IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

PEPTIC ULCER DISEASE: A BRIEF REVIEW OF CONVENTIONAL THERAPY AND HERBAL TREATMENT

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Abstract: Peptic ulcer disease is a chronic disease that affects 10% of the world's population. The formation of peptic ulcers depends on the presence of gastric acid pH and reduced mucosal protection. Nonsteroidal anti-inflammatory drugs (NSAIDs) and Helicobacter pylori (H. pylori) infection are two major factors that disrupt the mucosal resistance to damage. Conventional treatments for peptic ulcers, such as proton pump inhibitors (PPIs) and histamine-2 (H2) receptor antagonists, have been shown to have adverse effects, relapses, and various drug interactions. On the other hand, medicinal plants and their chemical compounds are useful in the prevention and treatment of many diseases. Therefore, this review presents common medicinal plants that can be used to treat or prevent peptic ulcer

KEYPOINTS: Peptic Ulcer Disease; Helicobacter Pylori Infection, Herbal Treatment

INTRODUCTION

Peptic ulcer disease is an acid-induced ulcer in the digestive tract, usually located in the stomach. or proximal duodenum, and is characterized by a bare mucosa with defect extending into the submucosal layer or muscularis propria [1]. The estimated prevalence of peptic ulcer disease in the general population is 5–10% [2], but recent epidemiological studies have shown a decrease in the incidence, hospitalization rate, and mortality associated with peptic ulcer disease [3,4]. This is most likely secondary to the introduction of new therapies and improved hygiene, which have led to a decrease in Helicobacter pylori (H. pylori) infections. Traditionally, mucosal disruption in patients with acid reflux disease has been considered to be the result of an acidic hypersecretory environment associated with dietary or stress factors. Risk factors for the development of peptic ulcer disease include H. pylori infection, alcohol and tobacco use, nonsteroidal anti-inflammatory drug (NSAID) use, and Zollinger-Ellison syndrome [5]. The major risk factors for gastric and duodenal ulcers are H. pylori infection and NSAID use [6]. However, only a small percentage of people with Helicobacter pylori or who use NSAIDs develop peptic ulcer disease, which means that Individual susceptibility is important in the initiation of mucosal damage. Functional polymorphisms in several cytokine genes are associated with peptic ulcer. For example, polymorphisms in interleukin 1 beta (IL1B) affect mucosal production of interleukin 1β, causing H. pylori-associated gastroduodenal disease [7]. On the other hand, the risk of complications from peptic ulcer disease is fourfold among NSAID users and doubled among aspirin users [8]. Concomitant use of NSAIDs or aspirin with anticoagulants, corticosteroids, and selective serotonin reuptake inhibitors increases the risk of upper gastrointestinal bleeding [9]. Although many people who use NSAIDs or aspirin are co-infected with H.Pylori, their interaction in the pathogenesis of peptic ulcer disease remains controversial. A meta-analysis of observational studies concluded that NSAIDs, aspirin use, and H. pylori infection independently increase the risk of peptic ulcer disease [10]. H. Idiopathic peptic ulcer, pylori-negative, NSAID-negative and aspirin-negative, classified as idiopathic ulcer, can be diagnosed in about one fifth of cases [11]. A Danish study has shown that psychological stress can increase the incidence of peptic ulcer disease [12]. Other etiologist include ischemia, drugs (steroids, chemotherapeutic agents) and radiotherapy, viruses, histamine, eosinophilic infiltration, gastric bypass surgery and metabolic disorders [13].

PATHOGENESIS OF PEPTIC ULCER :-

Pathogenesis of pectic ulcer Nearly half of the world's population is colonized by H. pylori, which remains one of the most common causes of peptic ulcer disease [14]. The prevalence of H. pylori is highest in developing countries, particularly in Africa, Central America, Central Asia, and Eastern Europe [15]. The infection is usually acquired during childhood in an environment with unsanitary conditions and overcrowding, especially in countries with low socioeconomic status. H.pylori causes degeneration and damage of epithelial cells, generally more severe in the antrum, by the inflammatory response of neutrophils, lymphocytes, plasma cells and macrophages. The mechanism by which H. pylori inducesthe development of different types of lesions in the gastroduodenal mucosa is not fully understood. H. H. pylori infection can lead to hypochlorhydria or hyperchlorhydria, thus determining the type of peptic ulcer. The main mediators of H. pylori infection are cytokines that inhibit parietal cell secretion, but H. pylori can directly affect the α subunit of H+/K+ATPase, activate calcitonin gene-related peptide CGRP)-sensitive neurons associated with somatostatin, or inhibit gastrin production [16]. Although gastric ulcer formation

