PATHOPHYSIOLOGY, DRUG OFFERED AND CURRENT APPROACHES OF TRADITIONAL SYSTEM OF MEDICINE IN THE TREATMENT OF PEPTIC ULCER

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ABSTRACT

Peptic ulcer generally occurs when there is an imbalance between aggressive gastric factors (acid, pepsin, *Helicobacter pylori*, refluxed bile salts) and defensive mucosal factors (gastric mucosal barrier, bicarbonate secretion, rapid cell turnover, high blood flow). The treatment of peptic ulcer is directed against reduction of aggressive factors or enhancement of mucosal defense of stomach and duodenum with cytoprotective agents. More recently, the role of mucosal factor in peptic ulceration has received much attention and the term "Cytoprotection" was first introduced by Andre Robert in 1979. In general it can be said that there is a plethora of mechanisms of gastric cytoprotection, their relative importance and interdependence being far from clarity. This itself is a point that gastric cytoprotection may be a multifactorial phenomenon. The present paper enumerates the various drug offered used in the treatment of peptic ulcer. Emphazises are made to co-relate the importance of various traditional system of medicine used.

Key-Words: Peptic ulcer, traditional system, allopathic medicine

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INTRODUCTION

Peptic ulcer disease refers to a group of disorders characterized by circumscribed lesions of the mucosa of the upper gastrointestinal tract (especially the stomach and duodenum). The lesions occur in regions exposed to gastric juices.

Epidemiology

Peptic ulceration is an increasing cause of morbidity. Geographically, though the disease is prevalent throughout the world, incidence is more severe in U.K., U.S.A., and tropical countries like India. It is estimated that approximately 10-15% of world's population has peptic ulcer, with about 16 million cases reported in the United States. There are over 4 million hospitalization / year with about 1.5% of them ending in death.

Incidence

- Peptic ulcer disease is the most common disorder of the upper gastrointestinal tract.
- Duodenal ulcers affect roughly 4-10% of the United States population; gastric ulcers occur in approximately 0.03-0.05% of the population.
- Nearly 80% of peptic ulcers are duodenal; the others are gastric ulcers.
- Most duodenal ulcers appear in people between the ages 20 and 50 years; onset of gastric ulcers usually occurs between the ages 45 and 55 years.
- Duodenal ulcers are twice as common in men as in women; gastric ulcers affect men and women equally.
- Approximately 10-20% of gastric ulcer patients also have concurrent duodenal ulcer.

Manifestations

- Duodenal ulcers almost always develop in the duodenal bulb (the first few centimeters of the duodenum). A few, however, arise between the bulb and the ampulla.
- Gastric ulcers form most commonly in the antrum or at the antral-fundal junction.
- Less common forms of peptic ulcer disease
    - Stress ulcers result from serious trauma or illness, major burns, or ongoing sepsis. The most common site of stress ulcer formation is the proximal portion of the stomach.

