

Exploring Indian medicinal plants for antiulcer activity

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ABSTRACT

Peptic ulcer disease (PUD) is a serious gastrointestinal disorder that requires a well targeted therapeutic strategy. A number of drugs including proton pump inhibitors and H₂ receptor antagonists are available for the treatment of peptic ulcer, but clinical evaluation of these drugs has shown incidence of relapses, side effects, and drug interactions. This has been the rationale for the development of new antiulcer drugs and the search for novel molecules has been extended to herbal drugs that offer better protection and decreased relapse. Drugs of plant origin are gaining popularity and are being investigated for a number of disorders, including peptic ulcer. The present article reviews the antiulcerogenic and ulcer healing property of *Ocimum sanctum*, *Allophylus serratus*, *Desmodium gangeticum*, *Azadirachta indica*, *Hemidesmus racemosus*, *Asparagus racemosus*, and *Musa sapientum*. We have highlighted some of the important plants reported for their anti-ulcer and ulcer healing properties, in our laboratory and elsewhere during the last few years. Ayurvedic knowledge supported by modern science is necessary to isolate, characterise, and standardise the active constituents from herbal sources for antiulcer activity.

KEY WORDS: Indian medicinal plants, peptic ulcer, *Ocimum sanctum*

Introduction

Peptic ulcer disease (PUD) encompassing gastric and duodenal ulcer is the most prevalent gastrointestinal disorder.^[1] The pathophysiology of PUD involves an imbalance between offensive (acid, pepsin, and *H. pylori*) and defensive factors (mucin, prostaglandin, bicarbonate, nitric oxide and growth factors).^[2] An estimated 15,000 deaths occur each year as a consequence of PUD.^[1] In India, PUD is common. In the Indian Pharmaceutical industry, antacids and antiulcer drugs share 6.2 billion rupees and occupy 4.3% of the market share. Today, there are two main approaches for treating peptic ulcer. The first deals with reducing the production of gastric acid and the second with re-enforcing gastric mucosal protection.^{[1],[2]}

Recently, there has been a rapid progress in the understanding of the pathogenesis of peptic ulcer. Most of the studies focus on newer and better drug therapy. These have been made possible largely by the availability of the proton pump inhibitors, histamine receptor blockers, drugs affecting the mucosal barrier and prostaglandin analog.^[3] However, the clinical evaluation of these drugs showed development of tolerance and incidence of relapses and side effects that make their efficacy arguable. This has been the rationale for the development of new antiulcer drugs, which includes herbal

drugs. Indian Medicinal plants and their derivatives have been an invaluable source of therapeutic agents to treat various disorders including PUD.^[4] An indigenous drug possessing fewer side effects is the major thrust area of the present day research, aiming for a better and safer approach for the management of PUD. Several plant species like *Allophylus serratus*,^[5] *Desmodium gangeticum*,^[6] *Ocimum sanctum*,^[7] *Hemidesmus indicus*,^[8] *Emblica officinalis*,^[9] *Convolvulus pluricaulis*,^[10] *Bidens pilosa*^[11] and *Asparagus racemosus*^[12] have shown encouraging findings.

This review summarises the features of some of these plants reported to possess antiulcer and ulcer healing properties. Although extensive research has been conducted in this area, recent studies with significant findings involving *Ocimum sanctum*, *Allophylus serratus*, *Desmodium gangeticum*, *Azadirachta indica*, *Hemidesmus indicus*, *Asparagus racemosus* and *Musa sapientum* are emphasised here.

Ocimum sanctum Linn. (Tulsi)

Ocimum sanctum (OS), popularly known as Tulsi in Hindi, is a sacred plant that belongs to the family *Labiatae*. OS contains a number of chemical constituents that interact in a complex way to elicit their pharmacodynamic responses. OS

is highly effective in a wide spectrum of diseases and reported to possess anticarcinogenic, anthelmintic, antiseptic, antirheumatic, antistress, and antibacterial properties.^[13-15] Clinical trails have reported the usefulness of OS in heart diseases^[16] and diabetes.^[17] OS also possess antiinflammatory and immunomodulatory properties, attributed to its potential to inhibit cyclooxygenase and lymphokines.^[18]

Previous studies have reported significant antiulcer activity by different parts of OS.^[14,19] Singh and Majumdar (1999) while working with fixed oil of OS showed that OS had potent antiulcer effect against ulcer induced by aspirin, indomethacin, histamine, serotonin, alcohol, reserpine and stress. They suggested that the strong antiulcer effect of OS was possibly due to the inhibition of 5- lipooxygenase in aspirin, indomethacin, and alcohol induced ulcer models. In histamine, reserpine, and stress induced ulcer models, the antiulcer effect was due to its antihistaminic, anticholinergic, and antisecretory properties, respectively. They concluded that OS was a potent antiulcer and antiinflammatory agent. The findings strengthen the view that a drug that possesses both antiinflammatory and antiulcer activity would be an additional benefit as most of the antiinflammatory drugs used today are ulcerogenic.

