Available online on 15.05.2016 at http://jddtonline.info
Journal of Drug Delivery and Therapeutics
An International Peer Reviewed Journal
Open access to Pharmaceutical and Medical research

REVIEW ARTICLE

HERBAL TREATMENT ALTERNATIVES FOR PEPTIC ULCER DISEASE

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Received 02 April 2016; Review Completed 28 April 2016; Accepted 29 April 2016, Available online 15 May 2016

ABSTRACT

From the ancient times, plants have afforded themselves for the treatment of wide variety of diseases. This herbal basket of the nature has been explored in this review to highlight some of its potential herbs for the cure of Peptic Ulcer Disease (PUD). The motto behind the review on PUD was due to the wide spreading nature of peptic ulcer in all class of population, which may be due to the rapidly changing food habits and stress, causing an imbalance between the gastric offensive and defensive factors. Plants are getting more reliability in current days, because they lack significant side effects and are safe. On the other hand, the synthetic antiulcer drugs are constantly reported to possess critical adverse effects like arrhythmia, gynaecomastia, impotency, arthralgia etc. The relapse rate of ulcer has also been reported to be high in such molecules. A few plants have been reviewed to bring their mechanism of anti-ulcerogenic properties to the front, to promote more research on them. Some phytoconstituents have been discussed along with the research conducted by researchers in different ulcer models for better understanding the activity of the plants. The review may hopefully put some light on this particular section of research oriented towards searching new herbal moieties to treat the PUD.

Keywords: Ulcerogenic, *H. pylori*, Defensive factors, ethnomedicinal, phytoconstituents, gastroprotective.

INTRODUCTION

Peptic ulcer disease (PUD), which includes gastric and duodenal ulcers, is the most common gastrointestinal problem and demands a well targeted therapeutic strategy. The most common sites for ulcers are the stomach and the first few centimeters of the duodenum. Peptic ulcer causes break off in the continuity of the mucosa of stomach or duodenum as a consequence of some medications like non-steroidal anti-inflammatory drugs (NSAIDS), gastric acids and pepsin, finally causing lesions[1]. Basically, word 'peptic' is derived from Greek term 'peptikos' whose meaning is related to digestion .Various reports indicate that old age group patients are more susceptible to gastric ulcer. Younger individuals have higher risk of duodenal ulcers[2,3,4]. The pathogenesis of peptic ulcer disease shows a complex imbalance between gastric offensive factors like acid, pepsin secretion, *Helicobacter pylori (H.pylori)*, bile salts, ethanol, some medications like NSAIDS, lipid peroxidation, Zollinger-Ellison syndrome and defensive mucosal factors like prostaglandins, nitric oxide, gastric mucus, cellular renovation, blood flow, mucosal cell shedding, glycoproteins, mucin secretion, proliferation and antioxidant enzymes like catalase , superoxide dismutase and glutathione levels[5].

Acute peptic ulcers involve tissues down to the depth of the submucosa, and the lesions may be single or multiple. Reasons for the development of acute ulcers include severe illness, shock, burns, severe emotional disturbance, and postsurgical complications. Chronic peptic ulcers penetrate through the epithelial and muscle layers of the stomach wall. There are several symptoms of ulcer like changes in appetite, nausea, bloody or dark stools, weight loss, indigestion, vomiting, and chest pain. Complications of peptic ulcers include haemorrhage, perforation, pyloric stenosis and the development of malignant tumors. Poor digestion and elimination, improper metabolism, mental and physical stress, and difficult to digest food enhance the development of ulcers. Peptic ulcer can be categorized on the basis of location and on the severity of disease. Numerous other factors are also responsible for progression of peptic ulcers like Tumor Necrosis Factor-α (TNF α), Reactive Oxygen Species (ROS), release of histamine, incidence of apoptosis and bile acids secretion[6,7].

A number of drugs are available for the cure of peptic ulcers, but clinical evaluation of these drugs indicates high relapse rate, side effects and drug interactions. These complications enforces for the development of new antiulcer drugs and the search for novel molecules from the drug basket of nature, which is the herbal resources. Plants have been a valuable source of new

molecules and considered as an alternative strategy in search for new drugs for numerous ailments. There are a number of plants used in traditional medicine known to possess antiulcer properties that may, after a few possible chemical modifications, provide new and improved antiulcer agents[8].