is associated with hyposecretion, 10 to 15% of patients with H. pylori increases gastric secretion caused by hypergastrinemia and reduced antral somatostatin [17]. This leads to an increase in histamine secretion, and subsequently to an increase in acid or pepsin secretion from parietal and gastric cells. Furthermore, eradication of H. pylori results in decreased gastrin mRNA expression and increased somatostatin mRNA expression [18]. In most patients, gastric ulcers are associated with hypochlorhydria and mucosal atrophy. The main mechanism of NSAID-associated gastroduodenal mucosal damage is the systemic inhibition of constitutively expressed Cyclooxygenase-1 (COX-1), which is responsible for prostaglandin synthesis and is associated with decreased mucosal blood flow, mucus and bicarbonate secretion, and inhibition of cell proliferation. NSAIDs inhibit the enzyme in a reversible, concentration-dependent manner. Simultaneous administration of exogenous prostaglandins and cyclooxygenase-2 (COX-2) selective NSAIDs reduces mucosal damage and the risk of ulcers [19]. However, the different physicochemical properties of NSAIDs lead to differences in their toxicity [20]. The main pathophysiological mechanisms and sites of action of antiulcer treatments are presented in

Figure 1. main pathophysiological mechanism and site of action of anti ulcer treatment
are shown in figure 1.

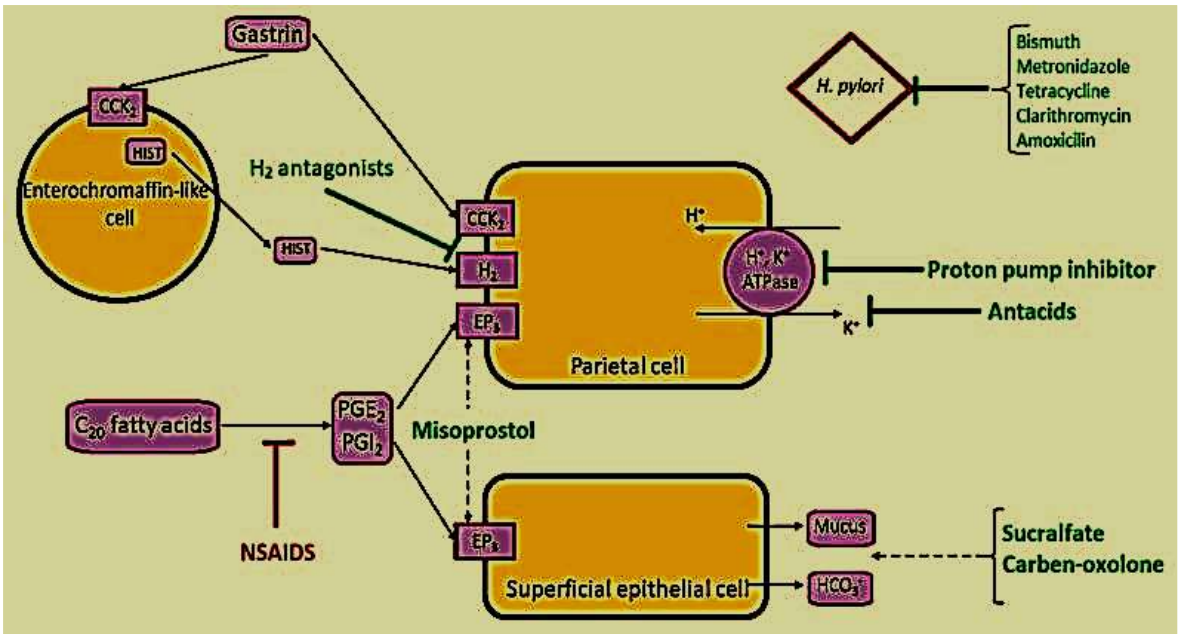

Figure 1.

