AN UPDATE REVIEW ON NATURAL ANTIULCER DRUGS

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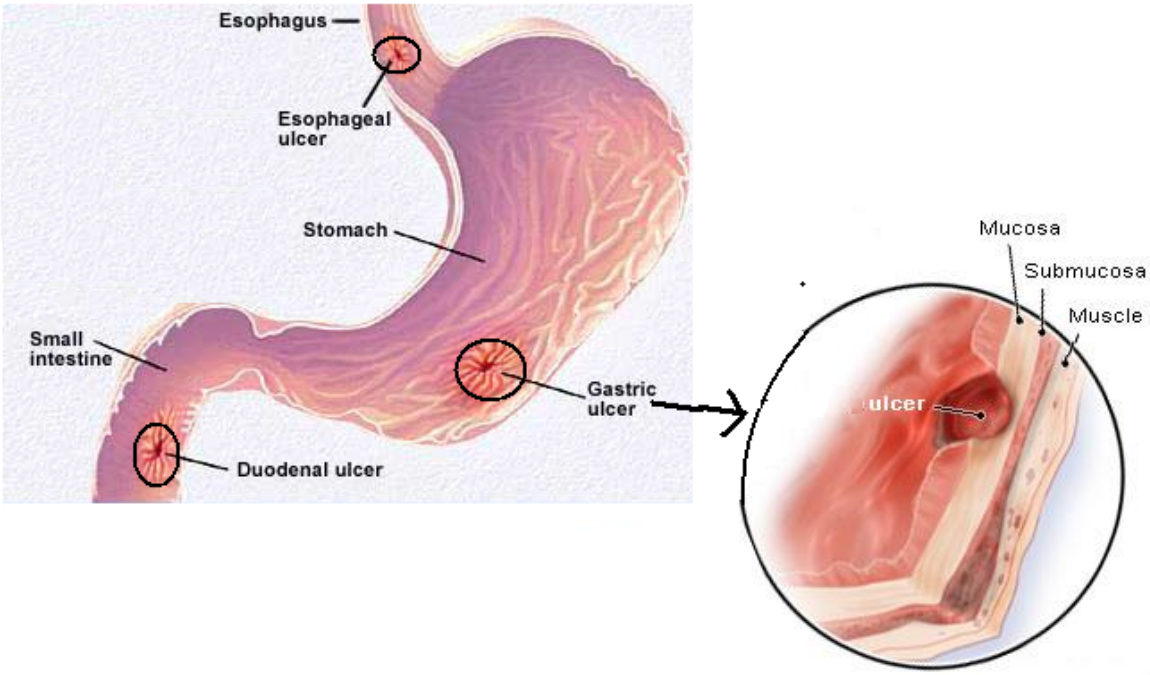
Summary

In clinical practice, peptic ulcer is one of the most prevalent gastrointestinal disorders, commonly occurs in developed countries. Most of the commonly used drugs such as H_2- blockers, M_1- blockers, proton pump inhibitors, decrease secretion of acid while, drugs like sucralfate and carbenoxolone promote mucosal defenses. Reports on clinical evaluation of these drugs show that there are incidences of relapses and adverse effects and danger of drug interactions during ulcer therapy. Therefore, people prefer natural product drugs for disease treatment. In recent years, special attention is being given on alternative safe natural bio-remedies to cure the infectious diseases because of their less or no side effects, high efficacy, less cost. In this paper an attempt has been made to give an overview of certain plants with their phytoconstituents and mechanism of action which have been studied for their antiulcer activity.

Key Words: Peptic ulcer, anti-ulcer activity, flavonoids, antioxidant activity

Introduction

Ulcer is defined as the erosion in the lining of the stomach or duodenum and is caused by the disruptions of the gastric mucosal defense and repair systems. In clinical practice, peptic ulcer is one of the most prevalent gastrointestinal disorders, commonly occurs in developed countries **[1]**. The common forms of peptic ulcer are duodenal ulcer, gastric ulcer, stress ulcer, nonsteroidal anti-inflammatory drug (NSAID) induced ulcers and recurrent oral ulceration (aphthous ulceration).



Figures showing ulcer on various position of gastrointestinal track.

Duodenal ulcer

Duodenal ulcer occurs commonly younger individuals **[2].** predominantly effects male **[3]**. In duodenum, there may appear ulcers on both the anterior and posterior walls called "kissing ulcer". Patient with duodenal ulcer produce more acids, particularly at night **[4]**.

Gastric ulcer

Gastric ulcer is particularly common in older age groups especially in females **[5]**. Although patients with gastric ulcer have normal or even diminished acid production, rarely may occur even in complete absence of acid **[4]**.

Stress ulcer

Stress ulcer are ulcers of stomach or duodenum that occurs in the context of a profound illness or trouma requiring insentive care. The etiology of stress related ulcers differs somewhat from that of other peptic ulcers involving acid and mucosal ischemia **[4]**.

Nonsteroidal anti-inflammatory drug (NSAID) induced ulcers

NSAIDs like aspirin and indomethacin are known to induce gastric ulceration **[5]**. Chronic NSAIDs ulcers have 2-4% risk of developing symptomatic ulcer, gastrointestinal bleeding and / or perforation **[4].**

Recurrent oral ulceration
Recurrent painful fibrin-covered ulcers are a common and troublesome problem, particularly in childhood and in elderly. It may be associated with vitamin B group deficiencies, Iron deficiency or various food allergies **[3]**.

