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Plants with Antiulcer Activity

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Abstract
Peptic ulcer is the most common gastrointestinal disorder in clinical practice. It mostly occurs due to imbalance between aggressive factor and the maintenance of mucosal integrity through endogenous defense mechanism. Moreover, changes in lifestyle, increase in stress and prolong use of NSAID's found to be responsible for increasing incidences of peptic ulcer. The modern medicines have its own limitations especially against ulcers with complex pathology indicating need of substitute medication from alternative system of medicine. This review has presented the recent research advancements of herbal medicine as an antiulcer agent with the view to aid the further research to prepare ideal antiulcer agents and or formulation.
Keywords:

INTRODUCTION

An ulcer is a craterlike lesion in a membrane (1) while peptic ulcer is an excoriated area of stomach or intestinal mucosa (2). It usually occurs at site where the mucosal epithelium is exposed to aggressive factors (3). It is one of the major gastrointestinal (GI) disorders, which occurs due to an imbalance between the offensive (gastric acid secretion) and defensive (gastric mucosal integrity) factors (4). Peptic ulcer disease is one of the common GI disorders in clinical practice (5).

Peptic ulcer exists in two main forms. First, the acute peptic ulcer, which penetrates the lamina muscularis mucosa but does not extend more deeply than the submucosa. It is mainly related to stress in the form of severe burns (Curlings ulcer) and brain damage (Cushing's ulcer). Second, the chronic peptic ulcer, which penetrates the full thickness of the muscularis propria and has its base in the serosal layer of the organ involved or outwith the gut altogether. It includes gastric and duodenal ulcers (6).

The common forms of peptic ulcer are duodenal ulcer (DU), gastric ulcer (GU), stress ulcer, non steroidal anti-inflammatory drug (NSAID) induced ulcers and recurrent oral ulceration (aphthous ulceration).

Duodenal ulcers (DU)

DU occurs commonly in younger individuals (5) and predominantly affects males (6). In the duodenum, there may appear ulcers on both the anterior and posterior walls called "kissing ulcers". Patients with DU produce more acids, particularly at night (7).

Gastric ulcers (GU)

GU is particularly common in older age groups especially in females (6). Although patients with GU have normal or even diminished acid production, ulcers rarely may occur even in complete absence of acid (7).

Stress ulcers (SU)

SU are ulcers of the stomach or duodenum that occurs in the context of a profound illness or trauma requiring intensive care. The etiology of stress related ulcers differs somewhat from that of other peptic ulcers involving acid and mucosal ischemia (7).

NSAID induced ulcers

NSAIDs like aspirin and indomethacin are known to induce gastric ulceration (8). Chronic NSAIDs users have 2%-4% risk of developing symptomatic ulcer, GI bleeding and/or perforation (7).

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 (6).

CURRENT PHARMACOTHERAPY FOR ULCER AND ITS LIMITATIONS

Reduction of gastric acid production as well as re-inforcement of gastric mucosal production has been the major approaches for current therapy of peptic ulcer disease (4). Various synthetic antiulcer drugs presently available in market includes antacids, proton pump inhibitors, anticholinergics, histamine H_2-antagonists and cytoprotectives, used to prevent or treat the various types of ulcers (9). The high recurrence rate even after complete healing of the ulcer is major hurdle of aforementioned therapy (10, 11). In addition, these drugs confer simpler to severe side effects ranging from diarrahoea, itching and dizziness to arrhythmia, impotence and gynaecomastia (12-16). The condition may be more worsen when it exhibit certain drug-drug interactions that may reduce the overall outcome of the therapy. The details are mentioned in Table 1 and 2.

IMPORTANCE OF HERBAL MEDICINE

Herbal medicines have maintained their importance due to socio-economical, cultural and historical reasons (20). In recent years, there has been growing interest in alternative therapies and the 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 GU (20-22). Also, many texa of medicinal plants have been assessed worldwide for their antiulcerogenic effects (23, 24).

Table 1: Major side effects of commonly used antiulcer drugs. (5,17,18)

Class of drug	Side effects
H_2 antagonists	Headache, dizziness, skin rash, arrhythmias, gynaecomastia, antiandrogenic, decreased sperm count, loss of libido and impotence.
Proton pump inhibitors (PPI's)	Dizziness, atrophic gastritis and hypergastrinemia.
Antacids	Stomach distension, belching, constipation, renal stones and risk of ulcer perforation.
Anticholinergics	Constipation, dry mouth, urinary retention, blurred vision, xerostomia and precipitation of glaucoma.
Ulcer protectives	Constipation, diarrhoea, dizziness, edema and hypophosphatemia.
Prostaglandin analogues	Diarrhoea, abdominal cramps, uterine bleeding and abortion.

