicine chilli has been used against various gastrointestinal complains such as dyspepsia, loss of appetite, gastroesophageal reflux disease, gastric ulcer, and so on. In chilli, more than 200 constituents have been identified and some of its active constituents play numerous beneficial roles in various gastrointestinal disorders such as stimulation of digestion and gastromucosal defense, reduction of gastroesophageal reflux disease (GERD) symptoms, inhibition of gastrointestinal pathogens, ulceration and cancers, regulation of gastrointestinal secretions and absorptions. However, further studies are warranted to determine the dose ceiling limit of chilli and its active constituents for their utilization as gastroprotective agents [57].

## Potato -*Solanum tuberosum*

About 84% reduction in ulcer index; enhanced mucosal recovery, normalization of H<sup>+</sup>, K<sup>+</sup>-ATPase, antioxidant and antioxidant enzymes substantiated the antiulcer potentials of PGP. Mucosal recovery could be attributed to cytoprotective and DNA protective ability of PGP (Potato Galactan Polysaccharide) that can help in mucosal layer regeneration. PGP was also effective in inhibiting *Helicobacter pylori* as per growth inhibition assay followed by scanning electron microscopic studies suggesting that PGP is effective in curbing the growth of *H. pylori*, which is responsible for 70% of gastric ulcer/cancer incidences [58]. Its gastroprotective effect can be availed by taking raw potato juice in water apart from continuing its use with processed conditions. Pectic polysaccharide, in other words dietary fibre from potato will be useful in offering health beneficial properties no matter how it is used, either in the cooked form or raw [59].

## Traditional Herbs and Medicinal Plants in Peptic Ulcer Disease

### Neem- *Azadirachta indica*

Azadiradione (azadiradione from the ethanolic extract of seeds of *Azadirachta indica* (neem) exhibited potent antiulcer activity through the inhibition of H<sup>+</sup> K<sup>+</sup>-ATPase (proton pump) activity via its cytoprotective effect and also via its antisecretory effect [60].

### Myrobalan - *Terminalia chebula*

The gastro protective mechanism of chebulinic acid isolated from *Terminalia chebula* fruit was investigated. Chebulinic acid was evaluated against cold restraint (CRU), aspirin (AS), alcohol (AL) and pyloric ligation (PL) induced gastric ulcer models in rats. Chebulinic acid significantly reduced free acidity, total acidity and upregulated mucin secretion. Further, chebulinic acid significantly inhibited H<sup>(+)</sup>K<sup>(+)</sup>-ATPase activity in vitro as compared to the omeprazole confirming its anti-secretory activity [61].

### Tropical almond - *Terminalia catappa*

*Terminalia catappa* is a species of the family Combretaceae, This plant was also listed in Pharmacopeia vegetables of the Caribbean, where the leaves of this plant are used in a decoction for gastritis and urinary infection [62].

Aqueous fraction obtained from the leaves of *Terminalia catappa* (FrAq) showed a marked gastroprotective effect, evidenced by the dramatic inhibition of the gastric damage produced by ethanol. Nunes et al. [63] evaluated the ethanolic extract of bark from this species against gastric ulcers induced by ethanol.

The action of aqueous fraction (FrAq) obtained from the leaves of *Terminalia catappa* was mediated by the activation of defensive mucosa-protective factors, such as increases in mucus production, the nitric oxide (NO) pathway and endogenous prostaglandins. FrAq from *Terminalia catappa* leaves has excellent preventive and curative effects on acute and chronic induced gastric

ulcers(induced by ethanol and ischemia/reperfusion injury) and showed an important profile against *Helicobacter pylori* [64].

Oral treatment with aqueous fraction of *Terminalia catappa* significantly decreased the extent of ulcerative lesions in the gastric tissue submitted to I/R injury. Chen et al [65] and Wang et al [66] observed that both polyphenols punicalagin and punicalin, present in *Terminalia catappa*, were able to attenuate oxidative stress and hypoxia-induced apoptosis.