Our research extended the findings of Singh and Majumdar (1999) further by evaluating ulcer healing properties of OS.^[7] We studied the ethanolic extract of leaves of OS in gastric ulcer induced by cold restraint (CRU), alcohol (AL), aspirin (ASP), and pyloric ligation (PL) model in rats, and histamine (HST) induced duodenal ulcer model in guinea pigs, for its antiulcer activity. In addition, healing effect of OS was examined in acetic acid (AA) induced chronic gastric ulcer model. It was found that the ethanolic extract of OS not only reduced acid secretion, but also potentially elevated the mucoprotective effect. Another important finding of our study was the dose dependent manner of OS activity, where 100 mg/kg body weight was found to be the most effective dose. However, the most important finding of our study was the effectiveness of OS extract in all the five models, indicating that OS extract exhibited antiulcerogenic activity through different mechanisms. Another possibility is the presence of more than one active component in OS extracts, which are effective against various ulcer induction mechanisms.

Ulcer healing is a complex process that involves combination of wound retraction and re-epithelialization.^[20] It also involves other factors, such as, growth factors and angiogenesis. OS significantly reduced the size of ulcer after 10 days of treatment. Furthermore, after 20 days of treatment, complete regeneration of the mucosal glandular structure was seen through histological studies of ulcer base. The ulcer healing property of OS seems to be based on its mucoprotective activity and its antisecretory effect. The ulcer base may have healed quickly because the basic fibroblast growth factor was protected from acid, which is considered to be chiefly responsible for epithelial regeneration.

Overall, our results fortify the ethnopharmacological importance of OS as an antiulcer and ulcer healing agent. Furthermore, OS and its active constituents may emerge as potent therapeutic agents against PUD. However, more experimentation and detailed molecular analysis of active constituents of OS is required for a definite conclusion.

***Allophylus serratus* Kurz**

Allophylus serratus Kurz (Synonym *Allophylus cobbe* Raeuschel; *Allophylus edulis* Radlk), is one of the largest genus of family *Sapindaceae* and carries a strong ethnopharmacological background. The plant is used in Ayurveda, to treat problems like inflammation, elephantiasis, oedma, and fracture of bones. It is also used in several gastrointestinal disorders including dyspepsia, anorexia, and diarrhoea.^{[21], [22]}

Pharmacognostic studies and phytochemical screening of *Allophylus serratus* (AS) showed the presence of various chemical compounds in different parts of AS plant. Leaves of the plant contain β -sitosterol. They also contain phenacetamide, a chemical known for its antiulcer activity.^[23] *A. edulis* has also been reported to contain two flavonoid glycosides that are effective against ulcer.^{[24], [25]}

We have studied the antiulcerogenic potential of AS by analysing the ethanolic extract of its dried, powdered leaves against different ulcer models. We have supported the finding further by studying biochemical parameters like free and total acidity, peptic activity, and mucin secretion. AS showed a substantial and significant protection against gastric ulcers in all the models.^[5]

Reduction in acid output and peptic activity and increase in mucin secretion were the major mechanisms behind the protection shown in the PL model. Reduced acid output was the major reason in the CRU model, while the tremendous increase of mucus content and a possible increase in prostaglandin level could be the protective mechanism in the AL and the ASP models.

Therefore, AS can be effectively used as an antiulcer drug. However, further insight into the precise mechanism of action is essential to exploit the complete potency of AS.

Desmodium gangeticum

Desmodium gangeticum DC (Leguminosae), popularly known as "Shaparni" in Hindi, is a well-known Indian medicinal plant.^[26] It is of great therapeutic value in treating diseases such as, typhoid, piles, inflammation, asthma, bronchitis, and dysentery.^[27] The root is prescribed in combination with other drugs for the treatment of snakebite and scorpion sting. This cure is mentioned in the Shrangdharasamhita and the Charakasamhita by Sushruta.