Table 2: Common Drug-drug interactions. (5,19)

Antiulcer drug	Interacting agent	Interaction effect
H_2 antagonists	Antihistamines	Increased suppression of wheal and flare response by antihistamines.
	Chlormethiazole	Increase in sedative and hypnotic effect of Chlormethiazole.
	Dipyridamole	Reduction in bioavailability of Dipyridamole.
	Antacids	Reduction in absorption of H_2 antagonists
	Linopirdine	Delayed absorption of Linopirdine.
	Pirenzepine	Increase H_2 antagonist induced reduction in gastric acid secretion.
	Phenobarbital, Phenytoin, Diazepam, Warfarin and Theophylline.	Reduction in clearance of interacting agents.
	Paracetamol and Isoniazide.	Enhanced hepatotoxicity of Paracetamol and Isoniazide.
Proton pump inhibitors (PPI's)	Dipyridamole	Reduction in bioavailability of Dipyridamole.
	Antiepileptic agents	Prolongation of half life of antiepileptic agents.
	Warfarin	Prolongation of half life of Warfarin
Antacids	Milk	Milk-alkali syndrome characterised by hypocalcaemia, alkalosis and renal insufficiency
	Gemfibrozil, Iron preparations, Tetracyclines, Antimuscarinics, Phenothiazines, Digixin, Fat soluble vitamins, Sulfadiazine and Indomethacin	Reduction in absorption and bioavailability of interacting agents.
	Ticlopidine	Increase in absorption of Ticlopidine.
	Enteric coated delayed release preparations	Premature dissolution of enteric coated delayed release preparation.
Anticholinergics	Cimetidine	Increase Cimetidine induced reduction in gastric acid secretion.
Ulcer protectives	Antacids and Levothyroxin.	Reduction in effect of antacids and Levothyroxin.

Table 3: Marketed herbal preparations claiming antiulcer use (25)

Brand Name	Active Ingredients	Mfg.Com-pany
Pepticare	*Glycyrrhiza glabra, Emblica officinalis* and *Tinospora cardifolia,* Sootsekharras, Praval Bhasma, Kapardi Bhasma (Calcium), SuvarnaMakshikbhasma (Ferri sulfuratum) and Sodhit gairik (silicate of alumina and oxide of iron).	Ayur Herbals Pvt.Ltd, Baroda
Zulcer (Capsule)	*Phyllanthus emblica, Picrorrhiza kurroa, Nardostychis jatamansi, Tinospora codifolia, Caryophyllus aromaticus, Hyoscymus niger, Sesbania grandiflora, Foeniculum vulgare, Acorus calamus, Celastrus panniculatus*, Calx of Oyster shells, Calx of Conch shells, Calx of Cowry, Calx of Gypsum, Calx of Corals, Calx of Chalcopyrite, Kamdudha Rasa and Sutshekhar Rasa.	Guphic Pharma, Ahmedab-ad
Zulcer (Syrup)	*Phyllanthus emblica*, *Tinospora codifolia, Glycyrrhiza glabra, Asparagus racemosus*, *Garcinia indica, Hedychium spicatum* and *Zingiber officinale.*	Guphic Pharma, Ahmedab-ad

Himcocid (Suspension and Tablet)	Cowrie shell, Soft stone, Oyster shell and *Glycyrrhiza glabra.*	Himalaya Herbal Health-care Bangalore
Amlant (Capsule)	*Zingiber officinate, Piper nigrum, Piper longum, Terminalia chebula, Terminalia bellirica, Cyperus rotundus, Cinnamonmum tamala, Elettaria cardamomum, Embelia ribes, Emblica officinalis, Syzygium aromaticum, Ipomoea turpethum, Glycyrrhiza glabra*, Sarjika kshar, Sheetal parpati and Mishri crystal sugar.	Maharshi Ayurveda, Delhi
Drakshavleha	*Vitis vinifera, Cinnamomum zeylanicu, Myristica fragrans, Elettaria cardamomum, Syzygium aromaticum, Musua ferrea, Nelumbium speciosus* and *Crocus sativus.*	Dabur India Ltd, Mumbai
Mebarid (capsule and Syrup)	*Holarrhena antidysenterica, Berberis aristata, Aegle marmelos, Punica granatum, Myristica fragrans, Salmalia malabaric* and *Panchamrut parpati.*	Phyto- Pharma, Kolhapur
DHC-1	*Bacopa monnieri, Emblica officinalis, Glycyrrhiza glabra, Mangifera indica* and *Syzygium aromaticum.*	Himalaya Drug Company, Bangalore

