A REVIEW ON ACID PEPSIN DISEASES: HISTORY, EPIDEMIOLOGY, ANTACIDS AND PLANT-BASED ALTERNATIVES

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ABSTRACT

Today estimate that about 80% of people in growing nations still believes on traditional medicine based chiefly on species of plants and animals for their basic well-being. Herbal medicines are presently in demand and their acceptance is growing day by day. About 500 plants with medicinal use are mentioned in ancient literature and around 800 plants have been used in indigenous systems of medicine. The World Health Assembly (WHA) has acquired several proposals depicting awareness to the aspect that a huge segment of the community in many growing nations still hopes on traditional medicine. Addition of verified traditional medicaments into national drug policies and regulatory measures is proposed. Understanding of their clinical, pharmaceutical and commercial value is still emerging, although this changes extensively between nations. This manuscript aims at a systematic brief review on few herbal drugs/dietary nutrients and their extracts having potent action (antiulcerogenic, gastroprotective and anti-inflammatory activity) on gastric disorders and their published data on effectiveness of these diseases. Literature (pharmacological investigations) for concerning medicinal plants and their chemical constituents/extracts were compiled from major databases and academic publishers, such as PubMed, Elsevier, etc. Various numbers of medicinal plants and their extracts are reported to have anti-ulcer activity, gastro-protective activity, and antibacterial activity comparable to the existing treatment (antulcer and antacids drugs) or sometimes even better in potency. Studies and screening of easily available plants with a well-defined strategy may help to develop effective new drugs or treatment giving permanent relief against acid peptic disorders without side effect.

Keywords: Acid-pepsin disorders, Traditional medicines, Amlapitta, Gastro-protective.

INTRODUCTION

Faulty dietary factors, living style and sequel of faulty drug or drug abuse habits lead to the gastric complaints like heartburn, reflux of food taken, abdominal pain, loss of appetite, nausea and vomiting. These gastric complaints mimic the symptoms of GERD. Gastro Esophageal Reflux Disease (GERD) is a complex disorder caused by the reflux of gastric contents into the esophagus either with or without complications. It negatively affects the quality of life and leads to serious complications like Barret’s esophagus, esophageal strictures and adenocarcinoma. GERD is accompanied with increased frequencies of inadequate activity and skipped work, introducing an economic load for both preventive medicine systems and business person alike.

Epidemiology & factors responsible for emergence

In the reflux group, irritable bowel syndrome and dyspepsia were the highest functional disorders. In a pan-Indian study on IBS, 37% of 1,301 patients reported heartburn. In a previous study from Mumbai, the prevalence of dyspeptic symptoms was 30%, while among subjects with IBS, the prevalence of dyspepsia was 58%. The reason for the increasing prevalence of GERD is not entirely clear, but it appears to be correlated with the increasing prevalence of obesity in many countries and, perhaps, to other dietary factors. Recent studies indicate that its prevalence in India ranges between 8-20% which is comparable to that in the west. This study of India reports inconsistent association with BMI, age, sex, alcohol, smoking and diet. On the other hand, other studies have found female gender, large fatty diet shorter dinner to bed time and younger age to be significant risk factors. H. pylori infection is virtually always associated with a chronic active gastritis. H. pylori organisms grow in the mucus secreting cells of the stomach lining and create ulcers or erosions or inflammation in gastric mucosa. Aspirin and other non-steroidal anti-inflammatory drugs like Diclofenac, Ibuprofen etc. inhibit cyclo-oxygenase, decreases prostaglandin E and decreases mucosal blood flow resulting in damage of gastric or duodenal mucosa. Pepsin and hydrochloric acid cause damage to the stomach or duodenum, if the stomach’s protective system is altered or damaged. Till now there are no clear findings of involvement of H. Pylori infection in Non-ulcer dyspepsia.