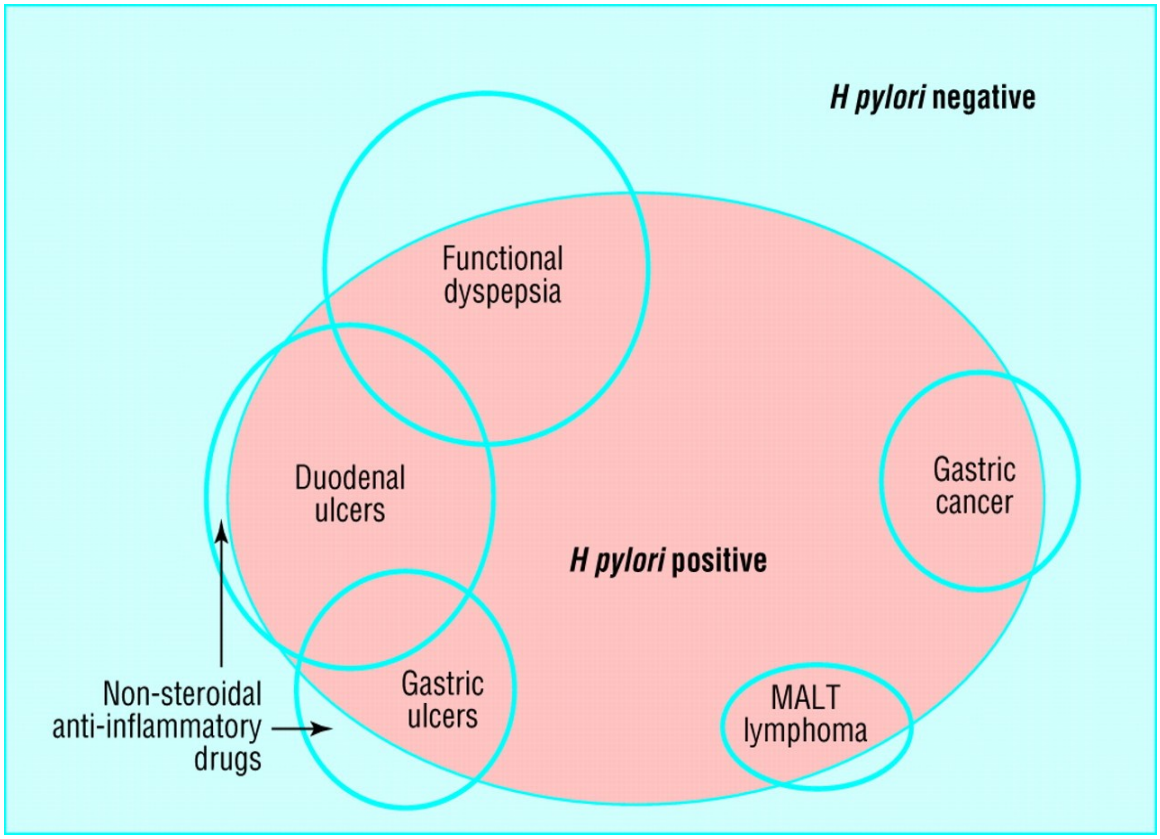
- Zollinger – Ellison syndrome is a severe form of peptic ulcer disease in which intractable ulcers are accompanied by extreme gastric hyperacidity and at least one gastrinoma (a non-beta islet cell tumor of the pancreas or another site).
- Stomal ulcers (also called marginal ulcers) may arise at the anastosis or immediately distal to it in the small intestine in patients who have undergone ulcer surgery and have experienced subsequent ulcer recurrence after a symptom-free period.
- Drug ulcers occur in patients who chronically ingest substances that damage the gastric mucosa, such as non-steroidal anti inflammatory drugs (NSAIDs)

Etiology

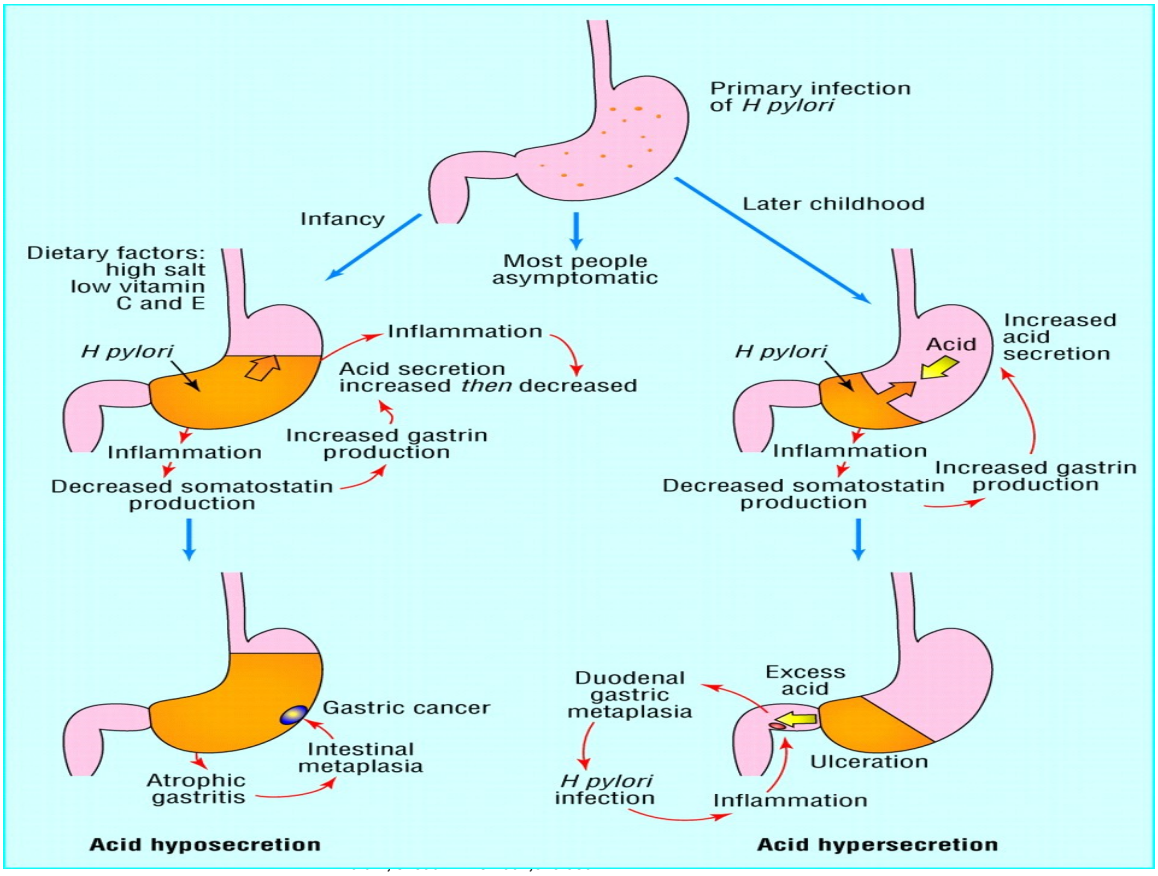
The precise cause of peptic ulcer disease has not been defined. However, certain factors are known to increase the risk of developing the disease. Various factors involved are

