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PEPTIC ULCER DISEASE AND ITS MANAGEMENT WITH EMPHASIS ON HERBAL MEDICINES

Jeswin Johny, Betty Carla and Christudas Sunil*

Department of Pharmacology, St. Joseph's College of Pharmacy, Cherthala, Kerala, India.

***Corresponding Author: Dr. Christudas Sunil**

Department of Pharmacology, St. Joseph's College of Pharmacy, Cherthala, Kerala, India.

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ABSTRACT

Peptic ulcer is a group of ulcerative disorders that occur in areas of the upper gastrointestinal tract that are exposed to acid-pepsin secretions. It is one of the most common diseases in the world. Peptic ulcers are usually treated with synthetic drugs such as proton pump inhibitors, H2 receptor antagonists and other non-steroidal anti-inflammatory drugs. But most of these drugs are shown to have adverse effects, relapses and drug interactions. Medicinal plants containing active chemical constituents are better alternative for synthetic drugs in prevention and treatment of various diseases. This is true in case of peptic ulcer disease also. Combination of ayurvedic knowledge with modern medicine can result in better antiulcer drugs of natural origin from medicinal plants with fewer side effects. This study has presented the review of peptic ulcer disease and commonly used anti-ulcer plants which are used for the treatment or prevention of peptic ulcers along with other reported activities of these plants.

KEYWORDS:

INTRODUCTION

Peptic ulcer is a group of ulcerative disorders that occur in areas of the upper gastrointestinal tract that are exposed to acid-pepsin secretions. Approximately 10% of the world population may experience peptic ulcer.[1] It can affect one or all layers of the stomach or duodenum. The ulcer may penetrate only the mucosal surface, or it may extend into the smooth muscle layers. Most common causes of peptic ulcer are *H. pylori* infection[2] and NSAID use.[2]

TYPES OF ULCER

Peptic Ulcer

Peptic ulcer is a broad term which includes ulcers of digestive tract in the stomach or the duodenum. The causative agent is infection caused by the bacteria H. Pylori or reaction to certain medicines like non-steroidal anti-inflammatory drugs (NSAIDs).[3] It was believed that stress and spicy food was a major cause for this type of ulcers, recent research has shown that these are just the aggravating factors. Symptoms of peptic ulcers include abdominal discomfort and pain. Other symptoms include weight loss, poor appetite, bloating, nausea and vomiting. Some may also experience blood in stool and vomit and black stools that indicate gastrointestinal bleeding.[4]

Aphthous Ulcers

Sores that develop in the inner lining of the mouth are referred to as mouth ulcers or aphthous ulcers. Mouth ulcers are common and are usually due to trauma such as from ill fitting dentures, fractured teeth, or fillings. Anaemia, measles, viral infection, oral candidiasis, chronic infections, throat cancer, mouth cancer and vitamin B deficiency are some of the common causes of ulcers or sores in the mouth.[5] Aphthous minor is amongst the most common form of oral ulcerative diseases and affects an estimated 15-20% of the population worldwide. It is especially common in North America.[6-7] The incidence of aphthous ulcers has been found to be lower in smokers than in nonsmokers.[8]

Esophageal Ulcers

Esophageal ulcers are lesions that occur in the esophagus (the food pipe). These are most commonly formed at the end of the food pipe and can be felt as a pain right below the breastbone, in the same area where symptoms of heartburn are felt. Esophageal ulcers are associated with acid reflux or GERD, prolonged use of drugs like NSAIDs and smoking.[9]