Historical background

The real references in Ayurveda about this clinical condition seems available, from the period of Samhithas itself. Acharya Charaka has not mentioned Amlapitta as a separate entity, but the treatise is contributing with many scattered references of Amlapitta by the name. Sushruta has mentioned a condition “Amlika” (resulting from excessive use of Lavana—salt) which resembles one of the symptoms of Amlapitta. Kasyapa explained the variants of Amlapitta as per the doshas, with the peculiarity in the symptoms in an enhanced manner. Madhava nidana is the first text available which gives importance to Amlapitta and describes its aetio-pathogenesis and symptoms in detail.
Antacid and alternative agents as therapy for acid peptic diseases

**Symptoms and diagnosis**

Upper abdominal pain which may or may not be related to food, Gastro-oesophageal reflux and heartburn, Anorexia, nausea, vomiting, Early repletion or satiety after meals, A sense of abdominal distension or bloating and flatulence. The diagnosis of dyspepsia is challenging because patients often exhibit changing symptoms and because characterization of the symptoms provides little information about the nature of the underlying physiologic abnormality. Diagnosis of acid-related disorders is mainly based on the clinical features, histopathology. The initial investigation may include routine hematological (full blood count and ESR) and biochemical (urea and electrolytes, liver function tests, serum calcium, phosphate) tests. Iron deficiency anemia suggests mucosal blood loss, whereas vit.B12 deficiency results from small intestinal, gastric or pancreatic disease. Severe vomiting or diarrhea elicits electrolyte disturbances, acid-base abnormalities and elevated blood-urea nitrogen. Luminal contents can be examined for diagnostic clues. Stool samples are cultured for bacterial pathogens or examined for leukocytes or parasites. Gastric Juice Analysis gives the concentration of the acid in gastric juice. Hyperchlorhydria, Hypochlorhydria and Achlorhydria can be easily diagnosed by this test. Duodenal Aspirates can be examined for parasites or cultured for bacterial overgrowth. Oesophageal pH testing is done for refractory symptoms of acid reflux. Urease test, ELISA test, Breath test and stool antigen test are performed for the diagnosis of *H. pylori*. Endoscopy evaluates the oesophagus, stomach and duodenum.

**ANTIULCEROUS DRUGS AND THEIR ADVERSE EFFECTS**

Description of various treatment groups of acid peptic diseases is explained in table 1. Adverse events associated with antacids are dose-related. Large doses of calcium-containing antacids can cause the milk-alkali syndrome, which consists of hypercalcemia, renal insufficiency and metabolic alkalosis. Magnesium-containing antacids can cause diarrhea if administered alone and may lead to hypermagnesemia in patients with renal insufficiency. Aluminum-containing antacids can cause encephalopathy and osteomalacia in end-stage renal patients and calcium carbonate is the preferred antacid in this population. Although specific interactions with medications are unusual, all antacids can produce drug interactions by changing gastric or urinary pH by altering rates of absorption, bioavailability, renal elimination and drug dissolution, or by reducing gastric acid hydrolysis of drugs. The side effects of most common used treatment proton pump inhibitors are: Headache, Diarrhea, Constipation, Abdominal pain etc. PPIs may increase the risk of clostridium difficile infection of the colon. Long-term use may increase the risk of osteoporosis – related fractures of the hip, wrist, or spine. Prolonged use also reduces absorption of vitamin B12 and causes hypomagnesemia. Analysis of patients taking PPIs for long periods of time showed an increased risk of heart attacks.

Eradication of *H. pylori* is almost impossible even by administrating ‘triple therapy’, which is a combination of proton pump inhibitor and antibiotics. One of the major reasons for the *H. pylori* treatment failure is the development of drug resistance. In India, approximately 85% of clinical strains of Kolkata are resistant to 5 mg/l metronidazole. Similarly, 91 and 96% of *H. pylori* strains from Mumbai and Hyderabad respectively showed resistance to clarithromycin; 73% of Mumbai and 80% strains of Hyderabad are resistant to amoxicillin. Frequent emergence of antibiotic resistance in microbial pathogens encourages the use of natural agents as alternative therapies.

Relief offered by present treatment is mainly symptomatic & for short time. Hence, there is a need to search and access the effect of the natural drug materials.