Studies already performed with the hydroalcoholic extract of **Terminalia catappa** and other species of this genus such as **Terminalia chebula** and **Terminalia fagifolia** have demonstrated the antisecretory effect of these species Kumar et al. [67], Mishra et al [61] and Nunes et al [68]. The pre-treatment of animals with NEM (a sulfhydrylinhibitor) did not change the gastroprotective effect of the FrAq. The Aqueous fraction from *Terminalia catappa* leaves has an important anti-*Helicobacter pylori* activity, excellent preventive and curative effects on acute and chronically induced gastric ulcers. The mechanisms involved in the gastroprotection are related to the Nitric oxide pathway, an increase in the mucus and the endogenous prostaglandins, and this fraction was able to heal ulcers through the inhibition of matrix metalloproteinase- 9 (MMP-9) and matrix metalloproteinase-2 (MMP-2) activities [64].

### **Kumbuk - Terminalia arjuna**

The methanol extract of the bark of *Terminalia arjuna* (Combretaceae) (TAE) showed marked antiulcer and ulcer healing activity against 80% ethanol (ETH), diclofenac sodium (DIC) and dexamethasone (DEX) induced ulcer models dose dependently. Pre-, post and co-administration of TAE offered 100% protection to the gastric mucosa against ETH, DIC and DEX induced ulcers as observed from the ulcer score. The gastro protective effect of TAE is probably related to its ability to maintain the membrane integrity by its anti-lipid peroxidative activity that protects the gastric mucosa against oxidative damage and its ability to strengthen the mucosal barrier, the first line of defense against exogenous and endogenous ulcerogenic agents [69].

*Terminalia arjuna* acts as an gastroprotective agent probably due to its free radical scavenging activity and cytoprotective nature. Histological studies confirmed the gastroprotective activity of *Terminalia arjuna* [70].

### **Behada - Terminalia bellerica**

70% methanolic extract of *Terminalia bellerica* increased resistance to necrotizing agents, providing a direct protective effect on the gastric mucosa and exhibited antiulcer effect against ethanol induced, aspirin induced, cold stress restraint and pylorus ligated ulcer in rats [71].

### **Buffalo calf plant - Combretum albidum**

*Combretum albidum* Don belonging to family Combretaceae is an unexplored medicinal plant in the Indian medicinal system. According to ethno botanical information, the leaves are used in the treatment of peptic ulcer [72].

## **Devil's backbone - *Cissus quadrangularis***

Pretreatment with *Cissus quadrangularis* extract (CQE) significantly prevented the gastric mucosal lesion development and decreased the gastric toxicity produced by aspirin-induced ulcerogenesis in pyloric ligated (ASP-PL) model in rats. *Cissus quadrangularis* extract CQE may protect the gastric mucosa against ulceration by its antisecretory and cytoprotective property [73]. Administration of CQE offered gastroprotective activity could be mediated by the antioxidant activity as well as by the attenuation of oxidative mechanism and proinflammatory cytokines [74].

Pretreatment with *Cissus quadrangularis* extract (CQE) showed an increase in vascular permeability, NOS-2 activity, TNF-alpha, IL-1beta levels and oxidative damage in aspirin administered rats. In addition, CQE prevents oxidative damage of DNA by reducing DNA fragmentation indicating its block on cell death. Ulcer protection in CQE treated rats was confirmed by histoarchitecture, which was comprised of reduced size of ulcer crater and restoration of mucosal epithelium. Thus, reduced neutrophil infiltration, antiapoptotic and antioxidant action have a pivotal role in the gastroprotective effect of CQE [75].

## ***Monolluma quadrangula***

**Monolluma quadrangula** (Forssk.) Plowes is used in Saudi traditional medicines to treat gastric ulcers. It is a succulent plant belonging to the family Apocynaceae. The fresh plant is eaten to treat gastric ulcers and diabetes and is also used as appetite suppressant [76].

## **Gum arabic tree- *Acacia nilotica***

The antiulcer effect of aqueous, 50% hydroethanolic (50:50), 70% hydroethanolic (70:30) and ethanolic extracts from the young seedless pods of *Acacia nilotica* Linn on pylorus ligation, swimming stress and indomethacin-induced gastric ulcers was studied. 70% hydroethanolic showed maximum activity therefore was only used in other animal ulcer models. In quantitative test the 70% hydroethanolic extract from the young seedless pods of *Acacia nilotica* Linn showed highest amount of total phenols and flavonoids content followed by 50% hydroethanolic. These results corresponds the results of in vivo studies in which the 70% hydroethanolic showed maximum protection. Hence the antiulcer activity of the extract might be due to the presence of polyphenolic components [77].