Figure 1. Schematic presentation of main pathophysiological mechanisms involved in the developmentof peptic ulcer disease, and the sites of action of the most commonly used pharmacological optionsin the treatment of peptic ulcer disease. CCK2 = Cholecystokinin Recaction of the most commonly used pharmacological options in the treatment of peptic ulcer disease. CCK2 = Cholecystokinin Receptor; PGE2 = Prostaglandin E2; PGI2 = Prostaglandin I2; EP3 = Prostaglandin

TREATMENT: - TABLE NO :- 1

MEDICINE	MECHANISM OF ACTION	ADVERSE EFFECT	REFERENCE
proton pump inhibitors (ppis) OMPRAZOLE LANSOPRAZOLE RABEPRAZOLE ESOMEPRAZOLE PANTAPRAZOLE	inhibition of gastric h^+ / k^+ -ATPase (proton pump) enzyme system	Diarrhea Headache Vomiting Constipation Abdominal pain Vit.b12 deficiency Osteoporosis nausea	[21] [22]
H2 receptor blockers Famotidine Nizatidine Ranitidine Cimetidine	Blocking the action of histamine at the histamine H2 receptors of parietal cells	Headache Anxiety Depression Dizziness Cardiovascular events Thrombocytopenia	[23]

antacids Magnesium hydroxide Aluminum hydroxide	Increases gastric pH to greater than four, and inhibits the proteolytic activity of pepsin Causes osmotic retention of fluid	Frequency not defined: Nausea Vomiting Hypophosphatemia Chalky taste Constipation Abdominal cramping Diarrhea Electrolyte imbalance Nasopharyngitis	[24]
Potassium-Competitive Acid Blocker Vonoprazan	Inhibits H+ K+ -ATPase in gastric parietal cells at the final stage of the acid secretory pathway	Fall Contusion Diarrhea Upper respiratory tract inflammation Eczema Constipation	[25]-[29]
Cytoprotective Agents Misoprostol Sucralfate	Stimulate mucus production and enhance blood flow throughout the lining of the gastrointestinal tract	Eczema Constipation Back pain Diarrhea Abdominal pain Headache Constipation	[30],[31]

Table 1. mechanism of action and adverse effect of the most commonly used anti-ulcer treatment options

TABLE NO: 2

TYPE	DURATION	EFFICIENCY	REFRENCES
First line Standard triple therapy: PPI + two antibiotics (clarithromycin + metronidazile or amoxicilin)	7-14 Days	70-85%	[32]
SECOND LINE Bismuth-containing quadruple therapy: PPI + bismuth salt + tetracycline + metronidazole Non-bismuth based concomitant therapy: PPI + clarithromycin + amoxicillin + metronidazole Levofloxacin triple therapy: PPI + amoxicillin + levofloxacin	14 Days	77-93%	[33,34]
Salvage regimens Rifabutin-based triple therapy: PPI + rifabutin +Amoxicillin	10Days	66-70%	**[35]**

Table 2. types and efficiency of helicobacter pylori h.pylori eradication treatment option

HELICOBACTER PYLORI ERADICATION

Although successful eradication of H. pylori alone is essential for healing of associated peptic ulcer and preventing recurrence, the increasing prevalence of antibiotic resistance has become a global challenge. The first effective treatment was introduced in the 1980s and consisted of a combination of bismuth, tetracycline, and metronidazole administered for two weeks . The standard first-line treatment is triple therapy consisting of a proton pump inhibitor (PPI) and two antibiotics such as clarithromycin plus amoxicillin or metronidazole administered for seven to 14 days [32]. However, with an increasing prevalence of antibiotic resistance, particularly to clarithromycin, the success of triple therapy has been significantly reducedover the past 10–15 years. Eradication of H. pylori should be based on antimicrobial susceptibility testing. Since susceptibility testing is not available in clinical practice, the choice of first-line treatment should be based on the local prevalence of antibiotic resistance, and clarithromycin-based regimens should be avoided in areas where the local rate of clarithromycin resistance is greater than 15% [33]. Eradication rates can be increased by using high-dose PPIs and extending the duration to 14 days [34]. The standard recommended first-line treatment is a 14-day bismuth-containing quadruple therapy (PPI, a bismuth salt, tetracycline, and metronidazole) or a 14-day concomitant treatment for bismuth-intolerant patients (PPI, clarithromycin, amoxicillin, and metronidazole); both regimens provide eradication rates greater than 90% [35]. Second-line treatment is prescribed if first-line treatment fails and should not include metronidazole or clarithromycin [36]. Triple therapy with levofloxacin (PPI,amoxicillin, and