While studying the ethanolic extract of DG for its antiulcerogenic potential in four-induction models, namely CRU, ASP, PL and AL we observed that a dose of 200 mg/kg was most effective in all the models. Efficacy of DG in the CRU model may be due to its antioxidant activity. This is in agreement with some earlier reports about the antioxidant activity of DG, which suggests the free radical scavenging effect of DG.^[28] Such activities may also be responsible for the antiulcer effect of DG. The reduced acid output measured after pyloric ligation, indicates the effect of the extract's protective mechanism on gastric mucosa, causing an inhibition of gastric secretion. The cytoprotective ability was depicted by increased mucin secretion in the AL and the ASP induced ulcer models.

Unlike OS and AS, antiulcerogenic efficacy of DG is mainly due to its better cytoprotective effect in comparison with its antisecretory effect. It is well documented^{[12], [29]} that natural

Table 1**Herbal plant extracts with antiulcerogenic property**

<i>Plant</i>	<i>Family</i>	<i>Extract</i>	<i>Models</i>	<i>Mechanism of action</i>
<i>Terminalia pallida</i> Brandis ^[51]	Combretaceae	Ethanollic extract	Indomethacin, HST, AL	Decreases acid secretion and is potent antioxidant
<i>Allophylus serratus</i> Kurz ^[5]	Sapindaceae	Ethanollic extract	CRU, AL, ASP, PL	Decreases acid secretion and peptic activity and increases mucin secretion
<i>Desmodium gangeticum</i> ^[6]	Papilionaceae	Ethanollic extract	CRU, AL, ASP, PL.	Increases mucin secretion
<i>Ocimum sanctum</i> Linn ^[7]	Labiatae	Ethanollic extract	CRU, AL, ASP, PL, HST	Decreases acid secretion and increases mucin secretion
<i>Hemidesmus indicus</i> ^[8]	Asclepiadaceae	Ethanollic extract	ASP, PL.	Increases mucin secretion.
<i>Asparagus racemosus</i> Willd. ^[12]	Liliaceae	Fresh juice	CRU, AL, ASP, PL, AA cysteamine	Has no effect on acid and pepsin, but increases mucin secretion
<i>Embolica officinalis</i> Gaertn ^[9]	Euphorbiaceae	Methanollic extract	AL, ASP, CRU, PL, AA	Decreases acid and pepsin secretion and increases mucin.
<i>Azadirachta indica</i> A Juss ^[34]		Aqueous extract	CRU, PL, Indomethacin, AL, HST, Mercaptomethylimidazole	Inhibits acid secretion and is an antioxidant
<i>Centella asiatica</i> Linn ^[52]		Fresh Juice	CRU, AL, ASP, PL	Has no effect on acid secretion, but increases mucin secretion
<i>Bacopa monniera</i> Wettst ^[53]	Scrophulariaceae	Fresh Juice	CRU, AL, ASP, PL	Has no effect on acid secretion, but increases mucin secretion
<i>Bidens pilosa</i> L ^[11]	Compositae	Ethanollic extract	AL, PL, Indomethacin	Inhibits gastric acid and pepsin and stimulates mucus secretion.
<i>Musa sapientum</i> ^[54]	Scitamineae	Powder	PL	Increases the component of mucin secretion

drugs augment the defensive factors and although slow in activity, are more reliable and safer. Therefore, the use of DG alone or in combination with other drugs requires serious consideration.

Azadirachta indica

Azadirachta indica A. Juss, commonly known as “Neem,” has been extensively used in India as an ayurvedic medicine for the treatment of various diseases, such as, leprosy, intestinal helminthiasis, and respiratory disorders in children.^{[30]–[33]}

Bandyopadhyay *et al.* have reported the gastroprotective property of dried bark extract of *Azadirachta indica* (AI) in the mercaptomethylimidazole, PL, CRU, indomethacin, AL, and HST induced ulcer models. It acts mainly by inhibiting acid secretion and blocking oxidative damage of the gastric mucosa.^[34] Inhibition of acid secretion was confirmed by inhibition of H⁺K⁺ATPase activity, while blockade of oxidative damage of gastric mucosa was evident from blocking of lipid peroxidation and scavenging of endogenous hydroxyl radical (OH[•]). Furthermore, they compared the bark extract with known antiulcer drugs, ranitidine and omeprazole in the PL and the stress ulcer models and found that the extract was almost

equipotent to the standard drugs. The bark extract exhibited more antioxidant activity than a variety of known antioxidants. Garg *et al.*, have also reported an antiulcer effect of neem leaf extract and the prevention of mucus depletion and mast cell degranulation as possible mechanism.^[35]

A phenolic glycoside has been isolated by Bandyopadhyay *et al.*, as an active constituent, whose characterisation and mechanism are under investigation. Therefore, *Azadirachta indica* offers another option for a safer and an effective antiulcer drug.