- Genetic factors
- Smoking
- Nonsteroidal anti-inflammatory drugs
- Alcohol
- Coffee
- Corticosteroids
- Associated disorders
- Advanced age
- *Helicobacter pylori*
- Psychological factors

Relation of *H Pylori* infection to upper gastrointestinal conditions


H pylori negative
Functional dyspepsia
Duodenal ulcers
H pylori positive
Gastric cancer
Gastric ulcers
MALT lymphoma
Non-steroidal anti-inflammatory drugs

With acid hyposecretion (left), the main effect of *H pylori* gastritis affecting the gastric body is to suppress parietal cells, leading to low acid secretion, which is associated with gastric cancer. With acid hypersecretion (right), antral *H pylori* gastritis increases acid secretion by suppressing somatostatin and elevating gastrin release, increasing the risk of duodenal ulceration. Orange areas indicate extent and location of gastritis



Pathophysiology

Ulcers develop when an imbalance exists between factors that protect the gastric mucosa and factors that promote mucosal corrosion.

Protective factors

- Normally, the mucosa secretes thick mucus that serves as barrier between luminal acid and epithelial cells. This barrier slows the inward movement of hydrogen ions and allows their neutralization by bicarbonate ions in fluids secreted by the stomach and duodenum.

- Alkaline and neutral pancreatic biliary juices also help buffer acid entering the duodenum from the stomach.
- An intact mucosal barrier prevents back-diffusion of gastric acids into mucosal cells. It also has the capacity to stimulate local blood flow, which brings nutrients and other substances to the area and removes toxic substances (e.g. Hydrogen ions). Mucosal integrity also promotes cell growth and repair after local trauma.

Corrosive factors

Peptic ulcer disease reflects the inability of the gastric mucosa to resist corrosion by irritants,such as pepsin, hydrochloric acid (HCl) and other gastric secretions.

- Exposure to gastric acid and pepsin is necessary for ulcer development.
- Disrupted mucosal barrier integrity allows gastric acids to diffuse from the lumen back into mucosal cells, where they cause injury.

CONVENTIONAL DRUGS

Allopathic system of medicine

Peptic ulcer patients usually are treated with antacids, histamine (H_2 antagonist), or both; other drugs are added as necessary. Drug regimens that suppress nocturnal acid secretion are found to result in the highest duodenal ulcer healing rates. Drug therapy typically provides prompt symptomatic relief and promotes ulcer healing within 4-6 weeks.