SCIENTIFIC DOCUMENTATION OF HERBS

Cheng et al., (26) studied the healing effect of oral administration of different concentration of *Centella asiatica* water extract (CE) and asiaticoside (AC), an active constituent of CE, on acetic acid induced gastric ulcers in rats which is pathologically similar to chronic gastric ulceration in humans (27). In this model, acetic acid produced mucosal injury, which was confined to the glandular stomach (28). The ulcer produced

by acetic acid is due to the release of histamine, which increases the capillary permeability and back diffusion of HCl (29). *Centella asiatica* enhanced tensile strength in wound tissue (30) and wound healing process was attributed to active ingredient asiaticoside (AC) (31). Myeloperoxidase is a marker of neutrophil infiltration during inflammation. CE and AC were found to reduce size of ulcer in dose dependent manner with concomitant attenuation of myeloperoxidase activity at ulcer tissue which in turn may decrease the production of reactive oxygen species and reduce concomitant tissue damage. CE and AC promoted angiogenesis, and thereby improved circulation to wound site. This in turn provided oxygen and nutrients essential for healing process (32-34). The effect of CE on angiogenesis may be due to its induction on bFGF expression, since bFGF is a strong angiogenic factor (35, 36). Results suggested that CE and AC contributed to healing of gastric ulcers with their angiogenic and anti-inflammatory properties.

Propolis is a resinous product collected by honeybees from plants (37). Modern herbalists recommended its use because it displays antibacterial, antifungal, antiviral, hepatoprotective, anti-inflammatory, immunomodulatory and antiulcer properties (38, 39). Havsteen et al., (40) attributed biological activities of propolis to its flavonoids. Barros et al. (41) evaluated antiulcer activity of green propolis hydroalcoholic crude extract by using models of acute gastric lesions induced by ethanol, indomethacin and stress in rats. The ability of gastric mucosa to resist injury by endogenous secretions (acid, pepsin and bile) and by ingested irritants can be attributed to mucosal defense (42). The formation of gastric mucosal lesion by necrotising agents such as ethanol has been reported to involve in the depression of these gastric defensive mechanisms (43). Also, ethanol administration reduces mucus production, increases the release of histamine and production of leukotrienes which aggravate ulcers (44). According to miller., (45), stress induced ulcers are caused by the increase in free radical generation apart from acid pepsin factor. Gastric mucus is believed to play an important role in the defensive mechanism against gastric ulceration (46). The protective effect of mucus as an active barrier may be attributed to the glycoproteins, which have the property of holding water in the interstices, thus obstructing the diffusion of hydrogen ions. Stress has been shown to increase the amount of mucus adhering to gastric mucosa (47). Prostaglandins are gastro protective and increase mucosal resistance to aggressive factors like acid and pepsin. NSAIDs like indomethacin have ability to suppress prostaglandin synthesis and hence causing gastro duodenal ulceration (42). Green propolis extract (500mg/kg) significantly reduced the indomethacin induced ulcers. Further, 250 and 500 mg/kg of green propolis inhibited the production of stress induced ulceration which are mediated by histamine release as well as reduced mucus production, called defensive factor. These results suggested possible use of green propolis in ulcer cases especially with impaired defence mechanism. It has been well reported that impaired defence is commonly observed due to modernisation of life in today's competitive world which finally leads to stress ulcer. The aforementioned findings are quite promising to prevent and control stress ulcers (41).