Articles published in different peer reviewed journals were analyzed. Pubmed, Academic journals, Elsevier, Google scholar, Google were searched with specific keywords along with print journals, reports and some textbooks. Ayurveda or plants or herbs or Shatavari or Anulom or Shuni or Shalini or Vamshlochan or Dalchini or Gokshur or Patol or Kamshand or Pippali or Chandan or Dhanu or Teijatra or Yashtimadhu or Traditional medicines or Alternative medicines or GERD or acid peptic or dyspepsia or gastritis or gastroprotective activity or anti-inflammatory or anti Helicobacter pylori or anti ulcerous or anti secretagogue or experimental, biochemical and histological study as title, abstract and keywords. There was no restriction in language and publication date. Medicinal plants, Herbs and dietary nutrients and spices that have been evaluated by various researchers to achieve a favorable outcome in gastric diseases have been shown to possess these activities (anti ulcer effects, gastro-protective, Anti H pylori activity). (Table 2)

**DISCUSSION**

Because of the worldwide health problem that gastric diseases represent, it is necessary to invent new drug and advancement that allow better control on gastric disorders. In this review, we have compiled the pharmacological information on fourteen medicinal plants taking account of their properties useful in acid peptic diseases. The detailed information on the drugs having potent action on gastric disorders has been summarized in Table 2. Amongst the various groups of phytochemical constituents, in majority, the methanol extracts have been found effective gastro protective, anti ulcer activity, anti *H pylori* effect. It is not possible to single out the most effective plant or phytochemical constituent. Use of plant extracts is increasing to treat various diseased states, with somewhat little understanding in respect of their modes of action. Moreover, pharmacological analysis on these medicinal plants and phytochemical component/ingredients may provide practical help for the development of new antitulcerous, gastroprotective drugs. With the help of modern science, the efforts should be made to discover the active ingredients from medicinal plants which still have to be isolated. Multidimensional approach should be followed i.e. searching should be for multiple compounds acting synergistically & those hit multiple targets in different pathways instead of single drug/component. The etiologies of these diseases are not clearly known. It results probably due to imbalance between aggressive (acid, pepsin, bile, & *H. pylori*) and the defensive (gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide, innate resistance of mucosal cells) factors.

The significance of *H. pylori* infection as a supporter to ulcer generation and regression has been identified. Commonly in gastric ulcer, acid release is standard or minimal. In duodenal ulcer, acid release is high in 50% of patients but adequate in rest 50%. Even the standard routine rate of acid secretion may be the basis of ulceration in the ruptured mucosa when some gastroprotective elements are disoriented. The current manner to command on gastric ulceration is to restrict gastric acid secretion, to support gastro-immunity, limit necrobiosis, and trigger epithelial cell multiplication for productive repairing.

An interpretation of the process and regulation of gastric acid secretion will clarify/explicate the position of antisecretory drug maneuver.

- The terminal enzyme H^+\text{K}^-\text{ATPase (proton pump)} which secretes H^+ ion in the apical canaliciuli of parietal cells can be
activates by histamines, Ach, and gastrin acting via their own receptors located on the basolateral membrane of these cells.

- Out of the three physiological secretagogues - Histamine (acting through H2 receptors) plays the dominant role, because the other two (Gastrin and Ach) act directly and to the greater extent indirectly by releasing histamine from paracrine entero-chromaffin like cells (histaminocytes) located in oxyntic glands.

- Prostaglandins have been ascribed a “cytoprotective” role in the gastric mucosa by augmenting mucus and bicarbonate secretion, as well as other actions. PGE2, produced by gastric mucosa, inhibits acid secretion by opposing cAMP generation (in parietal cells) and gastrin release (from antral cells). Aspirin produces direct erythrogenic effect and laminal injury by interrupting with prostaglandin synthesis and escalates acid secretion by escalating the H+ ion shift back outflow of H+ ions.

Because of antihistaminic, anticholinergic and antisecretory effects, these extract exhibit gastro-protective action against stress-induced ulceration which may be an indication of its effect on prostaglandin production. Also in experiments performed on extracts of single drugs, there found reduced values of lesion index as compared to the control group suggesting its potent cytoprotective effect which indicates towards gastro-immunity.