## **Needle bush - *Azima tetracantha***

Ethanol-induced gastric ulcer model was used to investigate the gastroprotective effects of friedelin isolated from the hexane extract of leaves of *Azima tetracantha*. Antioxidant enzyme activities, anti-inflammatory cytokines, prostaglandin E2 (PGE2), constitutive nitric oxide synthase (cNOS) and mucus weight have been increased. However, the vascular permeability, pro-inflammatory cytokines, inducible nitric oxide synthase (iNOS), caspase-3 and apoptosis level have been decreased after friedelin ingestion [78].

## **Red sandalwood- *Pterocarpus santalinus***

Rats treated with *Pterocarpus santalinus* showed a significant reduction in gastric lesions. The treated group showed a decrease in the activities of these enzymes (ATPases -  $H^{(+)}K^{(+)}ATPase$ ,  $Na^{(+)}K^{(+)}ATPase$  and  $Ca^{(2+)}ATPases$ ) and also had the ability to restore the sodium and potassium ion concentrations to near normal levels, which were altered by ibuprofen mediated acid stimulation. The results suggest that the antiulcer properties of *Pterocarpus santalinus* could be traced to its acid inhibiting potential, antioxidant activity and the ability to maintain functional integrity of the cell membranes [79]. *Pterocarpus santalinus* has been found to prevent mitochondrial dysfunction, provide mitochondrial cell integrity, through the maintenance of lipid bilayer by its ability to provide a hydrophobic character to the gastric mucosa, further indicating its ability to reverse the action of NSAIDs and mast cell degranulators in gastric mucosa [80].

## **Myrtle - *Myrtus communis***

Aqueous extracts of *Myrtus communis* Linn. berries and methanolic extracts were administered orally to animals prior to the exposure of ulcerogens. Oral administration of aqueous and methanolic extracts of *Myrtus communis* reduced the ulcer index in all models of ulcers. Low dose of aqueous extract and high dose of methanolic extract of *Myrtus communis* (*Myrtus communis* Linn. berries (common myrtle)) exhibited more significant effect in comparison to omeprazole (standard drug) in ethanol-induced ulcer model. Both the doses of aqueous and methanolic extracts also reduced the gastric juice volume, total acidity and increased the gastric pH and gastric wall mucus content [81].

## **Rough bryony- *Mukia maderaspatana***

The ethanolic extract of *Mukia maderaspatana* was able to decrease acidity and increase the mucosal defence in the gastric area; therefore it is justifying its use as an antiulcerogenic agent [82].

## **Silk cotton tree - *Salmalia malabarica***

*Salmalia malabarica* possesses anti-ulcerogenic, antisecretory, and cytoprotective potential and can be used as a supplement for the treatment of gastric ulcers in a dose dependant manner [5].

## **Broken bones plant - *Oroxylum indicum***

*Oroxylum indicum* (L.) Kurz has been used for centuries as a traditional medicine in Asia in ethnomedicinal systems for the prevention and treatment of several diseases, such as jaundice, arthritic and rheumatic problems, gastric ulcers, tumors, respiratory diseases, diabetes, and diarrhea and dysentery, among others. [83].

## Clearing nut tree - *Strychnos potatorum*

*Strychnos potatorum* (Fam: Loganiaceae) Linn seeds are useful in the treatment of gastropathy in Indian traditional system of medicine. The seed powder and aqueous extract of the *Strychnos potatorum* Linn seeds prevented ulcer formation by decreasing acid secretory activity and increasing the mucin activity in rats. The antiulcerogenic potential was further confirmed by the histopathological studies of stomach mucosa. The mucoprotective action of the seed powder and aqueous extract of the *Strychnos potatorum* Linn seeds may be due to the presence of polysaccharides in seeds. The antiulcerogenic potential of SPP and SPE was compared with the standard antiulcer drug, ranitidine [84].