levofloxacin) for 14 days appears to be an effective treatment, with eradication rates between 74 and 81% [37]. If a patient receives first-line treatment with clarithromycin-based therapy, a preferred treatment option is quadruple bismuth therapy with eradication rates of 77–93%, or high-dose double-dose therapy with amoxicillin and a PPI, because H. pylori rarely develops resistance to amoxicillin [38]. Despite well-developed recognition to select the appropriate treatment regimen, 5–10% of patients have persistent infection. The two most common reasons for treatment failure are suboptimal adherence or resistance of H. pylori to one or more antibiotics, in which case susceptibility testing is strongly recommended. When three or more recommended options have failed, one of the Usually recommended salvage treatments is triple therapy with rifabutin (PPI, rifabutin, and amoxicillin) for 10 days, with eradication rates of 66–70% [39], but side effects of rifabutin such as myelotoxicity and red secretions should be considered [40].

NSAIDS ASSOCIATED ULCER DISEASE AND THE USE OF PPIs

Several strategies are available for the prevention of NSAID- and aspirin-induced peptic ulcer disease and its complications, such as NSAID therapy combined with a PPI, an H2-receptor antagonist, or misoprostol, the use of COX-2-selective NSAIDs, or their combination gastroprotective agent. PPIs are the best-known and most effective prophylactic agents [41]. The mechanism of action is to reduce gastric acid production irreversibly binding to the hydrogen/potassium ATPase enzyme in the parietal cells of the stomach. The combination of COX-2-selective NSAIDs and a PPI provides the best protection against the complications of peptic ulcer disease . Standard doses of H2-receptor antagonists do not reduce the risk of gastric ulcer . Gastrointestinal disturbances and abortive actions limit the use of misoprostol for gastric protection, despite its effective prevention of peptic ulcer complications.[42]Side effects of PPIs, such as headache, diarrhea, constipation, and abdominal discomfort, are minor and easily manageable. However, recent studies have suggested an association between PPI use and some serious adverse events, which have been a major cause of concern for patients and physicians. Some of the side effects of PPIs are related to their suppression of gastric acid secretion, allowing ingested microbial pathogens that would otherwise be destroyed by stomach acid to colonize the upper gastrointestinal tract and cause infections. Reports suggest that PPI use may increase the risk of enteric infections such as Salmonella and Campylobacter, community-acquired pneumonia , Clostridium difficile infections and spontaneous bacterial peritonitis . With gastric acid suppression, there is no stimulation of endocrine D cells to produce somatostatin, and therefore no inhibition of G cells to release gastrin, resulting in hypergastrinemia. Gastrin is a growth factor that can enhance proliferation in Barrett's metaplasia and colon [43]. However, PPI-induced hypergastrinemia in humans is usually mild and rarely causes carcinoid tumors in human patients unless they have a genetic abnormality [44]. In addition, PPI use may protect against Barrett's esophagus cancer, as PPIs heal chronic inflammation of the esophagus from reflux esophagitis, which is a risk factor for the development of malignancy. The inhibition of gastric acid by PPIs may also affect the absorption of certain vitamins, minerals, and drugs. Cases of vitamin B12 deficiency and iron deficiency anemia have been reported in patients taking PPIs [45]. In addition, PPIs may increase the risk of osteoporosis and bone fractures by interfering with the ionization and dissolution of calcium salts required for their absorption . The underlying mechanism of hypomagnesemia is still unclear. PPI-induced gastric acid suppression decreases the absorption of ketoconazole and facilitates the absorption of digoxin [46]. since both are metabolized by the enzyme CYP2C19 . The clinical significance of the interaction remains controversial, but the Food and Drug Administration (FDA) has issued warnings to avoid the `use omeprazole or esomeprazole with clopidogrel. There has been a dramatic increase in reports of various adverse reactions and unpredictable PPI events in recent years, such as myocardial infarction, stroke, acute and chronic kidney disease, and eosinophilic esophagitis. The increased incidence of cardiovascular events in patients receiving Clopidogrel also with PPIs may result from competition between drugs for metabolism by CYP2C19, Although it is possible that PPIs may have cardiovascular effects independent of their effects on clopidogrel activation, possibly through reduced nitric oxide production and altered vascular homeostasis [47].