After treatment with mixture of Ayurvedic medicines (Glycyrrhiza glabra, Terminalia chebula, Piper longum, and Shankha bhasma), secretory status of Brunner’s glands and β-glucuronidase enzyme activity improved which indicate toward protection against duodenal ulcer.

At present, researchers are searching for bioactive compounds to treat bacterial infections due to an increase in drug resistance. Numerous reports have been published on various natural compounds and food supplements that inhibit H. pylori growth, adhesion or toxin secretion and the aim of these studies was to explore an existing natural compound, which may act against H. pylori. For example, results of study on piperine suggest that due to the suppression of the biosynthetic regulator gene fbpA (integral membrane component of the export apparatus) and flagellar hook gene fipE because of piperine treatment may lead to the reduction in motility confirmed by the motility test. Due to decreased motility of H. pylori, the organism may be less attracted towards gastric epithelial cells, which results in the less adhesion compared with the untreated bacteria. Daily consumption of black pepper, which is comprised of 5–9% piperine, reduces one’s chance of infection and of developing gastric cancer caused by H. pylori. Application of antibiotic coupled with antioxidant treatment may be very useful in controlling the pathogen growth and associated inflammation. In study on Amalaki, Ethanolic extract of E. officinalis is highly effective in controlling growth of H. pylori in vitro with MIC ranging from 0.91 to 1.87 µg/µl. The TLC separation followed by detection spray indicates that the bioactive spot is having mixed properties of both phenolics and essential oils. The extract also retained high level of antioxidant properties that makes it suitable for therapeutic use against gastric ulcer.

H2 antagonists block histamine induced gastric secretion. The only significant in vivo action of H2blockers is marked inhibition of gastric secretion. All phases (basal, psychic, neurogenic, gastric) of secretion are suppressed more completely. Secretory responses to not only histamine but all other stimuli (Ach, gastrin, insulin, alcohol, food) are attenuated. This reflects the permissive role of histamine in amplifying responses to other secretogogues. Plant extracts are some of the most attractive sources of new drugs and have been shown to produce promising results in the treatment of gastric ulcers.

According to the climatic and geographic conditions, special medicinal plants grow and many of them have unique medicinal properties. Today estimate that about 80% of people in developing countries still rely on traditional medicine based largely on species of plants and animals for their primary health care. About 500 plants with medicinal use are mentioned in ancient literature and around 800 plants have been used in indigenous systems of medicine.

The World Health Assembly (WHA) has acquired several proposals depicting awareness to the aspect that a huge segment of the community in many growing nations still hopes on traditional medicine. Addition of verified traditional medicaments into national drug policies and regulatory measures is proposed. Understanding of their clinical, pharmaceutical and commercial value is still emerging, although this changes extensively between nations.

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**TABLE 1: DIFFERENT GROUPS OF ANTIULCEROUS DRUGS AND THEIR DESCRIPTION WITH SUITABLE EXAMPLES**

<table>
<thead>
<tr>
<th>Description</th>
<th>Group</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutralization of gastric acids</td>
<td>Antacids</td>
<td>Systemic- Sodium bicarbonate, Sodium citrate, Non-Systemic-Magnesium hydroxide, Magnesium trisilicate, Aluminum hydroxide gel, Magaldrate</td>
</tr>
<tr>
<td>Reduction of gastric acid secretion</td>
<td>Prokinetic agents</td>
<td>Metoclopramide and Domperidone</td>
</tr>
<tr>
<td></td>
<td>H2 Receptor Antagonists</td>
<td>Cinetidine, Ranitidine, Famotidine</td>
</tr>
<tr>
<td></td>
<td>Proton Pump Inhibitor (PPI)</td>
<td>Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole</td>
</tr>
<tr>
<td></td>
<td>Anti-Cholinergics</td>
<td>Pirenzpine</td>
</tr>
<tr>
<td></td>
<td>Prostaglandin Analogues</td>
<td>Misoprostol</td>
</tr>
<tr>
<td>Anti- Helicobacter pylori drugs</td>
<td>Ulcer protectives</td>
<td>Sucralfate, colloidal bismuth subcratate</td>
</tr>
</tbody>
</table>

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TABLE 2: DESCRIPTION OF PLANTS WITH PROVEN PHARMACOLOGICAL ACTION OF THEIR EXTRACTS