EMERGENCE OF HERBAL DRUGS TO TREAT ULCER

From ancient times, herbs have been used to treat all types of ailment. The herbal medicines are advantageous than synthetic drugs as they are much safer than synthetic drugs. Synthetic medications are less stable than herbal medicines. Compared to synthetic medicines herbal medicines are less expensive. The use of herbal medicine can reduce toxicities and improve remedial outcomes. Synthetic drugs also lead to many deaths each year and are quickly becoming a major public health concern. In short we can say that natural therapies are less expensive, more valuable, and much safer. The plant drugs possessing the active principles such as flavonoid, tannins, terpenoids are found to show the antiulcer activity[9] **(Table: 1)**. The different classes of synthetic drugs are used in the treatment of peptic ulcer but many of these drugs exhibit serious side effects like arrhythmias, gynaecomastia, impotence, arthralgia, hypergastrinemia and haemopoeitic changes.

Alternative approach in recent days is the research of medicaments from ayurvedic or traditional medicinal system. The use of phytoconstituents as drug therapy to treat major ailments has proved to be clinically effective and less relatively toxic than the existing drugs and also reduces the offensive factors serving as a tool in the prevention of peptic ulcer. In this modern era also majority of the world populations still use herbal medicine mainly in developing countries, for primary health care because of better acceptability, compatibility with the human body and lesser side effects. The chemical constituents present in the herbal medicine or plant are a part of the physiological functions of living flora and hence they are believed to have better compatibility with human body. This review outlines the properties of some medicinal plants that exhibit antiulcer activity.

Table 1: Some ulcer protective phytoconstituents[10]

Name of the Plant	Phytoconstituents
Mangifera indica	Mangiferin
Azadirachta indica	Nimbidin
Ocimum sanctum	Fixed oil eugenol
Annona squamosa	Tannic acid
Mimosa pudica	Alkaloid mimosine
Terminalia chebula	Tannins, Gallic acid, chebullinic acid, sorbitol
Ficus religiosa	Flavonoids- Naringenin
Carica papaya	Chymopapain, papain
Aegel marmelos	Luvangetin
Moringa loeifera	Quercetin, beta setosterol, beta carotene
Psidium guajava	Quercetin, guaijaverin, flavonoids
Sesbania grandiflora	Tannins, saponins
Shorea robusta	Ursolic acid, amyrin
Allium sativum	Alliin, allicin
Aloe vera	Barbaloin, isobarbaloin, saponins
Bacopa moniera	Bacoside A

MECHANISM BASED STUDY OF SOME HERBAL ANTIULCER DRUGS

For the development of a successful antiulcer herbal agent, it is quite necessary to understand the possible mechanisms of the plant extract. Correlating the chemical nature of the constituents and their mechanisms may provide crucial information for the development of newer herbal drugs as potential antiulcer agent. Some herbal drugs reported to have antiulcer activity are described below with a special concern to their mechanism of action.

Azadirachta indica A.

It is commonly known as Neem and belongs to family Meliaceae. It has been identified to have potent gastroprotective and antiulcer effects. This was experimented in rats at a dose of 2.5 g/kg. It was studied on various parameters of possible mechanism for treating ulcer. The main mechanism is to prevent acid-pepsin secretion. Neem did not show any effect on mucin secretion though it improved life span of mucosal cells as evidenced by a decrease in cell shedding in the gastric juice. Thus the ulcer protective activity is due to its anti-secretory and proton pump inhibitory activity rather than on defensive mucin secretion. Bark extract of *Azadirachta indica* inhibits H+-K+-ATPase activity *in vitro*. It stops oxidative damage of the gastric mucosa by blocking lipid peroxidation and by scavenging the endogenous hydroxyl radical (OH), the major causative factor for ulcer[11,12,13].

Momordica charantia L.

It is commonly known as bitter gourd and karela and belongs to family Cucurbitaceae. The methanolic extract of *Momordica charantia* fruits is effective on gastric and duodenal ulcers. The extract was administered orally at two different doses of 100 mg/kg and 500 mg/kg. The antiulcer activity was suggested to be due to the increased secretion of mucus and anti-stress activity of its constituent. The olive oil extract of *M. charantia* fruit did show a healing effect in peptic ulcers[14,15].