Approaches for the treatment of peptic ulcer are

1. Reduction of gastric acid secreation
- **(a) H_2 antihistamines:** Cimetidine, ranitidine, famotidine, roxatidine
- **(b) Proton pump inhibitors**: Omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole
- **(c) Anticholinergics:** Pirenzepine, propantheline, oxyphenonium
- **(d) Prostaglandin analogues**: Misoprostol

2. Neutralization of gastric acid (Antacid)
- **(a)Systemic:** Sodium bicarbonate, sodium citrate
- **[b)Nonsystemic:** Magnesium hydroxide, Aluminium hydroxide, calcium carbonate, magaldrate, magnesium trisilicate

3. Ulcer protectives: Sucralfate, carbenoxolone
4. Anti-H.pylori drugs: Amoxicillin, clarithromycin, metronidazole, tinidazole, tetracycline

The high recurrence rate even after complete healing of the ulcer is major hurdle of aforementioned therapy **[6, 7]**. In addition, these drugs confer simpler to severe side effects ranging from diarrahoea, itching and dizziness to arrhythmia, impotance and gyneacomastia **[8, 9]**.
Harbal medicines have maintened their importance due to socio-economical, cultural and historical reasons **[10].** In recent years, there has been growing interest in alternative therapies and use of natural products, especially those derived from plants since medicinal plants are among the most attractive sources of new drugs and have been shown to produce promising results for treatment of gastric ulcer **[10,11,12]**.

Various models for evaluation of anti-ulcer activity

Aspirin (ASP)-induced ulcers
ASP in dose of 200 mg/kg (20 mg/ml) was administered to the animals on the day of the experiment and ulcers were scored after 4 h[13] . The animals were sacrificed and the stomach was then excised and cut along the greater curvature, washed carefully with 5.0 ml of 0.9% NaCl and ulcers were scored by a person unaware of the experimental protocol in the glandular portion of the stomach. Ulcer index has been calculated by adding the total

number of ulcers per stomach and the total severity of ulcers per stomach. The total severity of the ulcers was determined by recording the severity of each ulcer after histological confirmation as follows [14]: 0, no ulcer; +, pin point ulcer and histological changes limited to superficial layers of mucosa and no congestion; ++, ulcer size less than 1mm and half of the mucosal thickness showed necrotic changes; +++, ulcer size 1–2mm with more than two-thirds of the mucosal thickness destroyed with marked necrosis and congestion, muscularis remaining unaffected; ++++, ulcer either more than 2mm in size or perforated with complete destruction of the mucosa with necrosis and hemorrhage, muscularis still remaining unaffected. The pooled group ulcer score was then calculated according to the method **[14]**.

Cold-restraint stress [CRS]-induced ulcers

Rats were deprived of food, but not water, for about 18 h before the experiment. On day six, the experimental rats were immobilized by strapping the fore and hind limbs on a wooden plank and kept for 2 h, at temperature of 4–6 ◦C **[15]**. Two hours later, the animals were sacrificed by cervical dislocation and ulcers were examined on the dissected stomachs as described above.

Pylorus ligated [PL]-induced ulcers

Drugs were administered for a period of 5 days as described above and the rats were kept for 18 h fasting andcare was taken to avoid coprophagy. Animals were anaesthetized using pentobarbitone (35 mg/kg, i.p.), the abdomen was opened and pylorus ligation was done without causing any damage to its blood supply. The stomach was replaced carefully and the abdomen wall was closed in two layers with interrupted sutures. The animals were deprived of water during the post-operative period **[16].** After 4 h, stomachs were dissected out and cut open along the greater curvature and ulcers were scored by a person unaware of the experimental protocol in the glandular portion of the stomach as mentioned in aspirin induced ulcers.

Ethanol (EtOH)-induced ulcers

The gastric ulcers were induced in rats by administrating 100% EtOH (1 ml/200 g, 1 h) **[17]** and the animals were sacrificed by cervical dislocation and stomach was incised along the greater curvature and examined for ulcers. The ulcer index was scored, based upon the product of length and width of the ulcers present in the glandular portion of the stomach (square millimeters per rat).

Acetic acid-induced chronic ulcer

Induction of chronic gastric lesions was studied according to the methods of **[18].** A solution of 0.06 ml 50% acetic acid was instilled into the glass tube of 6mm in diameter and allowed to remain 60 s on the anterior serosal surface of the glandular portion of stomach 1 cm away from the pyloric end under anesthesia. After removal of the acid solution, the abdomen was closed in two layers and animals were caged and fed normally. Test drug was given in the dose of 100 and 200 mg/kg on day 1, orally, twice daily, 4 h after the application of acetic acid and continued either up to 5 or 10 days after induction of ulcer. The animals were than sacrificed after 18 h of the last dose of drug either on sixth or eleventh day of experiment to assess the ulcer size and healing. Ulcer index was calculated based upon the product of length and width [square millimeters per rat] of ulcers.

Cysteamine-induced duodenal ulcers

The method described by **[19]** was followed. Duodenal ulcers were induced by administrations of two doses of cysteamine hydrochloride, 400 mg/kg, p.o. in 10% aqueous solution at an interval of 4 h. Test drug at dose levels of 100 and 200 mg/kg, ranitidine (50 mg/kg, p.o.) were administered 30 min before each dose of cysteamine hydrochloride. All the animals were sacrificed 24 h after the first dose of cysteamine and duodena were excised carefully and opened along the antimesentric side. The duodenal ulcers were scored for intensity, using a scale of 0–3, where 0 = no ulcer, 1 = superficial mucosal erosion, 2 = deep ulcer or transmular necrosis, and 3 = perforated or penetrated ulcer [into the pancreas or liver].