## Wild rue - *Peganum harmala*

Peganine hydrochloride isolated from *Peganum harmala* seeds was evaluated against cold restraint (CRU), aspirin (AS), alcohol (AL) and pyloric ligation (PL) induced gastric ulcer models in rats. Peganine significantly inhibited H<sup>(+) K(+)</sup>-ATPase activity in vitro as compared to omeprazole confirming its anti-secretory activity [85].

## Skullcaps - *Scutellariae*

A study in Sprague Dawley rats implied that the co-administration of *Scutellariae radix* (Skullcaps) extract, the dried root of *Scutellariae baicalensis* Georgi (Baikal skullcap), and mefenamic acid potentiated the anti-inflammatory effects, alleviated the mefenamic acid induced stomach adverse effect while having minimal pharmacokinetic interactions [86].

## Indian beech tree - *Pongamia pinnata*

Methanolic extract of seeds of *Pongamia pinnata* (PPSM) when administered orally showed dose-dependent ulcer protective effects against gastric ulcer induced by 2 h cold restraint stress. It healed chronic gastric ulcer induced by acetic acid when given for 5 and 10 days. Methanolic extract of seeds of *Pongamia pinnata* tended to decrease acid output and increased mucin secretion and mucosal glycoproteins, while it decreased gastric mucosal cell shedding without any effect on cell proliferation. The ulcer protective effects of PPSM may be attributed to the presence of flavonoids and the actions may be due to its effects both on mucosal offensive and defensive factors [87].

## Mangrove cannonball- *Xylocarpus Molluccensis*

Air dried fruits were extracted with ethanol and fractionated into four fractions. *Xylocarpus Molluccensis* were isolated from the active fraction and were tested against different ulcer models. Xylocarpus were found to possess anti-ulcerogenic activity. The antiulcer activity might be due to its anti-secretory activity and subsequent strengthening of the defensive mechanism [88].

## **Nyireh bunga - *Xylocarpus granatum***

Chloroform fraction (Fr-CHCl<sub>3</sub>) of *Xylocarpus granatum* fruit was evaluated against cold restraint (CRU), aspirin (AS), alcohol (AL) and pyloric ligation (PL) induced gastric ulcer models in rats and histamine (HA) induced duodenal ulcer model in guinea pigs. Fr-CHCl<sub>3</sub> of *Xylocarpus granatum* was found to possess anti-ulcerogenic activity which might be due to its anti-secretory activity and subsequent strengthening of the defensive mechanism [89].

## **Cluster fig tree - *Ficus glomerata***

*Ficus glomerata* possess significant gastroprotective activity which might be due to gastric defence factors and phenolics might be the main constituents responsible for this activity. 50% ethanolic extract of *F. glomerata* fruit prevents the oxidative damage of gastric mucosa by blocking lipid peroxidation and by significant decrease in superoxide dismutase, H<sup>+</sup>K<sup>+</sup>ATPase and increase in catalase activity [90].

## **Conyza herb - *Conyza blinii***

*Conyza blinii* saponin (CBS), mainly composed of triterpenoidal saponins, is the total saponin of *Conyza blinii* H.Lév had a profound protection activity against acute gastric ulcer induced by ethanol. The efficacy of CBS was comparable with colloidal bismuth subcitrate. The mechanism involved is anti-lipid peroxidation, facilitating free radicals clearance [91].

## **Gems of the hills - *Caralluma Arabica***

*Caralluma arabica* this plant was able to reduce gastric acidity and secretion and increase mucin production [92,93]. *Caralluma* spp. are rich in sterols, steroidal glycosides, pregnane glycosides, flavonoid derivatives, and magastigmane glycosides [94-96].

## **Marking nut tree - *Semicarpus anacardium***

*Semicarpus anacardium* Linn. Seed extracts not only provides an excellent preventive effect in gastric ulcer models, but also possesses significant hepatoprotective effect. This may be due to the antioxidant nature of flavonoids present in them [97].

## **Night jasmine- *Nyctanthes arbortristis***

Arbortristoside-A (AT) and 7-O-trans-cinnamoyl-6 $\beta$ -hydroxyloganin (6-HL) from the seeds of *Nyctanthes arbortristis* exhibited antiulcer activity in experimentally induced ulcer models including cold restraint stress (CRU), alcohol (AL), pylorus ligation-induced gastric ulcer (PL) models and they also showed ulcer healing effect in chronic acetic acid-induced ulcer model (AC) [98].