Bacopa monniera

It is commonly known as Brahmi, belonging to family Scrophulariaceae. It is effective in treating various gastric ulcer models of rats. The main chemical constituent for curing the ulcer is bacoside A. It shows anti-ulcer and ulcer-healing activities. There are multiple possible mechanisms of bacoside A, which has been suggested. The first one is for treating ulcer is anti-*H. pylori* activity in the dose of 1000 mg/ml and increasing prostanoids (PGE and PGI2) in the dose of 10 mg/ml. Its other possible mechanism are mucosal offensive acid-pepsin secretion and defensive factors like mucin secretion, mucosal cell shedding, cell proliferation and antioxidant activity in rats[16,17,18].

Aloe barbadencis

It is commonly known as Aloe vera. It belongs to family Asphodelaceae (Lilliaceae). Aloe vera gel posses gastroprotective properties. The existing mucilage tissue at the center of leaves in this plant called aloe gel is used for various medicinal purposes. Its healing property is due to a compound called glucomannan, which is enriched with polysaccharides like mannose. The glucomannan affects fibroblast growth factor and stimulates the activity and proliferation of these cells. The mucilage of aloe vera not only increases amount of collagen on wound site, but also increases transversal connections among these bands rather than changing collagen structure fastening wound healing[19,20].

Ficus religiosa

It is commonly known as “peepal tree”. It belongs to family Moraceae. The alcoholic extract of *F. religiosa* has been reported for antiulcer activity against pylorus ligation induced ulcers, ethanol induced ulcers and asprin-induced ulcers at dose level of 250 mg\kg and 560 mg\kg in swiss albino rats. The stem bark ethanolic extract possesses antiulcer activity due to endogenous production of prostaglandins, which in turn promotes mucus secretion, apart from this, the plant also possesses anti-inflammatory and anti-oxidant properties, which comes together to make the plant as a potential antiulcer drug[21,22].

Carica papaya

It is commonly known as Papaya, belonging to family Caricaceae. The methanolic extract of the seed of the plant shows gastroprotective and healing effects on ulcer in rats at a dose of 125, 250, and 500 mg/kg. It significantly reduced the gastric lesion with 56, 76, and 82 % inhibition. The cytoprotective effect of papaya is responsible for its Anti-ulcerogenic activity. The enzyme P1G10 present in papaya has shown healing activity of chemically induced gastric ulcer[23,24,25].

Ananas comosus

It is commonly known as Pineapple, belonging to family Bromeliaceae. The dichloromethane extract of pineapple has been found with the ability to protect the gastric mucosa against injuries caused by 0.3 M HCl, absolute ethanol, non-steroidal anti-inflammatory drugs, and pylorus ligation, in mice and rats. The mechanism of action of the DCM extract suggested that the effective gastroprotective action is due to the sulfhydryl group. Vianain, present in pineapple has also shown wound healing property in a guinea pig ischemic ulcer model[26,27].

Cynodon dactylon

It is commonly known as Durva grass or Doob ghas, belonging to family Poaceae. Doob ghas was proved for antiulcer activity in albino rats at a dose level of 200, 400 and 600 mg per kg. Doob grass herb contains flavonoids. The alcoholic extract showed the presence of flavanoids, which is supposed to be responsible for antiulcer property[28,29,30].

Glycyrrhiza glabra

It is commonly known as licorice, belonging to family Leguminosae. It showed effective healing on ethanol-induced ulcers. It reduces stomach secretions and also produces thick protective mucus which covers the lining of stomach, therefore protects from peptic ulcers. Further it has been reported to increasing the local concentration of prostaglandins which promotes mucous secretion and cell proliferation in the stomach[31,32].

Ocimum sanctum

It is commonly known as Tulsi and belongs to family Lamiacae. It is considered as a sacred plant by the Hindus in India. Advanced studies on this plant have been reported that it has antiulcer activity. The fixed oil has proved to show antiulcer activity because of its lipoxygenase inhibitory activity, histamine antagonistic and anti-secretory effects[33,34,35].