Sl. No.	Drugs used for Peptic Ulcer	Mechanism of action	Precautions and monitoring effects	Significant interactions	Adverse reactions
1.	Antacids 1. Systemic antacids Sodium bicarbonate 2. Non-systemic antacids a. Magnesium hydroxide b. Aluminium hydroxide	Neutralize gastric acid and thus reduce concentration and total load of acid in the gastric contents. By increasing the gastric pH, they inhibit pepsin activity. Additionally, they strengthen gastric mucosal barrier.	➢ Calcium carbonate and magnesium-containing antacids should be used cautiously in patients with severe renal disease. ➢ $NaHCO_3$ is contraindicated in patients with hypertension, CHF, severe renal disease, edema. ➢ Used with caution in elderly and renally impaired patients. ➢ Aluminium containing antacids should be used cautiously in patients with dehydration or intestinal obstruction. ➢ Combination of $CaCO_3$ and alkaline substance like $NaHCO_3$ and milk may cause milk-alkali syndrome. ➢ Low- sodium antacids obviate fluid retention problem in hypertension and heart disease.	➢ Bind with tetracycline, inhibit its absorption and reduce its therapeutic efficacy. ➢ May destroy the coating of enteric-coated drugs, leading to premature drug dissolution in the stomach. ➢ May interfere with absorption of drugs like	With systemic antacids gastric perforation by sodium bicarbonate, systemic alkalosis and edema due to sodium retention may occur. With non-systemic antacids constipation, diarrhea, CNS depression, hypercalcemia,

			➢ Chronic administration of $CaCO_3$ – containing antacids should be avoided because of hypercalcemia and calcium ion stimulation of acid secretion. ➢ Encephalopathy of tissue deposition of aluminium only occurs in dialysis patients receiving aluminium hydroxide for control of hyperphosphatemia. ➢ Hypophosphatemia and osteomalacia can occur with long-term use of aluminium hydroxide, but can occur with short- term use in severely malnourished patients, such as alcoholics.	cimetidine, ranitidine, digoxin, isoniazid, anticholinergics, iron products, and phenothiazines. ➢ May reduce the therapeutic effects of sucralfate.	osteomalacia, encephalopathy is common
2.	H_2 receptor antagonist Cimetidine Ranitidine Famotidine	Competitively inhibit action of histamine at parietal cell receptor sites, reducing the volume and hydrogen ion concentration of	➢ Ranitidine must be used cautiously in patients with hepatic impairment. Hepatoxicity may occur during intravenous administration. ➢ Cimetidine may cause hematologic disorders as thrombocytopenia,	➢ Cimetidine binds to cytochrome P-450 and interfere with metabolism of	Skin rashes, hepatotoxicity, gynecomastia, muscle pain and granulo cytopenia.

	Nizatidine	gastric acid secretions.	agranulocytosis, and aplastic anemia. ➢ Cimetidine may lead to confusion, especially in patients over age of 60 years or if dosage is not adjusted for patients with decreased kidney or liver function. ➢ Cimetidine has a weak androgenic effect, possible resulting in male gynecomastia and impotence. ➢ Cimetidine and ranitidine rarely cause bradycardia.	drugs like phenytoin, theophylline, Phenobarbital, warfarin, diazepam ➢ Cimetidine results in reduced clearance of propranolol and lidocaine. ➢ Cimetidine inhibits excretion of procainamide by competing for proximal tubular secretion site.	

3.	Proton pump inhibitors Omeprazole Lansoprazole Pantoprazole Rabeprazole	Gastric proton pump H^+K^+ATPase has a sulfhydryl group near the potassium binding site on luminal side of the canalicular membrane. Omeprazole sulferiamide (active form) forms a stable disulfide bond with this specific sulfhydryl, thereby inactivating the ATPase and shutting off acid secretion.	➢ In long-term (2 years) rat studies, omeprazole produced a dose-related increase in gastric characinoid tumors. This may be related to the hypergastrinemia produced by the inhibition of acid secretion. This effect has not been observed in other animal species or in humans.	➢ Interferes with metabolism of diazepam, warfarin and phenytoin (CYP -450) ➢ But no interaction with theophylline and propranolol. ➢ Prolonged gastric acid inhibition decreases absorption of ketoconazole, ampicillin esters and iron salts.	Gastrinacmia due to prolong achlorhydria