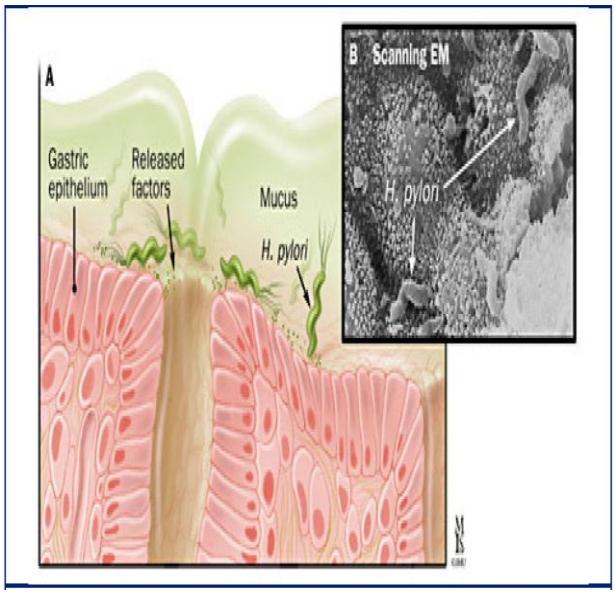
Symptoms

Small ulcers may not cause any symptoms however some big ulcers can cause serious bleeding. The common symptoms include feeling of fullness, unable to drink as much fluid, hunger and an empty feeling in the stomach often 1–3 h after a meal, mild nausea, pain or discomfort in the upper abdomen, upper abdominal pain that wakes you up at night, bloody or dark stools, chest pain, fatigue, vomiting and weight loss.

Common Causes of Peptic Ulcerations

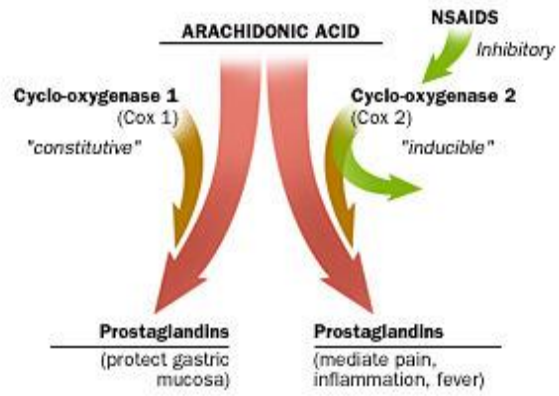
H. pylori

The gram negative bacterium *Helicobacter pylori*, remains present between the mucous layer and the gastric epithelium and is strategically designed to live within the aggressive environment of the stomach. Initially, *H. pylorus resides* in the antrum but over time, migrates toward the more proximal segments of the stomach. The genome of *H. pylori* has been sequenced and encodes 1500 proteins. Amongst this multitude of proteins there are factors that are essential determinants of *H. pylori*–mediated pathogenesis and colonization such as the outer membrane protein (Hop proteins), urease, and the vacuolating cytotoxin (Vac A). The first step in infection by *H. pylori* is dependent on the bacteria's motility and its ability to produce urease. Urease produces ammonia & carbondioxide from urea which is secreted from the stomach. This CO2 interact with environmental water produce H2CO3 in presence of carbonic anhydrase, an essential step in alkalinizing the surrounding pH. This H2CO3 converts into the H+ & HCO3- and resulting H+ ion react with NH3 to form NH4 + which can damage epithelial cells.[10]



Use of Non-steroidal Anti-inflammatory Drugs (NSAIDs)

The use of NSAIDs [Non selective Cox inhibitors] is common for the treatment of inflammatory responses; however, they may also inhibit certain gastroprotective prostaglandins causing destruction of stomach lining due to the corrosive effects of stomach acid. These protective prostaglandins are produced by an enzyme called Cox-1. By blocking the Cox-1 enzyme and disrupting the production of prostaglandins in the stomach, NSAIDs can cause ulcers and bleeding.[11]



Alcohol Consumption

Fermented and nondistilled alcoholic beverages increase gastrin levels and acid secretion. Alcoholic drinks containing succinic and maleic acid also stimulate gastric acid secretion. Low alcohol doses accelerate gastric emptying, whereas high doses delay emptying and slow bowel motility.[12]

Smoking & Tobacco

The relationship between the secretion of pepsin and the smoking habits of patients has been investigated. Significantly more cigarette smokers with peptic ulceration secreted pepsin in greater than trace amounts after pentagastrin or histamine than non-smokers with ulceration.[13]

Stress

Studies have well established that susceptibility to gastric as well as duodenal ulceration increases under stress conditions.[14] A number of preclinical screening methods also based on this approach.