Panax ginseng (Korean red ginseng)

It is a species of ginseng. It belongs to family Araliaceae. Korean red ginseng gives healing effect on gastric ulcer at a dose of 30, 100, and 300 mg/kg, peroral, occurred 1 hr before the ulcer induction in mice. The supposed mechanism of Ginseng species are significant increase in mucin secretion and inhibited malondialdehyde (MDA) and H+/ K+ ATPase activity in the stomach[36,37].

Musa sapientum

It is commonly known as Kela, belonging to Musaceae family. Musa at a dose of 100 mg/kg was studied for its antiulcer and mucosal defensive factors in NIDDM rats . Anti-ulcerogenic effect of Musa may be due to its anti-secretory and cyto-protective activity. This is a mucoadhesive agent that form lining in stomach and

duodenum and protect it from the corrosion of acid and pepsin[38,39].

Brassica oleraceae

It is commonly known as cabbage, belonging to family Brassicaceae. The aqueous extract of Brassica oleracea var. capitata plant was used in the gastric disorders like ulcer at a dose of 0.250, 0.50 and 1.0 mg/kg on Wistar rat. There is a chemical Lysophosphatidic acid (LPA), present in cabbage. It is a lipid mediator involved in a variety of physiological responses, like wound healing. This phospholipid shows an antiulcerogenic activity[40,41].

Solanum nigrum

It is commonly known as Potato, belonging to family Solanaceae. It has gastric antiulcerogenic effects. *Solanum nigrum* was found to possess antiulcerogenic as well as ulcer healing activities. Antiulcer activity was by blocking acid secretion through inhibition of H^+ K^+ATPase and decreasing secretion of gastrin hormone[42].

Commiphora molmol

It is commonly known as Guggul, belonging to family Burseraceae. It is widely used as an anti-inflammatory and wound healing agent. Its gastric ulcer activity at a dose of 500 mg/kg in rats was evaluated. The protective effect of *Commiphora molmol* has shown its effect on mucus production, increase in nucleic acid and non-protein sulfhydryl concentration. It has been also diagnosed for free radical-scavenging properties[43,44].

Vaccinium oxycoccos

It is commonly known as Cranberry, belonging to family Ericaceae. Cranberry juice is effective in peptic ulcer. Several *H. pylori* bacteria shows antibiotic resistance but can be treated well by cranberry juice. Regular consumption of cranberry juice could suppress *H. pylori* infection in endemically afflicted populations. The possible mechanism behind the antiulcer activity may be that, it causes immobilization of *H. pylori* strains in human mucus, erythrocytes, and cultured gastric epithelial cells[45,46,47].

Ceratonia siliqua

It is commonly known as Carob, belonging to Fabaceae (Leguminoceae) family. Carob has shown to reduce the effect of gastroesophageal reflux and vomiting in infants. It works by several activities of its constituents mainly the Flavonoid content. It possesses demulcent property and the flavonoid content imparts gastroprotective and antioxidant properties, which together lend the drug to exhibit antiulcerogenic potential.

A number of researches have been conducted on different plants for their antiulcer activity. A few pharmacologically tested Antiulcer plant drugs were studied and summarized in **Table 2**.

Table 2: Some pharmacologically tested Antiulcer plants.