				➢ Increased cyclosporin levels are reported after omeprazole administration.	
4.	Gastrointestinal anticholinergics (Belladonna leaf, atropine, propantheline)	Decrease basal and stimulated gastric acid and pepsin secretion.	Given in combination with antacids, anti-cholinergics delay gastric emptying, thereby prolonging antacid retention. Most effective when taken at night and in large doses.	-	Decreased salivation, blurring of vision, constipation, photophobia.
5.	Sucralfate (Mucosal protectant that is nonabsorbable disaccharide containing sucrose and aluminium)	Adheres to the base of the ulcer crater, forming a protective barrier against gastric acids and bile salts.	Constipation is common	➢ Antacids reduce mucosal binding of sucralfate, reduce its therapeutic efficacy. ➢ Interfere with absorption of	Constipation

				digoxin, tetracycline, phenytoin, iron, ciprofloxacin and cimetidine	

6.	Prostaglandins Misoprostol Mefepristone Anti Helicobacter pylori drugs (George, 2000) • Antibiotics: metronidazole, tetracycline,	Have antisecretory (inhibiting gastric acid secretion) and mucosal protective properties. NSAIDs inhibit prostaglandin synthesis and a deficiency of prostaglandin within gastric mucosa lead to diminishing bicarbonate and mucus secretion, contributing to mucosal damage caused by NSAIDs. Misoprostol increases bicarbonate and mucus production at doses of 200 and above – doses that can also be antisecretory.	➢ Because of its abortifacient property, Misoprostol is contraindicated in pregnant women.	No significant interactions have been reported.	Diarrhea, abdominal cramps, uterine bleeding, abortion.

Allopathic drugs used in peptic ulcer are directed against a single luminal agent. Inspite of this, we have yet to discover effective anti-ulcer drugs, which not only heal the peptic ulcers but also effectively prevent their recurrence because with the new and potent anti-ulcer drugs, healing of peptic ulcer is usually achieved within six to eight weeks in most patients and 89% of gastric ulcer patients experience ulcer recurrence with one year of successful healing with conventional anti-ulcer therapy. Allopathic drugs cause all sorts of adverse effects, toxic effects and cause drug interactions with other drugs on chronic administration besides their availability at high cost.

Traditional System of Medicine

The traditional medical system is also known as "Alternative Medical System". These are Ayurveda, Hakimi (Unani), Homeopathy and Siddha, which are, established systems, while the newer ones are acupuncture, magneto therapy, crystallotheraphy etc. All these alternative systems till recently did not use the modern methods of proving or disproving the claims, (e.g.) detailed documentation and analysis, clinical drug trials following a well described methodology like double blind and controlled trials. Fortunately, the Government is now actively encouraging research in different systems using modern methods.

Peptic Ulcer in Siddha System of Medicine

In siddha system of medicine, peptic ulcer is known as 'valigunmam' with its signs and symptoms matching the modern terminology 'peptic ulcer'. Also according to siddha valigunmam is the derangement of the metabolism in the stomach and duodenum resulting in the malfunctioning of the secretory process of the gastric mucosa. Copper is absorbed in stomach, intestine and mucosa membranes probably as a colloid and stored in liver. However, to the knowledge we observed that the dispensing of siddha medicine differ from individual to individual and mainly based on their biological system.

The Rationale of using metallic medicines

Metals, minerals, gems and jewels are in the medicine since Vedic period. But they were used extensively during the post buddhist era. Several buddhist saints carried out research and composed works on metallic medicines. Some of these metals like mercury, lead and arsenic are known to be poisonous to the body and some of them do not get absorbed in to the blood from the intestines. Therefore all metals, minerals, gems and jewels are processed with the following aims in view:

- To make them absolutely non-toxic,
- To make them easily absorbable through the intestine mucosa and to make them assimilable through the walls of the cells,
- To enhance their therapeutic efficiency so that these could be administered in very small dose,
- To make this therapeutic effects broad based and

- To make them delicious.

For the above-mentioned purposes these metals etc. are made to undergo process of shodhana (Purification) following marana (Calcinations).

It is keeping these above-mentioned facts in view, that the system of treatment with recipes containing metals etc., is called Davi Chikitsa (heavenly treatment).

There has been a worldwide interest in scientifically validating the therapeutic efficacy of old traditional medicines. There are inherent problems in the scientific validation of clinically acclaimed effectiveness of plant products which are further attenuated by the lack of availability of suitable experimental and clinical models. However that should not deter the development and quest for researching new drugs from these alternative systems of medicine.