In this paper an attempt has been made to give an overview of certain plants with their phytoconstituents and mechanism of action which have been studied for their antiulcer activity.

Ageratum conyzoides

Aqueous extracts of *Ageratum conyzoides* leaf (250 and 500 mg/kg) significantly reduced the formation of gastri*c* lesions in ethanol induced model compared to control group. Extracts of *A. conyzoides* leaf showed significantly marked inhibition of gastric lesions and marked reduction of submucosal edema compared to control group. Aqueous extracts of *A. conyzoides* was reported to posse's significant antioxidant activity. The flavonoids kaempferol and quercetin, in addition to several other flavonoids isolated from *A. conyzoides* are known to possess antioxidant activity. Antioxidant property of the *A. conyzoides* could link to its gastroprotective effect. *A. conyzoides* aqueous leaf extact exert

their anti-ulcer activity through the flavonoids since flavonoids are reported to protect the mucosa by various necrotic agents **[20]**.

Alhagi maurorum

Aqueous extract of *Alhagi maurorum* (Leguminosae) protected rats against water immersion restraint-stress and ethanol-induced ulcers in a dose-dependent manner. In water immersion restraint induced ulcerated rat, aqueous extract of the *A. maurorum* increased pH and reduced gastric acid content. *A. maurorum* aqueous extract has significant mucosal protective and antisecretory effects on gastric mucosa in rats. It is possible that the inhibitory effect of extract is due, at least partly, to the presence of terpenes in *A. maurorum*. Since, terpenes were associated to antiulcerogenic activity in other plants. Some triterpenes are known as anti-ulcer drugs and their action has been suggested to be due to the reduction of mucosal prostaglandins metabolism, cytoprotective action and reduction of gastric vascular permeability. Flavonoids have antiulcer and gastroprotective activity. Two flavonoids quercetin and catechin have been isolated from *Alhagi maurorum* with antioxidant activity which inhibit the lipid peroxidation and could counteract with free radicals. This effect contributes the ulcer peptic prevention. It has been shown that the flavanone glycosides have antiulcer activity. Since, two flavanone glycosides, alhagidin and alhagitin, have been isolated from the whole plant of *Alhagi pseudoalhag* ,8 possibly these constituents implicated in the anti-ulcer activity of this plant. The methanolic extract of this plant has calcium channel blocking activity on the gastrointestinal tract smooth muscle. It is possible, therefore, that the extract acts via an anticholinergic mechanism and blocks the gastric acid secretion. *Alhagi maurorum* markedly inhibits acid secretion and the occurrence of lesions in stomach **[11, 21]**.

Averrhoa carambola

The water-alcohol extract of leaves of *Averrhoa carambola*, at doses of 800 and 1200 mg/Kg, *p.o.,* only showed significant anti-ulcer activity in the acidified-ethanol-induced ulcer model in rats. In phytochemical studies of plants with antiulcer properties, activity due to the presence of triterpenes, flavonoids, and mucilage was observed. As the water-alcohol extract of leaves of *A. carambola* contains these constituents, the partial anti-ulcer activity could be due their effects. On the other hand, the mucilage present in the water-alcohol extract of leaves of *A. carambola* could act directly to protect the gastric mucosa, avoiding gastric damage induced by necrotizing agents **[22]**.

AzimaTetracantha

The ethanolic extract of *Azima tetracantha* leaves at a concentration of 200 and 400 mg/kg exhibited a protective effect on ulcer-induced models in a dose dependent manner and was comparable with the standard drugs ranitidine and omeprazole. The gastro duodenal ulcer protecting effect of ethanolic extract of *A. tetracantha* may be due to its predominant effect on the mucosal defensive factors rather than offensive factors. The extract of *A. tetracantha* had ulcer protective activity comparable with standard drugs ranitidine and omeprazole in aspirin and pylorus ligation and cold restraint stress induced ulcer models., which may be mediated by its antioxidant effects **[2]**.

Bauhinia racemosa

Aqueous extract in the dose rate of 200 mg/kg body weight and alcoholic extract (100 mg/kg & 200 mg/kg body weight) of *Bauhinia racemosa* fruit could produce antiulcer activity. *B. racemosa* decreased the ulcer index significantly, and showed some decreased in the ulcer index. This may due to the presence of flavonoids which may reduce the gastric secretion and peptic activity and prevent the formation of gastric ulcer**[23]**.

Benincasa hispida

Petroleum ether and methanol the extracts of *Benincasa hispida* fruit produced significant reduction in ulcer index ($P < 0.05$) in ethanol-induced gastric mucosal damage, pylorus ligated [PL] gastric ulcers, and cold restraint-stress (CRS)-induced gastric ulcer models. Significant eduction in vascular permeability ($P < 0.05$) was observed. In cold restraint-stress model, melondialdehyde content was significantly reduced along with increase in catalase levels as compared to control group. The mechanism of its gastroprotective activity may be attributed to reduction in vascular permeability, free radical generation, and lipid peroxidation along with strengthening of mucosal barrier. Besides, presence of phytoconstituents in this plant like flavone and sterols might be responsible for these actions **[24]**.