## **Ambrex**

Ambrex herbal formulation consists of six medicinal plants namely, *Withania somnifera* (100 mg), Pon amber (37.5 mg), *Cycas circinalis* (62.5 mg), Shalamisri (25 mg) and Roomi mastagi (25

mg). The plant herbs present in ambrex are mentioned in ayurvedic texts as a remedy for peptic ulcer [99]. In addition, ambrex has been reported to possess free radical scavenging activity [100]. Ambrex reduced lipid peroxidation, protein carbonyl content and conjugated dienes as compared to aspirin control. It has been demonstrated that intragastric administration of ambrex not only possess antioxidant property but also increase the lipid composition in the gastric mucosal surface and there by providing antiulcerogenic efficiency [101].

## Spices in Peptic Ulcer Disease

### Nutmeg- *Myristica malabarica*

Treatment with malabaricone B, malabaricone C and omeprazole reduced the ulcer indices against indomethacin. Total antioxidant status of plasma was significantly increased by malabaricone B, malabaricone C and omeprazole. Thiobarbituric acid reactive substances and protein carbonyls are reduced by these antioxidants [102].

### Turmeric - *Curcuma longa*

Curcumin (diferuloylmethane) is the major constituent of turmeric (a spice derived from the rhizome of *Curcuma longa*), which is extensively consumed in Asian foods as an additive, coloring, and preservative agent. It possesses strong antioxidant and anti-inflammatory substance [103]. Curcumin downregulated the acetylation of histone H3 at the site of the H<sup>+</sup>, K<sup>+</sup>-ATPase promoter gene, thereby inhibiting the transcription and expression of the H<sup>+</sup>, K<sup>+</sup>-ATPase gene. Curcumin was shown to have a preventive and therapeutic effect in gastric ulcer disease [104].

### Green tea - *Camellia sinensis*

*Camellia sinensis* (L.) Kuntze (Theaceae) is an evergreen shrub encompasses a wide range of polyphenols, including catechin, epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate [105]. Epigallocatechin gallate (EGCG), the main green tea polyphenol (about 40% of tea polyphenols), possesses anti-diabetic, anti-cancer, and cardioprotective functions. Oral treatment with GEt (hydroalcoholic extract from green tea) and GEAc (ethyl acetate fraction) reduced significantly the gastric ulcer area induced by acetic acid possibly through maintenance of mucin content and reduction of inflammation and oxidative stress. In addition, the compounds present in its ethyl acetate fraction could be responsible for the extract activity [106].

## Fish oil

Gastroprotective effects of fish oil have been reported in gastric ulcers induced by ethanol, aspirin, indomethacin, dexamethasone (, cold-restrain stress and pyloric ligation. Several mechanisms have been suggested to be involved in the gastroprotective effects of fish oil including a decrease in gastric acid secretion and lipid peroxidation as well as an increase in antioxidant enzymes during pylorus ligation and cold-restraint stress in rats [107].

## DHA

Omega-3 polyunsaturated fatty acids, such as DHA may exert beneficial effects by competing with omega-6 polyunsaturated fatty acids such as arachidonic acid for the production of lipid inflammatory mediators like leukotriene [108]. It has been shown that human ingestion of fish oil leads to a decrease in Leukotriene B4 and an increase in Leukotriene B5, a weak inducer of inflammation and a weak chemotactic agent [109]. DHA prevents the gastric toxicity of indomethacin; it is unclear whether chronic DHA will also block the gastric side effects of indomethacin and other NSAIDs. Future studies are needed to determine whether the co-administration of DHA with NSAIDs modifies the anti-inflammatory and analgesic effects of NSAIDs [110].

DHA did not reverse the indomethacin-induced reduction of PGE (2) gastric levels. In contrast, DHA partially prevented the indomethacin-induced increase in Leukotriene B4 gastric levels. This is the first report demonstrating DHA's gastro protective effect as a pure compound. Furthermore, the results reveal that the gastroprotective effect is mediated by a decrease in gastric Leukotriene B4 levels in indomethacin-induced gastric damage [111].