Current status of traditional systems of medicines

The 25th session of the South East Asia Regional Committee of the WHO, held in Colombo in 1972, mooted the idea of using the practitioners of traditional medicine to help improve the coverage of health services. In 1976, the 29th World Health Assembly took note of the role that traditional medicine could play in the extension of health services. The WHO regional committee for South East Asia likewise urged governments to lend greater support to the development and use of the traditional medical care system. Another World Health Assembly resolution in 1977 urged member states to give adequate importance to the utilization of traditional systems of medicine through appropriate regulations suited to the national health system.

The Ministry of Health and Family Welfare, Government of India, in the statement of National Health Policy, 1982, on traditional systems of medicine and their role in health care recommended that 'planned' efforts should be made to dovetail the functioning of the practitioners of these systems and integrate their services.

Three systems that are in practice in India are Ayurveda, Siddha and Unani, all of which are based on humoural pathology or, in other words, on the same physiological doctrine that the three humors called the tridoshas viz., wind, bile and phlegm (vazhi, azal, iyyam) are the three supports of the body. They represent respectively air, fire and the water of the

five elements, which form the connecting link between microcosm or man and macrocosm or the world (in Siddha this is known as anda pinda thathwam). When in imbalance, they bring about diseases.

CONCLUSIONS

Currently allopathic system of medicine has been used widely in suppressing and treating the peptic ulcer disease. Conventional allopathic drugs used in peptic ulcer have been directed mainly against a single luminal agents and plethora of drugs like antacids, anticholinergics, histamine (H_2) receptor blockers and proton pump inhibitors (PPI) have flooded the market to heal ulcers. However these drugs may cause all sorts of adverse effects, toxic effects and produce drug interaction with other drugs on chronic administration besides their availability at high cost. Despite the fact that a wide range of drugs is available, we have to yet discover a drug, which not heals the ulcer, but effectively prevent their recurrence. So there is an urgent need for finding alternative drugs from traditional system of medicine. Similarly plant based products are gaining importance in recent years. Search of plants, which possess anti-ulcer activity by neutralization, mucosal protection and antistress activity or an herbal formulation, which can reduce the ulcer formation and also reduce the relapse rate, will be a worthwhile effort in this direction. Taking lead from ancient literatures, we can do the search for plants with antiulcer activity. The clinical assessment of *Eclipta alba* on gastritis shows significant reduction in the gastric acidity. The clinical assessment of "charcosal" (a proprietary herbo mineral) was found effective in decreasing the gastric acidity. The treatment of dyspepsia with amlaki (*Embelica officinalis* Linn.) as an alternative to antacid in the management of ulcer and non-ulcer dyspepsia was reported. In 60% of the duodenal ulcer cases, Bringaraja was found to be efficacious. Further 'Kaiyantharai parpam', a siddha preparation containing dried *Eclipta alba*, *Phyllanthis embelica*, *Terminalia chebula, Terminalia beler*ica and *Allium sativum* was studied for its gastric and duodenal antiulcer activity and concluded potential antiulcer activity of the formulation than the individual ingredients at a specific dose which indicates the synergism of the formulation. It is clearly evident from the literature that the herbs having varying phytoconstituents and efficacy were found to be promising in healing the ulcers. Hence, it can be stated that combination of these herbs may

be beneficial in fulfilling the observed lacunae with the present ulcer treatment. The present lacunae in the allopathic system is that the drugs available are specific to one system, one disease and hence to correct various factors arising in the etiology of the disease, it requires more than two drug regimen. It is necessary to develop a formulation that possess anti-cholinergic property (to decrease the acid secretion), antistress (to decrease the psychological stress), increase the prostaglandin synthesis (as a cyto protective) and increase the mucous formation and bicarbonate secretion (the defensive factors in ulcer formation) so that the efficacy in the ulcer treatment can be achieved. The maximum formulations having such quality definitely prevent the ulcer formation and it will be a unique formulation. To summarize the available literature in allopathic system, the etiology for the development of ulcer is multi focused (factorial) and lack of drugs in the allopathic system of medicine to control all these factors and thereby prevent ulcer formation. On the other hand, in traditional system of medicine enough herbs and minerals are available with different ways of healing / preventing the ulcer formation. The disadvantage with the traditional system of medicine is lack of scientific validation in terms of its standardization, clinical trials etc.

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