Byrsonima crassa

The oral administration (250, 500 and 1000 mg/kg) of all the *Byrsonima crassa* leaves extracts (Malpighiaceae) reduced the formation of lesions associated with HCl/ethanol administration in mice. The 80% MeOH extract significantly reduced the incidence of gastric lesions by 74, 78 and 92%at doses of 250, 500 and 1000 mg/kg, respectively ($P < 0.01$). The MeOH extract reduced the ulceration by 93 and 99% only at the doses of 500 and 1000 mg/kg ($P < 0.01$). The lower gastroprotective action (69%) was observed when animals were treated with $CHCl_3$ extract at the

dose of 1000 mg/kg ($P < 0.01$). Phytochemical investigation of *B. crassa* afforded five known substances: quercetin-3-*O*-β-D-galactopyranoside, quercetin-3-*O*-α-L-arabinopyranoside, the biflavonoid amentoflavone, (+)-catechin and (−)-epicatechin. The presence of these phenolic compounds may probably explain the antiulcerogenic effect of the extracts of *B. crassa* leaves **[9]**.

Casearia Sylvestris

In stress-induced acute lesions, the preventive effect of *Casearia sylvestris* extract from dried leaves is more effective than extract from fresh leaves. In acetic acid-induced chronic ulcer, both extracts reduce the size of ulceration and increase the number of collagen fibers after 5 days of treatment, and these effects are similar with both extracts. The antiulcer activity of *C. sylvestris* may be due to the presence of volatile oils, tannins and triterpene related compounds **[25]**.

C*issampelos mucronata*

The fraction and crude methanolic extract of leaf extract of *Cissampelos mucronata* (Menispermaceae) exhibited 63.25 % and 57.26 % inhibition of ulcer induced by histamine while 57.15 % and 47.14 % inhibition were recorded against stress-induced ulcer respectively. The inhibitions of ulcer induction were significant ($P < 0.05$) except for the crude methanolic extract against stress-induced ulcer. The crude methanolic extract contained many constituents including alkaloids and flavoniods, which have been shown various properties necessary for protection against ulcer induction. The ability of the fraction, which contained only alkaloids and sterols/triterpenes to exhibit better inhibition of ulcer induction than the crude methanolic extract may be related to the purer nature of the fraction. The fraction contained higher quantity of the bioactive component per unit weight **[26]**.

Cissus quadrangularis

Cissus quadrangularis extract showed significant antiulcer activity in aspirin-induced ulcerogenesis in pyloric ligated model in rats by decreasing the gastric secretions and by enhancing glycoprotein levels. *C. quadrangularis* extract prevented indomethacin-induced ulcer lesions by its cytoprotective property. The antiulcer activity of *C. quadrangularis* extract might be attributed to the presence of biological compounds such as triterpenoids, glycosides, saponins, tannins, sitosterol and aminoacids in the extract. Triterpenoids and glycosides have been shown to inhibit gastric acid secretion and enhancement in gastric mucus content against several experimental ulcer models. These plant constitutents present in *C. quadrangularis* extract might

have the ability to protect against ulceration induced by aspirin-induced ulcerogenesis in pyloric ligated model in rats **[27]**.

Cordia dichotoma

Ethyl acetate, butanol and butanone extracts of *Cordia dichotoma* fruits (300mg/kg body weight) significantly ($p< 0.001$) decrease the volume of gastric secretion, free acidity, total acidity and ulcer index with respect to control. The possible mechanism of anti-ulcer action of *C. dichotoma* fruits may be due to its flavanoids content. *C. dichotoma* provides significant anti-ulcer and cytoprotective effect against gastric ulcers in rats **[28]**.

Combretum dolichopetalum

The ethanolic root extract of *combretum dolichopetalum* possessed significant dose-dependent anti-ulcer activity in experimentally-induced acute gastric ulcers with indomethacin and cold stress. The anti-ulcer effect of the extract could be due to its content of tannin and saponin or to its anticholinergic and antihistaminic activities, or a combination of these factors **[29]**.

Croton zambesicus

The ethanolic root extract of *Croton zambesicus* (Euphorbiaceace) (27- 81mg/kg) produced a significant ($P<0.005$-0.001) dose-dependent effects against the ulcerogenic effect of differents agents used; indomethacin, ethanol and reserpine. The effect of the extract was lower than that of the standard drug, cimetidine (100mg/kg) in the indomethacin and reserpine-induced ulcer models and higher than that of propranolol (40mg/kg) in ethanol-induced ulcer model. Antiulcer activity of the extract against reserpine-induced ulceration could in part be due to its inhibition of histamine, anticholinergic and antisecretory effects. The extract may have ability to inhibit oxygen-derived free radicals formation in rat gastric mucosa and stimulate endogenous prostaglandin synthesis **[30]**.

Cucumis sativum

The methanolic extract of *Cucumis sativum* showed maximum reduction of gastric acid volume, free and total acidity such as 41, 48 and 29% at 300 mg kg^{-1} dose, respectively. The ulcerative index inhibition in Pyloric Ligation and Water Immersion Stress models was found to be 52.5 and 62.7%, respectively at 300 mg kg^{-1}. The methanolic extract of *C. sativum* seeds possessed significant antiulcer potential which could be due to its antioxidant activity and can be used as a future natural anti-ulcerogenic agent **[31]**.