POTASSIUM COMPATETIVE ACID BLOCKERS

Since up to 13% of patients treated with lansoprazole still experience ulcer recurrence, research into alternative treatments is ongoing. Vonoprazan is an acid-competitive potassium channel blocker that inhibits the H+, K+-ATPase in gastric parietal cells in the final step of the acid secretion pathway . The difference in mechanism of action between vonoprazan and PPIs is that vonoprazan inhibits the enzyme competitively and reversibly with respect to K+, and does not require an acidic environment for its activation. In addition, vonoprazan exhibits a rapid onset of action and prolonged control of intragastric acidity . Vonoprazan at doses of 10 mg and 20 mg was non-inferior to lansoprazole for prevention of peptic ulcer recurrence in Japanese patients on NSAID treatment , or those who required aspirin treatment for cardiovascular or cerebrovascular protection , with good tolerability, a similar safety profile and no new safety concerns. Furthermore, five weeks of vonoprazan treatment significantly reduced bleeding after endoscopic submucosal dissection compared with eight weeks of PPI treatment. Similarly, it was found to be superior to esomeprazole and rabeprazole or healing of the artificial ulcer, which may help make endoscopic submucosal dissection a safer procedure.

ALTERNATIVE THERPY FOR PEPTIC ULCER

The usage of medicinal plants in healing numerous diseases is as old as human beings, and well-known as phytotherapy. Moreover, in the past few years, there has been a rising interest in alternative therapies and the usage of herbal products, in particular, those produced from medicinal plants [48]. Also, due to appearance of various side effects by usage of conventional drugs for numerous diseases, medicinal plants are considered the major reservoir of potentially new drugs. Plant extracts and their crude are the most significant sources of new drugs, and have been shown to cause promising results in the treatment of gastric ulcer as well [49]. It is known that numerous pharmaceutical agents such proton pump inhibitors, anticholinergics, antacids, antimicrobial agents, H2-receptor antagonists, sucralfate, and bismuth are not fully effective, and produce numerous adverse effect, arrhythmia,hematopoietic alterations, hypersensitivity, and gynecomastia [50]. Due to that, investigations of the new pharmacologically active agents through the screening of different plant extracts led to the discovery of effective and safe drugs with gastroprotective activity. Especially, plants with antioxidant capability as the main mechanism are used as the herbal reservoir for the treatment of ulcer disease [51]. Medicinal plants have achieved their therapeutic properties from their capability to produce renewable and various secondary metabolites, which are known as phytochemical constituents. Hence, numerous plants have used these phytochemicals as a protection mechanism against pathogens [52].On the other hand, the appearance of resistant pathogens has had a significant influence on the pharmaceutical companies to change their strategy in the development of conventional antibiotics and design new antimicrobial drugs derived from medicinal plants [53]. Nevertheless, the synthetic antibiotics are still dominant as antimicrobial drugs. As a matter of fact, incidences of infectious diseases have enlarged within the last three decades, involving infections with different properties as well as new infections, and it has been shown that around 60% of them are of zoonotic origin (spread among human and animals). H. pylori is one of the

major representatives in that group, and may cause chronic gastritis, peptic ulcer disease, and stomach cancer. Therefore, one of the aims in this review was to highlight some medicinal plants that demonstrated significant antibacterial and antioxidant activity against H. pylori and peptic ulcer disease. However, some of plants lose their efficiency against H. pylori consequent to the emergence of resistant strains. Consequently, the isolation of various constituents from the most active plant extracts is encouraged. It is important to emphasize that herbal products may contain numerous bioactive constituents with dangerous, but also beneficial effects. Therefore, the higher education of doctors and patients about herbal therapy is necessary, as well as legislation to control the quality of herbal products, especially for further randomized investigations to determine the effectiveness and safety of many products in digestive and other disorders. Finally, the Ayurvedic knowledge and modern medicine could generate preferable antiulcer drugs derived from medicinal plants with less side effect .Numerous medicinal plants with significant antibacterial activity against H. pylori and benefits for gastric ulcer disease.[54]