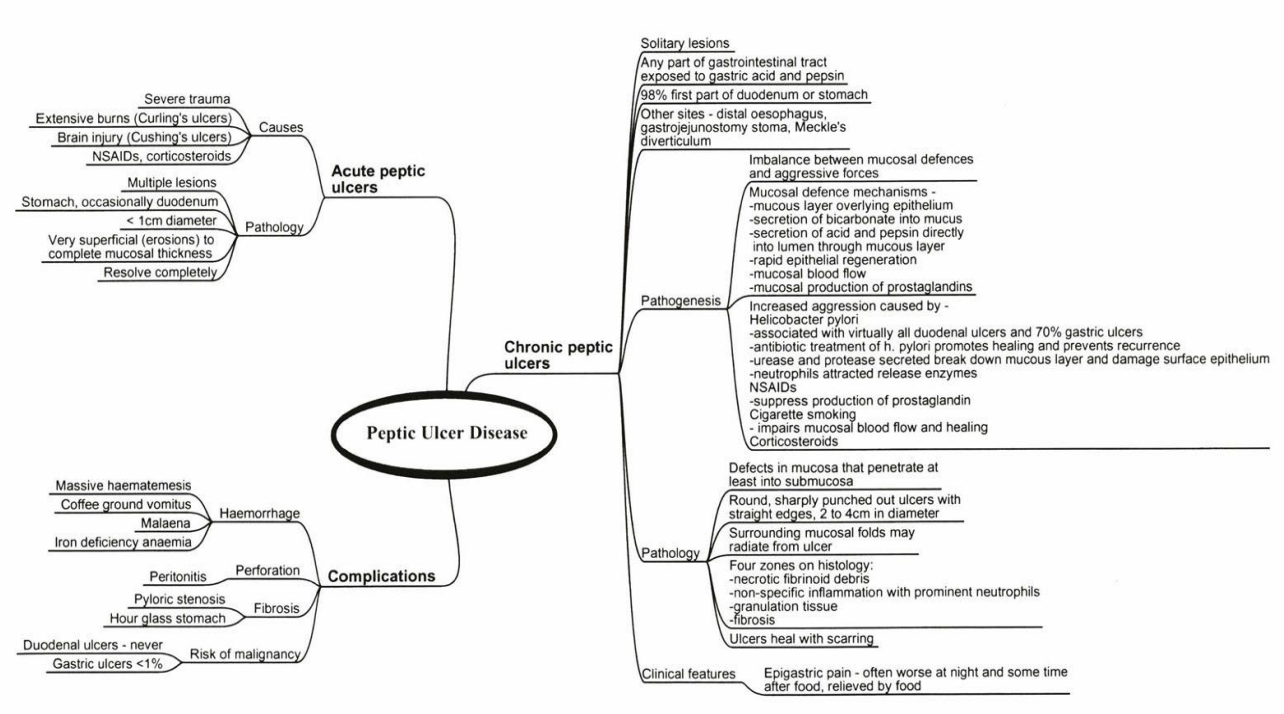
Fasting Condition

Fasting condition causes gastric empty which in some cases cause ulcers.

Radiation

Ulcers are wounds caused by the acute or chronic effects of ionizing radiation. The most common cause of radiation injury is an adverse effect of therapeutic radiation therapy. Other causes are occupational or environmental exposures.[15]

OVERVIEW OF PEPTIC ULCER



MANAGEMENT OF ULCER

ANTIMICROBIAL AGENTS
Amoxicillin
Bismuth compounds
Clarithromycin
Metronidazole
Tetracycline
H2 – HISTAMINE RECEPTOR BLOCKERS
Cimetidine
Famotidine
Nizatidine
Ranitidine
PROTON PUMP INHIBITORS (PPIs)
Dexlansoprazole
Esomeprazole
Lansoprazole
Omeprazole
Pantoprazole
Rabeprazole
PROSTAGLANDINS
Misoprostol
ANTIMUSCARINIC AGENTS
Dicyclomine
ANTACIDS
Aluminum hydroxide
Calcium carbonate
Magnesium hydroxide
Sodium bicarbonate
MUCOSAL PROTECTIVE AGENTS
Bismuth subsalicylate
Sucralfate

Antimicrobial agents

Patients with peptic ulcer disease (duodenal or gastric ulcers) who are infected with H. pylori require antimicrobial treatment. Infection with H. pylori is diagnosed via endoscopic biopsy of the gastric mucosa or various noninvasive methods, including serology and urea breath tests Eradication of H. Pylori results in rapid healing of active ulcers and low recurrence rates (less than 15% compared with 60% to 100% per year for initial ulcers healed with acid-reducing therapy alone). Successful eradication of H. Pylori (80% to 90%) is possible with various combinations of antimicrobial drugs. Currently, triple therapy consisting of a PPI combined with *amoxicillin* (*metronidazole* may be used in *penicillin*-allergic patients) plus *clarithromycin* is the therapy of choice. Quadruple therapy of *bismuth subsalicylate*, *metronidazole*, and *tetracycline* plus a PPI is another option. Quadruple therapy should be considered in areas with high resistance to *clarithromycin*. This usually results in a 90% or greater eradication rate. Treatment with a single antimicrobial drug is much less effective, results in antimicrobial resistance and is not recommended. Substitution of antibiotics is also not recommended.