Curcuma longa

Ethanol extract of *Curcuma longa* (500 mg/kg, oral) produced significant anti-ulcerogenic activity in rats subjected to hypothermic-restraint stress, pyloruic ligation and indomethacin and reserpine administration. Turmeric extract significantly protected gastric mucosa againts several known necrotizing agents, namely 80% ethanol, 0.6 M HC1, 0.2 M NaOH and 25% NaCl. The extract had a highly significant protective effect against cystodestructive agents. Turmeric extract not only increased the gastric wall mucus significantly but also restored the non-protein sulfhydryl content in the glandular stomachs of the rats. The replenishment of sulfhydryl levels in gastric mucosa by turmeric extract may contribute to its anti-ulcer activity. The ethanolic extract of turmeric has significant anti-ulcer, antisecretory and cytoprotective activity in rats **[32]**.

Eruca sativa

The ethanolic extract of *Eruca sativa* extract significantly attenuated gastric ulceration induced by necrotizing agents (80% ethanol, 0.2 mol/L NaOH, 25% NaCl), indomethacin and hypothermic restraint stress. In pylorus-ligated Shay rats, the ethanolic extract of Eruca sativa significantly and dose-dependently reduced the basal gastric acid secretion, titratable acidity and ruminal ulceration. The extract significantly replenished gastric wall mucus and non protein sulfhydryls levels, as well as the malondialdehyde level significantly reduced by extract pretreatment. The ethanolic extract of *Eruca sativa* possesses antisecretory, cytoprotective, and anti-ulcer activities against experimentally-induced gastric lesions. The anti-ulcer effect of the ethanolic extract of *Eruca sativa* is possibly through prostaglandin mediated activity and/or through its anti-secretory and antioxidant properties. The extract contains substances, which might increase endogenous prostaglandins and mucus synthesis through its potent antioxidant activity **[33]**.

Ficus arnottiana

Methanolic extract of *Ficus arnottiana* leaf possess gastroprotective activity, as evidenced by its significant inhibition in the formation of ulcers induced by ethanol. It has muco-protective activity and gastric antisecretory when compared with that of reference drug omeprazole. The anti-ulcer activity *of* methanolic extract of *F. arnottiana* leaf is probably due to the presence of antioxidant activity of flavanoids **[34]**.

Ficus thonningii

250 mg/kg, 500 mg/kg, and 1000 mg/kg body weight of aqueous leaf extract of *Ficus thonningii* exhibited 15.43, 71.24, and 82.83% inhibition of histamine induced ulcers respectively. There was no significant (P> 0.05) difference between the mean ulcer score of the plant treated groups and the group administered Cimetidine (100 mg/kg), a standard anti-ulcer drug except in the group administered 250 mg/kg. *F. thonningii* aqueous leaf extract is an effective anti ulcer drug. The antiulcer activities of the aqueous leaf extract may be attributed to its flavonoids content. Flavonoids possess antiulcergenic and inhibit gastric secretion as well as the ability to inhibit acid secretion. Most of these effects have been attributed to the influence of flavonoids on arachidonic acid metabolism and their ability to interfere with the formation of histamine in the gastric mucosa **[35]**.

Landolphia owariensis

The extracts of *Landolphia owariensis* exhibit potent and dose related anti-ulcerogenic activities. Pre-treatment of animals with the aqueous extracts (100mg/kg and 200mg/kg) orally once daily for two weeks significantly reduced formation of ulcers induced by HCl/ethanol mixture, the percentage inhibition being 43.8% and 55.27% respectively. The Chloroform extract afforded the least protection with 23.07% and 14.77% inhibition. In pylorus ligated rats, total volume of gastric juice and gastric acidity was significantly decreased as compared to control group, to levels comparable to that produced by cimetidine. The extracts of *L. owariensis* may therefore be affording their gastroprotective effects via an increase in the defensive mechanisms of the stomach. These activities may be linked to the presence of flavonoidal compounds in *L.* Owariensis. Many plants with flavonoidal activities have been shown to be promising in the development of potent antiulcer drugs **[36]**.

Lasianthera africana

The ethanolic leaf extract of *Lasianthera africana* (1000 – 3000mg/kg) inhibited ethanol-induced, indomethacin – induced and reserpine –induced ulcer models in a dose dependent fashion. The various degrees of inhibitions were statistically significant ($p<0.01$). The effect of the extract was comparable to that of the standard drugs used. Thus, *L. africana* extract demonstrated a good antiulcer activity which supports the antiulcer effect of this plant in traditional medicine. Leaf extract contains flavonoids, terpenes, saponins, alkaloids and cardiac glycosides. Flavonoids such as quercetin have been reported to prevent gastric mucosal lesions in various experimental models by increasing the amount

of neutral glycoproteins. Flavonoids have been reported to protect the gastric mucosa from damage byincreasing the mucosal prostaglandin content and by inhibiting histamine secretion from mast cells by inhibition of histidine decarboxylase. Free radical scavenging ability of flavonoids has been reported to protect the gastrointestinal tract from ulcerative and erosion lesion. Saponins, especially triterpenes type have been implicated in antiulcer activity mediated by formation of protective mucus on the gastric mucosa and also protect the mucosa from acid effects by selectively inhibiting prostaglandin $F_{2\alpha}$ **[37]**.

Mentha arvensis

Petroleum ether, chloroform, or aqueous extracts of *Mentha arvensis* (375 mg/kg body weight) shows a protective effect against acid secretion and gastric ulcers in ibuprofen plus pyloric ligation, 0.6 mol/L HCl induced and 90% ethanol-induced ulcer models. The aqueous extract shows the best antiulcerogenic action, due to the presence of tannins and flavonoids. The effects obtained on acute and chronic gastric lesions suggest a multifactorial mechanism, involving *M. arvensis* influence on free-radical scavenging properties, on endogenous prostaglandins and sulphydryl groups **[3]**.