Name of Plants (Family)	Solvent of Extraction (Plant part)	Dose Range (mg/Kg)	Ulcer induction method	Researcher
Emblica officinalis (Euphorbiaceae)	Methanol (Leaves)	20-50	Ethanol, Aspirin, Cold Restraint Stress(CRS)	Goel et al, 2002[49]
Asparagus racemosus (Liliaceae)	Methanol (Roots)	25-100	CRS, Pyloric ligation, Aspirin, Cysteamine	Goel et al, 2003[50]
Bambusa arundinaceae (Poaceae)	Methanol (Leaves)	200	Aspirin	Muniappan et al, 2003[51]
Urtica dioica L. (Urticaceae)	Water (Nettle)	200	Ethanol	Kufrevioglu et al, 2004[52]
Utleria salicifolia (Asclepiadaceae)	Ethanol (Rhizome)	50-200	CRS, Pyloric ligation, Aspirin, Ethanol	Rao et al, 2004[53]
Elettaria cardamomum (Zingiberaceae)	Methanol (Fruits)	100-500	Pyloric ligation, Aspirin	Jafri et al, 2004[54]
Bauhinia purpurea (Fabaceae)	Water (Leaves)	100-1000	Absolute ethanol, Indomethacin	Zakaria et al, 2011[55]
Zingiber montanum (Zingiberaceae)	Methanol (Rhizomes)	200-400	1N HCl	Hossain et al, 2012[56]
Aerva persica Merrill (Amaranthaceae)	Ethanol (Root)	200	Ethanol, Pyloric ligation	Vasudeva et al, 2012[57]
Toona ciliate (Meliaceae)	Ethanol (Heart wood)	300	HCl-Ethanol, Pyloric ligation	Malairajan et al, 2007[58]
Excoecaria agallocha (Euphorbiaceae)	Water (Bark)	125	Diclofenac	Thirunavukkarasu et al, 2009[59]
Abutilon indicum L. (Malvaceae)	Methanol (Leaves)	250-500	Ethanol, Pyloric ligation	Dashputre et al, 2011[60]
Heliotropium indicum (Boraginaceae)	Ethanol (Leaves)	500	Pyloric ligation, Aspirin	Shenoy et al, 2011[61]

Nigella sativa L. (Ranunculaceae)	Ethanol (Seeds)	150	Pyloric ligation, Aspirin	Rajkapoor et al, 2002[62]
Centella asiatica (Apiaceae)	Water (Leaves)	100-400	Ethanol	Al-Bayati et al, 2010[63]
Buchanania lanzan (Anacardiaceae)	Ethanol (Root)	200-400	Ethanol, Pyloric ligation	Pareta et al, 2010[64]
Terminalia chebula (Combretaceae)	Methanol (Fruits)	250-500	Ethanol, Pyloric ligation	Raju et al, 2009[65]
Piper aleyreanum (Piperaceae)	Essential oil, (Aerial part)	1-30	Ethanol	Santos et al, 2012[66]
Scoparia dulcis (Scrophulariaceae)	Water (Aerial part)	50, 100, 200	Indomethacin	Babincova et al, 2008[67]
Pithecellobium dulce (Fabaceae)	Hydroalcoholic, (fruit)	200	Ethanol, Aspirin, CRS	Megala et al, 2012[68]
Lafoensia pacari) (Lytraceae)	Methanol (Stem bark)	12.5, 50, 200	Ethanol, Indomethacin, CRS, Acetic acid	Martins et al, 2012[69]
Albizia lebbeck (Mimoceae)	Ethanol (Bark, Leaves)	200, 400	Ethanol, Indomethacin, CRS, Acetic acid	Lawande et al, 2012[70]
Andrographis paniculata (Acanthaceae)	Hydroalcoholic (Aerial part)	200, 400	Cysteamine	Gupta et al, 2011[71]
Picralima nitida (Apocyanaceae)	Methanol (Seeds)	100	Pyloric ligation, Aspirin	Ogochukwu et al, 2011[72]
Cordial sebestena L. (Boraginaceae)	Methanol (Root)	150-300	Ethanol	Trivedi et al, 2015[73]

CONCLUSION

Research on natural products often is guided by ethnomedicinal knowledge, and their contribution to drug innovation by providing novel chemical structures and mechanisms of action is substantial. Large number of herbal extracts is used in folk medicine to treat various types of disorders. The synthetic drugs used to treat it are having side effects and it has been seen that some synthetic drugs have ulcer as their adverse effect. In that case, the herbal natural remedy is the obvious alternative, which is safe and equally effective as the synthetic drug. Several plant sources have been highlighted in this article on the basis of traditional knowledge and reports of different researchers. Apart from this, searching for new pathways to treat ulcer can be developed only by understanding the mechanism of ulcerogenesis, by which it can be targeted. The investigative parameters which are the major aspects for herbal drug screening has also been mentioned at required places in the paper, which will hopefully help the researchers working in this area.

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How to cite this article:

Tripathy S, Afrin R, Herbal treatment alternatives for peptic ulcer disease, Journal of Drug Delivery & Therapeutics. 2016; 6(3):27-33

 ISSN: 2250-1177 CODEN (USA): JDDTAO