H2-receptor antagonists and regulation of gastric acid secretion

Gastric acid secretion is stimulated by acetylcholine, histamine and gastrin. The receptor-mediated binding of acetylcholine, histamine, or gastrin results in the activation of protein kinases, which in turn stimulates the H+/K+-adenosine triphosphatase (ATPase) proton pump to secrete hydrogen ions in exchange for K+ into the lumen of the stomach. By competitively blocking the binding of histamine to H2 receptors, these agents reduce the secretion of gastric acid. The four drugs used in the United States—*cimetidine*, *ranitidine*, *famotidine* and *nizatidine*—potently inhibit (greater than 90%) basal, food-stimulated and nocturnal secretion of gastric acid. *Cimetidine* was the first histamine H2-receptor antagonist. However, its utility is limited by its adverse effect profile and drug– drug interactions.

Actions

The histamine H2-receptor antagonists act selectively on H2 receptors in the stomach, but they have no effect on H1 receptors. They are competitive antagonists of histamine and are fully reversible.

Therapeutic uses

All agents are effective in promoting the healing of duodenal and gastric ulcers. However, recurrence is common if H. pylori is present and the patient is treated with these agents alone. Patients with NSAID-induced ulcers should be treated with PPIs, because these agents heal and prevent future ulcers more effectively than H2 antagonists do. These drugs are also given as an intravenous infusion to prevent and manage acute stress ulcers associated with high-risk patients in intensive care units.

Adverse effects

In general, the H2 antagonists are well tolerated. *Cimetidine* can have endocrine effects because it acts as a nonsteroidal antiandrogen. These effects include gynecomastia and galactorrhea (continuous release/discharge of milk). The other agents do not produce the antiandrogenic and prolactin-stimulating effects of *cimetidine.* Other central nervous system effects (such as confusion and altered mentation) occur primarily in elderly patients and after intravenous administration. *Cimetidine* inhibits several cytochrome P450 isoenzymes and can interfere with the metabolism of many other drugs, such as *warfarin*, *phenytoin* and *clopidogrel*. All H2 antagonists may reduce the efficacy of drugs that require an acidic environment for absorption, such as *ketoconazole*.

PPIs: Inhibitors of the H+/K+-ATPase proton pump

The PPIs bind to the H+/K+-ATPase enzyme system (proton pump) and suppress the secretion of hydrogen ions into the gastric lumen.

The membrane-bound proton pump is the final step in the secretion of gastric acid (Figure 31.4). The available PPIs include *dexlansoprazole*, *esomeprazole*, *lansoprazole*, *omeprazole*, *pantoprazole* and *rabeprazole*. *Omeprazole*, *esomeprazole* and *lansoprazole* are available over-the counter for short-term treatment of GERD.

Actions

These agents are prodrugs with an acid-resistant enteric coating to protect them from premature degradation by gastric acid. The coating is removed in the alkaline duodenum and the prodrug, a weak base, is absorbed and transported to the parietal cell. There, it is converted to the active drug and forms a stable covalent bond with the H+/K+-ATPase enzyme. It takes about 18 hours for the enzyme to be resynthesized and acid secretion is inhibited during this time. At standard doses, PPIs inhibit both basal and stimulated gastric acid secretion by more than 90%. An oral product containing *omeprazole* combined with *sodium bicarbonate* for faster absorption is also available over the counter and by prescription.

Therapeutic uses

The PPIs are superior to the H2 antagonists in suppressing acid production and healing ulcers. Thus, they are the preferred drugs for stress ulcer treatment and prophylaxis and for the treatment of GERD, erosive esophagitis, active duodenal ulcer and pathologic hypersecretory conditions (for example, Zollinger-Ellison syndrome, in which a gastrin-producing tumor causes hypersecretion of HCl.