Morinda Citrifolia

The protection afforded by the methanol extrat of *M. citrifolia* fruits (Rubiaceae) against alcohol and Aspirin-induced gastric ulceration could also be due to inhibition of 5-lipoxygenase pathway or to leukotriene's antagonistic activity. *M.citrifolia* (400mg/kg) showed maximum inhibition of gastric acid, free acid and total acid to 53.54%, 52.55% and 30.30%, respectively. The ulcer index in the *M.citrifolia* treated animals was found to be significantly less in all the models compared to standard drug treated cases. The antiulcer activity of *M.citrifolia* was, however, less than that of ranitidine. *M.citrifolia* possesses significant antiulcer property which could be due to cytoprotective action of the drug or strengthening of gastric and duodenal mucosa with the enhancement of mucosal defence **[6]**.

Morus alba

Morus alba extract exhibits significant anti-ulcerogenic activity in rats. *M. alba* extract possesses a potential anti-inflammatory activity and may prevent organ or tissue injury during acute endotoxemia or sepsis by suppressing inflammatory mediators and thus facilitates ulcer healing. *M. alba* leaves contain anti-inflammatory and antioxidant properties. A direct protective effect of *M. alba* extracts on gastric mucosal damage and that the

gastroprotective action of this plant may be due to its anti-inflammateroy and antioxidant properties **[38]**.

Mouriri pusa

Methanolic extract of *Mouriri pusa* (Melastomataceae) was effective in experimentally healing rat ulcers after 14 or 30 days of treatment. *M. pusa* showed elevated mucus secretion and thicker regenerative gastric mucosa, denoting increased cell proliferation, which was confirmed by PCNA immune histochemical analysis. The mucus production was improved, mainly after 30 days, when there was also a mobilization of mast cells and neutrophils, which play a great role in regeneration of the injured area. Phenolic compounds present in the MeOH extract like tannins, flavonoids and epicatechin are the probable agents involved in the healing effects of this medicinal plant **[39]**.

Nigella sativa

The alcoholic extract of *Nigella sativa* (Ranunculaceae) significantly ($P < 0.001$) decreases the volume of gastric acid secretion, free acidity, total acidity and ulcer index with respect to control. The preliminary phytochemical studies revealed the presence of flavonoids in alcoholic extract of *N. sativa*; various flavonoids have been reported for its anti-ulcerogenic activity with good level of gastric protection. So the possible mechanism of anti ulcer action of *N. sativa* may be due to its flavonoids content. *N. sativa* provides significant anti-ulcer activity against gastric ulcers in rats **[4]**.

Ocimum minimum

The essential oil from *O. minimum* has the significant antiulcerogenic activity concerning to the gastric lesion induced by indometacin and ethanol. The antiulcerogenic activity presented by the essential oil in gastric ulcer induced by indometacin was detected by the reduction of the gastric lesion in 83.80% and induced by ethanol showed a reduction of 70.0%, both at the same dose (0.125 mL/Kg). The oil presented an antioxidant activity when the sample was diluted 10 times (4.69 μmol/1h and 5.92μmol/2h) which was quite similar to the control (6.29 μmol/1h and 6.16 μmol/2h). The antioxidant effect presented by the *O. minimum* essential oil can be probably one of the mechanism involved in the mucosa gastric protection **[40]**.

Phyllanthus amarus

Pretreatment with aqueous extract of *Phyllanthus amarus* (500 mg/Kg) and cimetidine inhibited the ulceration damage of absolute ethanol by 59.3 and 41.2% and decreased the serum alanine aminotransferase (ALT) by 35%, 24% and aspartate aminotransferase (AST) by 7 and 6% respectively. Aqueous and

acetone extracts of *P. amarus* are gastroprotective against acute ethanol-induced ulcer. Their gastroprotective activities might be mediated, at least partially, by their inductive effect on antioxidant enzymes such as CAT, SOD and GST that constitute endogenous scavengers of ROS **[41]**.

Polyalthia longifolia

Ethanol extract of leaves of Polyalthia longifolia produced antiulcerogenic effects possessing antisecretory, cytoprotective and proton pump inhibition mechanism. The antiulcer activity of *P. Longifolia* in this experimental model may be due to the alkaloids and terpenoids. Pylorous ligation showed significant ($P<0.01$) reduction in gastric volume, free acidity and ulcer index as compared to control. It also showed 89.71% ulcer inhibition in HCl- Ethanol induced ulcer and 95.3% ulcer protection index in stress induced ulcer. *P. longifolia* leaves extract have potential anti ulcer activity in the three models tested **[42]**.

Psidium guajava

The ethanolic extract of the leaves of *Psidium guajava* decreased the gastric volume and gastric acid secretion significantly by pretreatment with aspirin. There is increase in gastric mucus secretion ($p<.01$). The antiulcer and acid secretion inhibitory effect of *P.guajava* may be mediated through prostaglandins. Prostaglandins are known to have an antisecretory effect on gastric acid production. Prostaglandins are also known to stimulate the synthesis of mucus the acid inhibiting and mucus production effect of prostaglandins is the major mechanism by which *P. guajava* extract promotes ulcer healing **[43]**.