THE EFFECT OF ON THE H. PYLORI ERIDICATION

Several factors influence the failure of conventional treatment. These include: low bioavailability of antibiotics, because the gastric mucosa is a barrier to the administration of antibiotics and drugs, thus they cannot reach the underlying gastric epithelium ; the stomach has an acidic to neutral pH, and only a few antibiotics are active over a wide pH range ; bacterial antagonism to antibiotics, where coinfection by multiple strains is a very important feature ; lack of patient tolerance to therapy; patient lifestyle and diet [55]. Many studies have been reported on various medicinal plants and their anti-H. pylori activities. In recent years, it has been shown that the suppression of enzymatic activity (dihydrofolate reductase, DNA gyrase, myeloperoxidase N-acetyltransferase and urease) and adhesion, The high redox potential and the hydrophilic/hydrophobic nature of the compounds play an important role in anti-H. pylori mechanisms of action. Gastric inflammation stimulated by H. pylori can lead to superficial gastritis and atrophic gastritis, but also to gastric cancer. Several natural products been shown to have anti-inflammatory activity, and the underlying mechanisms involve inhibition of nuclear factor-κB and activation of the mitogen-activated protein kinase pathway and suppression of oxidative stress. Considering the role of H. pylori in relation to carcinogenesis is to enhance carcinogenesis rather than play a key role as a direct carcinogen, its eradication alone cannot prevent H. pylori-related gastric cancers. Medicinal plants such as Allium sativum, Zingiber officinalis, Korean red ginseng and Cistus laurinols are known to suppress H. pylori colonization, reduce gastric inflammation by releasing chemokines, inhibiting cytokines and suppressing precancerous changes by removing the nuclear factor-DNA binding kappa B, which suppresses mutagenesis and produces abundant levels of apoptosis. Other outstanding issues need to be resolved before phytochemicals can be accepted as standard treatment for H. Pylori infection [56].

KOREAN RED GINSENG

Korean red ginseng extract plays a significant role in inhibiting H. pylori-induced 5-LOXactivity, such as inactivating c-jun, repressing NF-κB-DNA binding, inhibiting H. pylori-induced5(S)-hydroxy eicosatetraenoic acid biosynthesis, and preventing pro-inflammatory interleukin (IL)-8 or5-LOX mRNA. Consequently, these mechanisms decrease gastric carcinogenesis.5-lipoxygenase(5-LOX) mRNA and enzyme activities, and consequently the decreased synthesis of5-hydroxy-eicosatetraenoic acid. Similarly, green tea extract may prevent the activation of multiple transcription factors and their target genes, involving COX-2 and inducible nitric oxide synthase (iNOS) mitogen-activated protein kinase activation, as well as the lipopolysaccharide of H.pylori-activated TLR-4. Due to that, these blockades increase the pro-inflammatory factors that induce gastric mucosal lesion. Kim et al. reported on the protective effect of Korean red ginseng againstH. pylori-induced cytotoxicity in vitro.Meanwhile, in a previous clinical study, a supplementary administration of Korean red ginseng increased the eradication rates of H. pylori, reduced gastricinflammation, and decreased oxidative DNA damage and apoptosis [57].

ALLIUM SATIVUM

Throughout history, the health benefits of garlic have been well documented and the main use of Allium sativum was for its medicinal properties. Organosulfur components of Allium sativum, in particular the sulfoxides S-allyl-L-cysteine (SAC) and δ-glutamyl S-allyl-L-cysteine, are known to be the main compounds of its bioactivity. Raw Allium sativum is easy to convert into bio inactive form. Therefore, several types of its extract with different compositions of bioactive components have been developed, and their efficacy has been observed and evaluated in numerous studies [58]. The main role (ROS), inhibition of lipoprotein oxidation and reduction of blood sugar induction by antioxidant enzymes. Furthermore, it has shown a suppressive effect on H. pylori-induced gastric inflammation in vivo , and an antitumorigenic effect by promoting apoptosis and inducing cell cycle arrest . Allicin and allyl-methyl plus methyl-allyl thiosulfin from acetone extracts of Allium sativum have limited the growth of H. pylori in in vitro studies . The extract of Allium sativum has been observed to have an antioxidant effect by eliminating reactive oxygen species[59].

CISTUS LAURIFOLIUS:-

Flavonoids are one of the most important components of the human diet, with a key role in organisms and an important responsibility in many biological activities, especially antioxidants. Due to their limited availability and high cost, the rapid synthesis of polyoxygenated flavones, has been developed from accessible and inexpensive flavanones. According to the methoxylation and bromination protocol, 30 -demethoxysudachitin, a limited flavone with antimicrobial activity against H. pylori, was engineered. Most research on flavonoids has been done with an extract of Cistus laurinols. It was shown in antimicrobial activity tests against H. pylori that 3'-demethoxyudachitin and Suda chitin were the most active compounds. o Similar studies have shown that the chloroform extract of Cistus laurinols has the great anti-H. pylori activity. According to this research, the isolated flavonoids can be used as additive ingredients for the standard treatment of H. pylori [60]. HQ et al. different levels of anti-H. pylori activity were observed several isoflavones [61]. The experiment evaluated several series of metronidazole-flavonoid extracts that were used for this Antimicrobial activity against H. pylori [62].