<table>
<thead>
<tr>
<th>Plants</th>
<th>Parts used</th>
<th>Extract / Active principle</th>
<th>Proven pharmacological action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eletraria cardamomum (Eléchi)</td>
<td>Fruit</td>
<td>Methanolic extract</td>
<td>Gastro protective&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bambusa arundinacea (Vamshlochana)</td>
<td>Leaves</td>
<td>Methanol extract</td>
<td>Antiulcer activity, Anti-Inflammatory effect&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cinnamomum Zeylanicum (Dalcchini)</td>
<td>Bark</td>
<td>Ethanol methylene chloride extracts</td>
<td>Anti-secretagogue, antiulcer&lt;sup&gt;3&lt;/sup&gt;-anti-inflammatory &amp; wound Healing properties&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
<tr>
<td>Terminalia chebula (Haritaki)</td>
<td>Fruit</td>
<td>Water extract, hydroalcoholic extract</td>
<td>Anti-bacterial activity&lt;sup&gt;17&lt;/sup&gt;, Anti-ulcerogenic activity&lt;sup&gt;20&lt;/sup&gt;</td>
</tr>
<tr>
<td>Emblica officinalis (Amalaki)</td>
<td>Fruit Pulp</td>
<td>Methanolic extract ethanolic extract</td>
<td>Antiulcerogenic effect&lt;sup&gt;19&lt;/sup&gt;, Anti-Helicobacter pylori&lt;sup&gt;21&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tribulus terrestris (Gokshur)</td>
<td>Fruit</td>
<td>Methanolic extract</td>
<td>Analgesic and anti-inflammatory&lt;sup&gt;40&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trichosanthes dioica (Patol)</td>
<td>Leaves</td>
<td>Methanolic extract</td>
<td>Antiulcer activity&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td>Piper nigrum (Pappali)</td>
<td>Fruit</td>
<td>Piperine</td>
<td>Inhibitory action on H pylori growth and adhesion&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>Santalum album (Chandana)</td>
<td>Stem</td>
<td>hydro-alcoholic extract</td>
<td>Antibacterial activity against H. pylori&lt;sup&gt;34&lt;/sup&gt;, anti-ulcer activity&lt;sup&gt;34&lt;/sup&gt;</td>
</tr>
<tr>
<td>Coriandrum sativum (Dhaniva)</td>
<td>Seeds</td>
<td>Hydroalcoholic extract</td>
<td>Anti-ulcer activity against stress and aspirin-induced ulcer&lt;sup&gt;45&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cinnamomum tamala (Tejpatra)</td>
<td>Leaf</td>
<td>-</td>
<td>Gastroprotective activity&lt;sup&gt;37&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glyceritiza glabra (Yashinadhya)</td>
<td>Root</td>
<td>Aqueous extracts</td>
<td>Antiadhesive effects against H. Pylori&lt;sup&gt;38&lt;/sup&gt;</td>
</tr>
<tr>
<td>Asparagus racemosa</td>
<td>Fresh Roots</td>
<td>Methanolic extract</td>
<td>Gastro-duodenal ulcer protective&lt;sup&gt;35&lt;/sup&gt; &amp; anti-ulcer activity&lt;sup&gt;20&lt;/sup&gt;</td>
</tr>
<tr>
<td>Zingiber officinale (Sunhi)</td>
<td>Rhizome</td>
<td>Aqueous extract phenolic acids</td>
<td>HAKER inhibitory activity&lt;sup&gt;36&lt;/sup&gt;- anti-ulcer&lt;sup&gt;42&lt;/sup&gt;, gastro protective&lt;sup&gt;43&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CONCLUSION

Acid-pepsin disorders are a burning issue of today’s society with palliative need only. Uses of chemical-based medicine have various local & systemic side effects and on longer use exaggeration of symptom of existing and precipitation of new diseases occurs. Herbal medicines which formed the basis of health care throughout the world since the earliest days of mankind are still widely used and have considerable importance in international trade. Search for natural drug possess easily available, cost effective, high efficacious treatment with minimal side effect and permanent relief of disease.

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