Pterospermum acerifolium

The Pet. Ether, chloroform and ethanol extract of *Pterospermum acerifolium* bark (Sterculiaceae) demonstrated significant antiulcer activity against aspirin, indomethacin & ethanol induced ulcerations, significant inhibition of gastric secretary volume, and total acidity in pylorus ligated rats. The antiulcer effect of P.acerifolium may be due to (i) the inihibition of 5-LO enzyme (ii) blockade of LTC4, LTD4 synthesis (iii) generation of free radicals; and/or (iv) inhibition of histamine release following mast cell degranulation **[5]**.

Qualea grandiflora

The oral administration of hydroalcoholic extract of *Qualea grandiflora* bark exhibited antiulcer activity decreasing the ulcerative index induced by HCl/ethanol solution, indomethacin/bethanechol and stress. The efficacy of *Qualea grandiflora* in preventing and healing ulcers is based on its ability

to stimulate mucus synthesis (an important feature in the gastroprotection) as well as on the stimulation of an antisecretory effect. The presence of isoprenoid-derived compounds ract of bark of *Qualea grandiflora* may be responsible for the strong antiulcer effect on the surface of the gastric mucosa **[8]**.

Solanum nigrum

The methanol extract *of Solanum nigrum* fruits at higher dose significantly inhibited the gastric lesions induced by CRU (76.6%), IND (73.8%), PL (80.1%) and EtOH (70.6%), respectively, with equal or higher potency than omeprazole. *S. nigrum* fruits extract showed concomitant attenuation of gastric secretory volume, acidity and pepsin secretion in ulcerated rats. *S. nigrum* fruits extract (200 and 400 mg/kg b.w.) accelerated the healing of acetic acid induced ulcers after the treatment for 7 days. *S. nigrum* fruits extract significantly inhibits H+K+ATPase activity and decreases the gastrin secretion in EtOH-induced ulcer model. *S. nigrum* fruits extract, offers antiulcer activity by blocking acid secretion through inhibition of H+K+ATPase and decrease of gastrin secretion. *S. nigrum* fruits extract was found to possess antiulcerogenic as well as ulcer healing properties, which might also be due to its antisecretory activity. The oral administration of *S. nigrum* fruits displayed a significant antiulcer activity without any apparent toxicological effects. Due to presence of anthocyanin content and other bioactive compounds in this plant may be involved in the ulcer preventing action **[44]**.

Spathodea falcate

Oral administration of petroleum ether, chloroform and methanol extracts of *Spathodea falcate* shows significant reduction in ulcer lesion index as well as increase in volume and pH of gastric content in ethanol induced and indomethacin induced gastric ulcer models, being TSF is the most effective, it increased the gastric mucosal defense mechanism due to its high levels of terpenoids. It significantly reduced gastric lesion index (80.48%), in comparison to omeprazole (71.20%) and petroleum ether extract at a dose of 500 mg/kg (80.67%). Increased gastric mucosal defense mechanism by terpenoids and steroids fraction is due to its high levels of terpenoids like β amyrin, lupeol. The antiulcer effect of *Spathodea falcata* against various irritants has been mainly due to cytoprotective effect mediated through prostaglandin and partly due to free radical scavenging activity **[45]**.

Tephrosia purpurea

The ulcer index in the aqueous extract of roots of *Tephrosia purpurea* treated animals was found to be significantly less in all the models compared to vehicle control animals. This antiulcer

property was more prominent in animals in whom ulcers were induced by HCI, indomethacin and pyloric ligation. The anti-ulcer activity of aqueous extract of roots of *T. purpurea* was however, less than that of omeprazole. Aqueous extract of roots of Tephrosia purpurea possesses significant antiulcer property which could be either due to cytoprotective action of the drug or by strengthening of gastric and duodenal mucosa and thus enhancing mucosal defence **[46]**.

Terminalia chebula

Methanolic extract of *Terminalia chebula* (Combretaceae) fruits at doses of 250,500 mg/kg p.o produced significant inhibition of the gastric lesions induced by Pylorus ligation induced ulcer & Ethanol induced gastric ulcer. The extract (250 mg/kg & 500 mg/kg) showed significant ($P<0.01$) reduction in gastric volume, free acidity and ulcer index as compared to control. The extract shows protection against characteristic lesions produced by ethanol administration this antiulcer effect of methanolic extract of *T. chebula* may be due to both reductions in gastric acid secretion and gastric cytoprotection. Methanolic extract was found to possess antiulcerogenic as well as ulcer healing properties, which might be due to its antisecretory activity **[47]**.

Trigonella foenum

The aqueous extract and a gel fraction isolated from the seeds of *Trigonella foenum* showed significant ulcer protective effects. The cytoprotective effect of the seeds seemed to be not only due to the anti-secretory action but also to the effects on mucosal glycoproteins. The *T. foenum* seeds also prevented the rise in lipid peroxidation induced by ethanol presumably by enhancing antioxidant potential of the gastric mucosa thereby lowering mucosal injury. The soluble gel fraction derived from the seeds was more effective than omeprazole in preventing lesion formation **[48]**.

Terminalia pallida

Ethanol extract of *Terminalia pallida* at the doses of 250 and 500 mg/kg per os (p.o.) exhibited significant protection against ulcers produced by indomethacin, histamine in Swiss albino rats. The extract also afforded significant protection against ethanol-induced gastric ulceration. Ethanol extract of *T. pallida* exhibited significant anti-ulcer activity by enhancing antioxidant potential of the gastric mucosa, thereby reducing mucosal damage **[49]**.