H2 antagonists reduce the activity of the proton pump and PPIs require active pumps to be effective. PPIs also reduce the risk of bleeding from ulcers caused by *aspirin* and other NSAIDs and may be used for prevention or

treatment of NSAID-induced ulcers. Finally, they are used with antimicrobial regimens to eradicate H. pylori.

Adverse effects
The PPIs are generally well tolerated. Prolonged acid suppression with PPIs (and H2 antagonists) may result in low vitamin B12 because acid is required for its absorption in a complex with intrinsic factor. Elevated gastric pH may also impair the absorption of *calcium carbonate*. Diarrhea and Clostridium difficile colitis may occur in community patients receiving PPIs.

Prostaglandins
Prostaglandin E, produced by the gastric mucosa, inhibits secretion of acid and stimulates secretion of mucus and bicarbonate (cytoprotective effect). A deficiency of prostaglandins is thought to be involved in the pathogenesis of peptic ulcers. *Misoprostol*, an analog of prostaglandin E1, is approved for the prevention of NSAID-induced gastric ulcers. Prophylactic use of *misoprostol* should be considered in patients who are taking NSAIDs and are at moderate to high risk of NSAID-induced ulcers, such as elderly patients and those with previous ulcers.

Adverse effects
Misoprostol is contraindicated in pregnancy, since it can stimulate uterine contractions and cause miscarriage. Dose-related diarrhea and nausea are the most common adverse effects and limit the use of this agent.

Antacids
Antacids are weak bases that react with gastric acid to form water and a salt to diminish gastric acidity. Because pepsin (a proteolytic enzyme) is inactive at a pH greater than 4, antacids also reduce pepsin activity. Commonly used antacids are combinations of salts of aluminum and magnesium, such as *aluminum hydroxide* and *magnesium hydroxide* [Mg(OH)2]. *Calcium carbonate* [CaCO3] reacts with HCl to form CO2 and CaCl2 and is also a commonly used preparation. Systemic absorption of *sodium bicarbonate* [NaHCO3] can produce transient metabolic alkalosis. Therefore, this antacid is not recommended for long-term use.

Adverse effects
Aluminum hydroxide tends to cause constipation, whereas *magnesium hydroxide* tends to produce diarrhoea.

Mucosal protective agents
Also known as cytoprotective compounds, these agents have several actions that enhance mucosal protection mechanisms, thereby preventing mucosal injury, reducing inflammation and healing existing ulcers.

1. Sucralfate
This complex of *aluminum hydroxide* and sulphated sucrose binds to positively charged groups in proteins of both normal and necrotic mucosa. By forming complex gels with epithelial cells, *sucralfate* creates a physical barrier that protects the ulcer from pepsin and acid, allowing the ulcer to heal. Although *sucralfate* is effective for the treatment of duodenal ulcers and prevention of stress ulcers, its use is limited due to the need for multiple daily dosing and drug–drug interactions. Because it requires an acidic pH for activation, *sucralfate* should not be administered with PPIs, H2 antagonists, or antacids. *Sucralfate* is well tolerated, but it can interfere with the absorption of other drugs by binding to them. This agent does not prevent NSAID-induced ulcers, and it does not heal gastric ulcers.

2. Bismuth subsalicylate
This agent is used as a component of quadruple therapy to heal peptic ulcers. In addition to its antimicrobial actions, it inhibits the activity of pepsin, increases secretion of mucus and interacts with glycoproteins in necrotic mucosal tissue to coat and protect the ulcer.

PLANTS USED IN ULCER DISEASE

***Aloe vera* (L.) Burm.f.**
Aloe vera (L.) Burm.f. is commonly known as Aloe. It belongs to the family Xanthorrhoeaceae. Reported constituents in plant are aminoacids, anthraquinones, enzymes, hormones, lignin, minerals, salicylic acid, saponins, sterols, sugars, vitamins.[16] The anti-ulcer activity of the plant is reported in Indomethacin induced ulcer model. The mechanism involved in production of antiulcer activity of the plant is due to its antioxidant, anti-inflammatory, mucus secreting, cytoprotective or healing activities.[17] Reported pharmacological activities of the plant are hypoglycemic, hypolipidemic, woundhealing, imunomodulatory, antifungal, hepatoprotective.[18]