ZINGIBER OFFICINALIS AND ZINGIBER ZERUMBET: -

Zingiber officinalis is known as ginger, which is consumed as a flavouring agent. Plant extract has shown antitumor effects on colon cancer cells by inhibiting their growth, increasing DNA synthesis and inducing apoptosis. In addition, the main pungent phenolic compound of Zingiber officinalis is 6-gingerol, which has several pharmacological activities. Zingiber officinalis extracts containing gingerols play a key role in the inhibition of prostaglandin E2 (PGE2) [63]. On the other hand, active phenolic compounds such as gingerol and zingerone have

a significant impact on the inhibition of H + ATPase. K+ parietal cells. Therefore, the activity of gingerol and zingerone plays a very important role in inhibiting the proton pump and reducing gastric acid secretion. It also has a protective effect against ulcers caused by H. pylori. Jiang et al. demonstrated the therapeutic effect of Zingiber officinalis as a natural antioxidant against gastric ulcers [64]. They reported limitations of free extracts of Zingiber officinalis, such as lower solubility in gastric juices, which will decrease further when passing through the higher pH regions of the duodenum or ileum in rats; many drugs have a limited transit time of less than two to four hours in the stomach; whatever part is dissolved will be absorbed instantly, because the extract of Zingiber officinalis shows rapid absorption, therefore, the local therapeutic effect cannot be well achieved [65]. Furthermore, Sidahmed et al. showed that of Zingiber zerumbet has a major role in gastroprotective activity against the ethanol-induced gastric ulcer model in rats. They showed that pretreatment with zerumbone or omeprazole in rats significantly reduced the formation of ulcer areas compared to the ulcer control group. Furthermore, pretreatment with omeprazole at 20 mg/kg body weight ($p < 0.05$) prevented ulcer formation by 76.77%, while pretreatment with zerumbone at 5and10 mg/kg body weight prevented ulcer formation by 75.59% and 88.75%, respectively. On the other hand, zerumbon and its gastroprotective mechanisms have not been tested against other ulcer models; therefore, other mechanisms may be involved and their impact needs to be studied and elucidated [66

CAMELLIA SINENSIS (GREEN TEA POLYPHENOLS):-

Nowadays, Camellia sinensis is one of the most commonly used beverages. The chemo preventive effects of Camellia sinensis depend on its activity as an antioxidant, but also on its molecular regulatory functions on cellular growth, development, and apoptosis; and a selective improvement in the function of the intestinal bacterial flora. Between the numerous constituents of green tea, polyphenols and epigallocatechin gallate (EGCG) suppress tumour necrosis factor-alpha (TNF-α) gene expression. On the other hand, the urease of H. pylori is crucial for its colonization, and investigations concentrated on Camellia sinensis extract demonstrated the inhibitory activity of this enzyme. That results in the inhibition of bacterial colonization. Numerous similar studies demonstrated the inhibitory effect of Camellia sinensis extract by increasing cell vacuolation by vacuolating cytotoxin A (vacA) and urea conduction in H. pylori infection. Consequently, it could pursue anti-H. pylori activity in vivo In 2008, Rao et al. reported on the gastroprotective activity of 50% ethanolic extract of merit fruit (FGE) in gastric ulcer models in ratsFGE was administered per mouth (50, 100, and 200 mg/kg body weight), twice daily for five days for prevention from ethanol (EtOH), pylorus ligation (PL), and cold restraint stress (CRS), which induced ulcer formation. It demonstrated a dose-dependent suppression of ulcer, and it had a significant role in preventing the oxidative damage of gastric mucosa by preventing lipid peroxidation and significantly reducing in H+/K+-ATPase and superoxide dismutase. Their results showed that F. glomerate has an important gastroprotective effect that might be consequent to the gastric defence factors [67].