Hemidesmus indicus

Hemidesmus indicus var. *indicus* (family Asclepiadaceae), is a widely distributed medicinal plant in India. It has been used in various diseases and disorders, such as, antinociceptive, antidiarrhoeal, renoprotective, antiatherogenic, and skin carcinogenesis.^{[36]–[41]} Jain and Singh have reported that *Hemidesmus indicus* (HI) is employed in traditional medicine for gastric ailments.^[42]

Anoop and Jagdeesan have recently studied the aqueous ethanolic extract of HI and have reported that the doses of 300 and 450 mg/kg are effective in the PL, cysteamine, and aspirin induced ulcer models in rats.^[8] The antiulcerogenic

effect of HI was mainly because of its high mucoprotective activity, depicted by a selective increase in prostaglandin content.

Hemidesmus indicus, therefore, provides another alternative for ulcer treatment. It aims at enhancing the defensive factors so that the normal balance between offensive and defensive factors is achieved.

Asparagus racemosus

Asparagus racemosus (AR), belonging to the family *Liliaceae*, is a well-known ayurvedic rasayana. AR is reported to be antiarrhoeal, antibacterial, antilithiatic and antiulcer.^{[43]-[46]}

Sairam *et al.*, have reported antiulcerogenic activity of methanolic extract of fresh roots of AR in the CRU, AL, ASP, and PL induced gastric ulcer models and cysteamine induced duodenal ulcer model.^[12] AR was found to be effective in the CRU, AL, and cysteamine induced ulcer models, but was ineffective in PL and ASP models. The plant did not show any significant effect on acid and peptic activity, but it increased mucin secretion tremendously, suggesting cytoprotective property as the possible mechanism. The plant did not show any effect on acid secretion. However, its effect in the CRU model, apart from its effect on defensive mucosal factors, was attributed to its adaptogenic activity.^[47] This defensive system showed protection in the PL induced model. In the ASP model, both local and systemic effects produced ulcers.^[12] It may be possible that AR was not able to overcome all the factors that play a role in ulcerogenesis. Along with the above-mentioned properties, AR was also reported to have antioxidant effect.^{[48],[49]} Apart from finding AR to be antiulcerogenic, authors found that it accelerated gastric ulcer healing in 10 days of treatment.

Overall, AR has shown gastroduodenal ulcer protecting and gastric ulcer healing effects, which are mainly due to increase in mucosal defensive factors.

Miscellaneous plants

Several other plant species that have utility in ulcer therapy have also been reported in the literature. Some of these plants like *Musa sapientum* and *Zingiber officinale* have been reviewed extensively by Goel and Sairam.^[50] These herbal plants along with other plants reportedly possessing antiulcerogenic property are summarised in Table 1. Some of these herbal drugs have been chemically characterized, and the entities involved in the activity have been isolated.

Conclusion

According to the old hypothesis, acid secretion was thought to be the sole cause of ulcer formation and reduction in acid secretion was thought to be the major approach towards therapy. However, in the light of recent evidences this concept has changed. Now, treatment of ulcer mainly targets the potentiation of the defensive system along with lowering of acid secretion.

Chemical substances derived from plants have been used to treat human diseases since the dawn of medicine. Roughly 50% of new chemical entities introduced during the past two decades are from natural products. Recent technological

advances have renewed interest in natural products in drug discovery. Therefore, efforts should be directed towards isolation and characterisation of the active principles and elucidation of the relationship between structure and activity. Furthermore, detailed analysis of the active constituents of natural drugs should be directed towards clinical relevance. Standardisation is indispensable to maintain reproducible quality in biological evaluation. Although the clinical efficacy of these preparations is reported by traditional practices, they have not been scientifically validated.

Ayurveda, the oldest medicinal system in the world, provides leads to find therapeutically useful compounds from plants. Therefore, ayurvedic knowledge supported by modern science is necessary to isolate, characterise, and standardise the active constituents from herbal source. This combination of traditional and modern knowledge can produce better antiulcer drugs with fewer side effects. Herbs are widely available in India and other countries. The wide spectrum makes them attractive candidates for further research.

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