***Capsicum annuum* L.**
Capsicum annuum L. is commonly known as Chilli pepper and it is most widely cultivated throughout the world. It belongs to the family Solanaceae. The fruit is proved to possess antiulcer activity[19], antioxidant activity.[20] The methanolic seed extract of the plant reported antiobesity activity in 3T3-L1 adipocyte.[21] The fruit and vegetable peel extracts of the plant exerted radicalscavenging properties.[22] Solasonine present in the plant reportedplatelet aggregation inhibitory activity.[23]

***Curcuma longa* L.**
Curcuma longa L. is commonly known as Turmeric and also a household remedy for biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders, rheumatism and sinusitis which belongs to the family Zingiberaceae. Evaluation of turmeric has been done for gastric and duodenal antiulcer activity in rats.[24] Volatile oil of *Curcuma longa* possess anti-inflammatory and anti-arthritic activities.[25]

Water and fat soluble extracts of curcumin exhibited strong antioxidant activity comparable to vitamins C and E. Protective effect of curcumin in rat liver injury induced by carbon tetrachloride was reported.[26] Curcumin inhibited cell proliferation and tumor growth in case of prostate cancer. The plant is reported to possess pharmacological activities such as anti-fertility, antibacterial, antifungal.[27]

***Glycyrrhiza glabra* L.,**

Glycyrrhiza glabra L., is a sweet, moist, soothing, flavoring herb commonly known as Liquorice belonging to the family Fabaceae. The plant is widely used as a medicine from the ancient medical history of ayurveda. The glycyrrhetinic acid of Liquorice showed potent *in vitro* activity against *H. pylori* indicating its antiulcer effect on peptic ulcers. The ether, chloroform, acetone root extracts of the plant exerted significant antibacterial activity against *Bacillus subtili, Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa*. The active compound glabridin present in liquorice reported anti-fungal activity against *Arthrinium sacchari M001, Chaetomium funicola M002* and potent antioxidant activity towards LDL oxidation. Reported pharmacological activities of the plant are anti-inflammatory, anti tussive, hepatoprotective, Estrogenic.[28]

***Mangifera indica* L**.

Mangifera indica L. is commonly known as Mango. It belongs to the family Anacardiaceae. The petroleum ether and ethanol plant leaf extracts reported antiulcer activity. The mangiferin, polyphenolic constituent of the plant reported *in vivo* antioxidant[29] activity in OF1 mice, exerted radioprotective effect against radiation-induced micronuclei formation in cultured human peripheral blood lymphocytes and in DBAxC57BL mice, reported *in vivo* immuno modulatory activity on thioglycollate-elicited mouse macrophages which were stimulated with lipo polysaccharide (LPS) and gamma interferon (IFN-γ).[30] The ethyl acetate and ethanol root extracts proved to exhibit anti-inflammatory activity.[31] Miscellaneous pharmacological activities reported by the plant are anti-diabetic, anti-viral, ant helmintic, anti-allergenic, anti-parasitic, anti-bacterial, anti-tumor, antispasmodic, anti-pyretic, anti-diarrhoeal, anti-fungal, hepatoprotective, gastroprotective.[32]

Panax ginseng

Panax ginseng is commonly known as Ginseng belonging to the family Araliaceae and medicinally used as an adaptogen, restorative tonic. Phyto chemical studies proved the presence of ginsenosides, amino acids, alkaloids, phenols, proteins, polypeptides, vitamins B1 and B2. Ginsenosides are reported for antiulcer activity.[33] The plant is reported for anti-sterility activity in an untreated control group by improving sperm count and motility which causes male fertility. Numerous studies reported that ginseng increases physical endurance and causes physiological changes that helps the body in adapting to adverse conditions. The plant is reported to possess pharmacological activities such as antiinflammatory, anti-diabetic, anti-proliferative.[34]