## PUFA

Increased dietary intake of polyunsaturated fatty acids (PUFAs) is known to be associated with a decrease in the incidence of peptic ulcer disease possibly due to increase in the synthesis of prostaglandins. The fatty acid profile showed an increase in LA and a decrease in other PUFAs like GLA, AA, EPA and DHA. When PUFAs were supplemented in the form of Fish oil and AA rich oil or when the animals were treated with H2-blocker, famotidine, there was a decrease in the incidence of ulceration in the animals associated with near normalization of changes in the phospholipid fatty acid profile. The levels of lipid peroxides, nitric oxide, and anti-oxidant activity also reverted to control values. Dexamethasone induced gastric ulceration was prevented by PUFAs. Further, PUFAs are known to inhibit the growth of *Helicobacter pylori in vitro* [112].

## Linolenic Acid

*H. pylori* is susceptible to FFAs including linolenic acid (LLA) *in vitro* [113]. The antibacterial effect of FFAs against *H. pylori in vivo* has remained unclear, since most of the effective FFAs for *H. pylori* are poorly soluble and unstable. In addition, various FFA characteristics including carboxyl protonation, oxidation, esterification, and lipid-protein complexation in the gastric environment reduce the final concentration of FFAs at the mucus layer and therefore making them ineffective [114]. Indeed, a clinical study showed that orally ingested LLA did not inhibit the *H. pylori* colonization nor change the severity of *H. pylori* infection [115].

The fusion of liposomal LLA (LipoLLA) with *H. pylori* was previously confirmed and showed comparable antibacterial efficacy against *H. pylori* with free LLA in inhibiting both spiral and coccoid forms of the bacteria *in vitro*. LipoLLA was effective against several *H. pylori* clinical

isolates including Shi470, SouthAfrica7, India7, Gambia94/24, PeCan4, Lithuania75, and SJM180 [113]. LipoLLA penetrated the mucus layer of mouse stomach and was retained in the gastric lining. LipoLLA had superior in vivo antibacterial efficacy compared to the standard triple therapy in the mouse stomach [116].

## Mushroom in Peptic Ulcer Disease

### Black hoof fungus - *Phellinus linteus*

Mushroom extracts and constituents have a long history of traditional use for treating various diseases. *Phellinus linteus*, a medicinal fungus known as “Sang-hwang” in Korea and “Mesimakobu” in Japan, are extremely rare to find in the nature. They can be found rarely on wild mulberry trees that have grown for many decades in deep forest. 4- (3, 4-dihydroxyphenyl)-3-buten-2-one (DHP) as a lipid-soluble organic compound and a naturally occurring antioxidant is purified in *Phellinus linteus*. DHP effectively prevents naproxen-induced gastric antral ulcers through elimination of the lipid peroxides and activation of radical scavenging enzymes. Therefore, DHP is one of the powerful remedies of gastric antral ulcers and its use may offer an attractive and effective strategy for curing gastric antral ulcers in humans. Ibrahim et al [117].

The gastric mucosa protection effect of three natural plant extracts, *Hericum erinaceus* (HE), *Centella asiatica* (CA) and *Amomum villosum* (AV) were evaluated using the indomethacin damage model. Compared with a single extract, a combination of HE/CA/AV, especially with the ratios of 80:10:10, 45:45:10 and 45:10:45, showed significant synergistic effects for protection of the gastric mucosa with gastric ulcer inhibition [118].

### Manuka honey

Manuka honey, which is rich in flavonoids, increased the glycoprotein production in the ethanol model of gastric damage. It also preserved the gastric mucosal GSH [119]. Natural honey prevented gastric mucosal lesions induced by ethanol through the production of nonprotein sulfhydryls and endogenous NO Al-Waili [120]. The antioxidant activity of manuka honey may be attributed to its antioxidant flavonoid content.

Manuka honey was the most effective antioxidant and antibacterial honey compared to both acacia honey and wild carrot honey, possibly because of its high phenol content [123]. Manuka honey has been known to exert antimicrobial function based on its abundant methylglyoxal content [124].

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