CURCUMA LONGA AND ARTEMISIA ASIATICA:-

Medicinal plants with antioxidant and anti-inflammatory activities have been shown to have an effect in gastroesophageal reflux disease (GERD). Medicinal plants and herbal preparations that have antioxidant and anti-inflammatory mechanisms include Curcuma longa, Panax quinquefolium, Artemisia asiatica and Lonicera japonica. In addition, other mechanisms include: negative regulation of genes encoding proteins that play a key role in acute inflammation, including intercellular adhesion molecule 1 (ICAM-1) and cytokine-induced neutrophil chemoattractant-2-beta (CINC-2-2) beta) (Panax quinquefolium); improving mucus and stomach function (Morus alba, Curcuma longa); Stomach acid reducers, such as Curcuma longa, Morus alba and acidinol syrup, increase tonic contractions of the lower oesophageal sphincter (LES) (Salvi,STW)and inhibit proinflammatory cytokines IL-1b and TNF-a (STW [68]. It is important to mention that a study on mice pretreated with compounds of Artemisia asiatica (DA-9601) reduced the overall oesophageal wall density and ulcer volume beyond the ranitidine group. Manhattanite showed in his study on mice that Curcuma longa rhizome plays a protective role in the formation of acid reflux esophagitis (ER), but was not effective in preventing chronic acid However, its combination with dimethyl sulfoxide as an antioxidant compound reduced the severity of the esophagitis ulcer index to approximately that of lansoprazole. On the other hand, lansoprazole tended to increase the severity of all histopathological changes in control and curcumin-treated animals. Therefore, it seems that the antioxidant and anti-inflammatory activities of curcumin play a major role in its beneficial effects in GERD [69]

HERB–DRUG INTERACTIONS :-

increasing use of herbal dietary supplements worldwide, the number of adverse events and drug interactions is increasing. Interactions can occur between an herbal dietary supplement and a medication by a pharmacokinetic or pharmacodynamic interaction. A pharmacokinetic interaction results from the use of the same mechanism of absorption, distribution, metabolism, or secretion between an herbal dietary supplement and a co-administered drug, resulting in a change in the blood drug concentration. and its pharmacological action. A pharmacodynamic interaction involves a direct effect on the mechanism of action of a co-administered drug without changing the drug concentration, but only by antagonizing or worsening the clinical effects of the drug Allium sativum extract reduces the concentration of drugs transported by P-gp, such as digoxin, doxorubicin, rosuvastatin, and verapamil. The most studied interaction with Allium sativum is with warfarin, although this has not been confirmed in controlled clinical trials. It also inhibits platelet aggregation, so it should be used with caution in patients with coagulation disorders or on anticoagulant treatment. Zingiber officinalis prolongs bleeding time by inhibiting thromboxane synthetase, but this has not been confirmed in a clinical trial [70]. Ginkgo biloba can increase the risk of bleeding, especially in combination with anticoagulant drugs, due to inhibition of platelet aggregation. Ginkgo biloba flavonoids have antiplatelet activity, but have not affect on blood coagulation or platelet function in humans [71]. In combination with NSAIDs, it can cause serious bleeding [72]. Panax ginseng induces cytochrome P450 3A4 (CYP3A4), which decreases the effectiveness of calcium channel blockers, some antihypertensive drugs and statins, and some. antidepressants Panax ginseng has hypoglycaemic activity in patients with diabetes and can cause headaches, tremors and manic behaviour in patients treated with phenelzine. Green tea extract has been shown to increase the concentration of simvastatin [73] or inhibit drug transporters, organic anion transporter protein 1a1 (OATP1A1) and anion transporter protein 1a12 (OATP1A2), which are responsible for the transport of fluoroquinolones, beta-blockers and imatinib. Among conventional anti-ulcer treatments, it is important to note the many drugs' interactions cimetidine. Studies have reported clinically significant interactions with warfarin, phenytoin, diazepam, chlormethiazole, propranolol, lidocaine, and a variety of other drugs in addition, cimetidine may increase the level or effect of green tea through inhibition of CYP1A2, which in turn inhibits hepatic oxidative metabolism of caffeine [73].

CONCLUSIONS:-

The combination of herbal products and standard anti-ulcer medications may have a synergistic effect against H. pylori and gastric ulcers and improve outcomes for patients with gastric ulcers. With only a few human studies, it is suggested that more clinical trials with larger samples be conducted on the efficacy and safety of medicinal plants with antiulcer activity. It would also be beneficial to design studies to further investigate and elucidate the mechanisms of action of medicinal plants used to treat or prevent peptic ulcer disease. Finally, herbal products used for medicinal purposes require licensing to improve their safety and quality and to ensure that randomized controlled trials support claims for their potential efficacy. While reports of interactions between medicinal plants and drugs are increasing, there is still a research gap in this area and no action has been taken to address it. Therefore, pharmacists and physicians should be particularly aware of the risks associated with the use of herbal medicinal preparations, whether used alone or in combination with other medicinal plants or standard conventional therapies.

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