Tulbaghia violacea

The methanolic extract of extract of Tulbaghia violacea was able to protect ($p< 0.01$) the stomach lining against indomethacin-

induced ulceration. Methanolic extracts of T. violacea root (5mg/100ml) of the plant showed little free radical scavenging activity against DPPH (29%) and ABTS (20%) and exhibited a low reducing power. the extract significantly inhibited the activities of lipooxygenase, xanthine oxidase, and other lipid peroxidative reactions. T. violacea root extract has little hydrogen atom donor potential and may not break free radical chain reactions but could act as an anti acid. Its potential in the inhibition of free radical generation, along with its antimicrobial activity justify its use by traditional healers for the treatment of peptic ulcers **[50]**.

Wilbrandia ebracteata

Protective anti-ulcer effects of leaf fractions of *Wilbrandia ebracteata* (Cucurbitaceae) were detected only in the ethanol-induced ulcer. Seven flavonoids, 3',4',5,6,7,8-hexahydroxyflavonol, orientin, isoorientin, vitexin, isovitexin, luteolin, 6-methoxi-luteolin were isolated from the leaves of *W. Ebracteata.* Flavonoids are active anti-ulcerogenic compounds from leaves of *W. ebracteata* **[51]**.

Withania somnifera

Treatment with methanolic extract of Withania somnifera (100 mg/Kg/day p.o.) for 15 days significantly reduced ulcer index as compared to control group in stress plus pyloric ligation induced gastric ulcer in rats. Extract also significantly reduced volume of gastric secretion, free acidity and total acidity. Anti ulcerogenic effects of Withania somnifera extract are approximately similar to commonly prescribed allopathic drug rantidine. Withania somnifera have not only inhibitory effects on release of gastric hydrochloric acid but it also increase various defensive factors including antioxidant defense to protect gastric mucosal damage **[52]**.

Ayurvedic preparation

Mukta Bhasma

Mukta bhasma is an unique oral ayurvedic preparation synthesized by trituration and calcination of pearl. Mukta bhasma produces significant anti-ulcer activity in rats. It may act as gastric cytoprotective agent by modulating scavenging of free radicals as Mukta bhasma exhibits a potent antiperoxidative effect. Mukta bhasma produced significant ($P<0.001$) 57.53% and 59.18% protection in cold restraint stress induced gastric ulcer and 54.19 % and 61.39% protection in Diclofenac induced ulcer at 60mg/Kg and 120 mg/Kg dose levels respectively, when compared with control. The thiobarbituric acid reactive substance (TBARS) of

stomach in ulcer induced rat was also reduced by Mukta bhasma. This ayurvedic preparation possesses significant gastro protective and antiulcer activity in lower doses of therapeutic range and its effect is not dose dependent **[53]**.

Pepticare

Pepticare, a herbomineral formulation of the Ayurveda medicine consisting of the herbal drugs: *Glycyrrhiza glabra, Emblica officinalis* and *Tinospora cordifolia*. The reduction in ulcer index in pylorus-ligation and on ethanol-induced gastric mucosal injury in rats along with the reduction in volume and total acidity, and an increase in the pH of gastric fluid in pylorus-ligated rats proved the anti-ulcer activity of Pepticare. Pepticare was more potent than *G. glabra* alone in protecting against pylorus-ligation and ethanol-induced ulcers. The increase in the levels of superoxide dismutase, catalase, reduced glutathione and membrane bound enzymes like(Ca.sup.2+) ATPase, (Mg.sup.2+) ATPase and (Na.sup.+) (K.sup.+) ATPase and decrease in lipid peroxidation in both the models proved the anti-oxidant activity of the formulation. Pepticare possesses anti-ulcer activity, which can be attributed to its anti-oxidant mechanism of action **[54].**

UL-409

UL-409 is a multiconstituent herbal preparation. In doses 25, 50 and 100 mg/kg, p.o. it significantly reduced the gastric secretory volume and ulcer index in pylorus ligated rats, and showed significant mucoprotective effect at 100 mg/kg dose on both acute and chronic treatment. UL-409(50 and 100 mg/kg doses) prevented immobilization induced gastric ulceration and showed significant mucosal protection. In forced swimming induced ulcers, UL-4093(50 and 100 mg/kg) completely abolished the ulcerogenesis and strengthened the mucosal barrier. It also protected the indomethacin-induced gastric ulcers and significantly increased the mucosal content. UL-409 has anti-ulcerogenic effects due to its mucoprotective effect. The preparation can be used alone or in combination with other ulcer healing agents **[55].**

Conclusions

There are several plants known for their antiulcer activity, with different mode of action and phytoconstituents. This is an effort to streamline the phytoconstituents of specific family with specific mode of action to ulcer. The need for newer, more effective, and most importantly, cheaper antiulcer drugs has become a

paramount issue to tackle this present situation. The studies regarding possible mechanism of action have suggested that detailed phytochemical investigation of plants, identification of particular fractions followed by isolation of particular active principle can result in development of ideal lead compounds. Morever, the effectiveness of herbal extracts towards majority of type ulcers that coupled with comparatively lesser side effects compared to existing allopathic medication can leave a unique footmark in the therapy. Hence, pharmacologists need to take more active interest in evaluation of herbal drugs for potential antiulcer activity and standardization of such herbal drugs to be clinically effective and globally competitive.

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