***Syzygium aromaticum* L.**

Syzygium aromaticum L. is commonly known as Clove which belongs to the family Myrtaceae and esteemed as a flavouring agent, used as a spice for scenting, chewing tobacco, an ingredient of betel chew and to control nausea, vomiting, cough, diarrhoea, dyspepsia, flatulence, stomach distension and gastro intestinal spasm, relieve pain, cause uterine contractions and stimulate the nerves . Dried flower buds of the n-butanol portion of the plant are reported for anti-ulcerogenic and anti-secretory activity in rats.[35] Reported chemical constituents are volatile constituents such as bud oil, leaf oil, stem oil, fruit oil and non-volatile constituents such as tannins, sterols, triterpenes, flavanoids. Reported pharmacological activities of the plant are anti-microbial, anti-viral, anti-oxidant, anti-diabetic, anti-inflammatory, anti-platelet, antistress, anti-pyretic, chemo preventive, hepato protective, anaesthetic, aphrodisiac, insecticidal.[36]

***Terminalia chebula* Retz.**

Terminalia chebula Retz. belongs to the family Combretaceae and commonly called as King of medicine and active ingredient of the well-known herbal preparation Triphala. The main phyto constituents reported are tannins such as chebulic acid, chebulinic acid, chebulagic acid, gallic acid, corilagin, ellagic acid and flavonoids, sterols, amino acids, fructose, resin, fixed oils etc.,[37] The methanolic extract of the fruits of the plant are reported for anti-ulcer activity.[38] Reported pharmacological activities of the plant are antibacterial, antifungal, antiviral, antiamoebic, immunomodulatory, antiplasmodial, antidiabetic, retinoprotective, antianaphylactic, adaptogenic, antinociceptive, cardioprotective, hepatoprotective, chemopreventive, hypolipidemic, hypocholesterolemic, antispermatogenic, mollusicidal, anthelmintic, anti-mutagenic, anticarcinogenic, antioxidant, anti-arthritic, wound healing, cyto protective, anti-aging, radioprotective.[39]

***Triticum aestivum* L.**

Triticum aestivum L., is commonly known as Wheat grass belonging to the family poaceae. Phyto constituents reported are vitamins A, B1, 2, 3, 5, 6, 8, 12 and C, E, K, enzymes such as protease, amylase, cytochrome oxidase, transhydrogenase, superoxide dismutase and amino acids. The plant leaf juice is reported for the treatment of active distal ulcerative colitis. The wheat grass juice taken during FAC (5–fluorouracil, doxorubicin, cyclo phospamide) chemotherapy reduced myelotoxicity, dose reduction and need for granulocyte colony stimulating factors support, without diminishing efficacy of chemotherapy reporting anti-cancer activity. The plant is also reported to possess anti arthritic activity, anti-oxidant activity.[40]

***Vinca minor* L.**

Vinca minor L. is an ornamental plant which is commonly known as Common periwinkle with lilac-blue flowers and belongs to the family Apocynaceae. The plant is used internally for circulatory disorders, cerebral circulatory impairment and brain's metabolism support.[41] Indole alkaloids such as vincaminorine, vincaminoreine, minovine, minovincine and vincamine were isolated from the aerial parts of the plant. The alkaloid vincamine, present in the plant leaves shows cerebrovasodilatory and neuroprotective activity. The plant leaves proved for anti-ulcer activity against experimentally induced gastric damage in rats.[42]

***Zingiber officinalis* Roscoe**

Zingiber officinalis Roscoe is commonly known as Ginger which is consumed as a flavoring agent, spice belongs to the family Zingiberaceae. The plant extract reported antitumor effects on colon cancer cells by suppressing its growth, striking the G0/G1- phase, reducing DNA synthesis and inducing apoptosis. The aqueous ethanol extract of the plant (200 and 400 mg/kg) reported nephroprotective effect against doxorubicin-induced (15 mg/kg) acute renal damage in rats. The plant root extract reported neuroprotective effect against monosodium glutamate toxicity by the antagonistic action of root extracts on monosodium glutamate. Reported pharmacological activities of the plant are antioxidant, anti migraine, antiemetic, anti inflammatory, anti-microbial, anti thrombotic, anti analgesic, anti proliferative, anti osteoarthritic, hepato protective.[43]

CONCLUSION

Peptic ulcer remains a frequent clinical problem in todays world affecting almost all age groups. Although the etiology of peptic ulceration is not clear, the various causative agents have been suggested and identified for that. The various approaches have also been established for their treatment using chemical agents, but are not strictly advisable due to their unwanted effects. The herbal products are continuously growing recognition as a safe remedy for treatment of peptic ulcers. A need for further research is necessary to separate and characterize the active constituents of those medicinal plants in response to their pharmacological activities.

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