Kielmeyera coriacea Mart. is a Brazilian cerrado plant belonging to family Guttiferae and is popularly known as "Pau Santo". Audi et al., (48) reported anxiolytic activity of *Kielmeyera coriacea* using elevated plus maze test in rats. Xanthone, triterpenes and a biphenyl from *Kielmeyera coriacea* had shown antifungal activity against *cladosporium cucumorinum* and *candida albicans* (49). Oral administration of 30mg/kg of *Kielmeyera coriacea* showed significant antiulcer activity in ethanol-acid and indomethacin models but not in acute stress model suggesting a direct protective effect of *Kielmeyera coriacea* on gastric mucosa and increased resistance to necrotizing agents (50). Ethanol-acid causes gastric mucosal ulcers either by a direct effect on gastric epithelium, or are modulated indirectly by release of vasoactive products from mast cells (51), resulting in release of mediators such as histamine (52). Endogenous histamine formation and its release from mast cells in gastric mucosa

have also been implicated in pathogenesis of gastric ulcers produced by acute stress (53). Indomethacin induces gastric ulceration by inhibition of prostaglandin biosynthesis which is known to play important role in maintaining mucosal integrity. The exact mechanism underlying the protective action of extract against ethanol and indomethacin induced gastric lesions are yet to be investigated. However it may be employed with long term NSAID treatment (eg: Arthritis) in order to prevent associated ulcer formation and thereby may improve the outcome of NSAID therapy too (50).

Benincasa hispida (Thunb) Cogn. is a widely used vegetable in India and other tropical countries and it belongs to family cucurbitaceae (54). In Ayurveda, *Benincasa hispida* is recommended for management of peptic ulcer, haemorrhages from internal organs, epilepsy and other nervous disorders (55, 56). Uchikoba et al., (57) isolated the protease enzyme from sarcocarp of *Benincasa hispida* var. Ryukyu and found it suitable for food technology. Oral administration of fresh juice, supernatant and alcoholic extract was dose dependently effective in lowering mean ulcer size in swimming stress induced ulcer model in mice. This activity was further attributed to its antihistaminic, anticholinergic and CNS effects. Antiulcerogenic activity in indomethacin plus histamine induced ulcers was also studied in rats and mice wherein supernatant alone showed dose dependent effect (20). Development of duodenal ulcers induced by indomethacin plus histamine involves both an increase in gastric acid secretion and an impairment of acid induced duodenal bicarbonate secretion. While histamine increases acid secretion, indomethacin inhibits mucosal defence. (58).

Casa et al., (59) evaluated ulcer protecting effect of rutin, a natural flavone, against lesions induced by 50% ethanol in rats. Pretreatment with highest dose of rutin (200mg/kg), 120min before 50% ethanol, resulted in most effective prevention of necrosis by inhibition of thiobarbituric acid (TBA, as index of lipid peroxidation) levels. A lipid peroxidation result in the production and release of substances that recruit and activate polymorphonuclear leukocyte (60) and the degree of neutrophil infiltration in gastric mucosa has been related to the genesis of lesions (61). Results suggested that gastroprotective effect of rutin was mediated via antilipoperoxidant effect, enhancement of glutathione peroxidase (GSH-Px, an important antioxidant enzyme) with possible involvement of sulphydryl compounds (SH). It is reported that SH containing compounds are gastroprotective agents and may maintain high blood flow that allows an energy dependent rapid recovery from initial epithelial surface damage (62). Moreover they limit the production of oxygen derived free radicals, and could be related with cellular protection (63).

Maytenus ilicifolia Mart. Ex. Reiss. (Celastraceae) is a native plant from Tropical Atlantic forest. The leaves of some Celastraceae plants are used in traditional medicine due to their analgesic, anti-inflammatory and antiulcerogenic activities (64). Souza Souza-Formingoni et al., (65) proved the protective action of the tea prepared by pouring boiling water on fresh or dried leaves of *Maytenus ilicifolia* and *Maytenus aquifolium* against the experimental development of ulcer in rats. The presence of phenolic metabolites such as condensed tannins (66), flavonoids (67) and triterpene (68, 69), could justify the usage of some species of *Maytenus* as anti-inflammatory and antiulcerogenic remedies. Jorge et al., (70) further validated antiulcer activity of *Maytenus ilicifolia* against cold-restraint stress induced ulcer in rats using hexane and ethylacetate extracts.

The formulations which contain herbal drugs along with mineral ingredients are called herbomineral formulation. Pepticare, a herbomineral formulation consists of *Glycyrrhiza glabra*, *Emblica officinalis*, *Tinospora cardifolia*, Praval Bhasma, Kapardi Bhasma (Calcium), Suvarna Makshikbhasma (Ferri sulfuratum) and Sodhit gairik (silicate of alumina and oxide of iron) (71). *Emblica officinalis* and *Tinospora cardifolia* are categorised as "rasayanas" (rejuvenatives), a non toxic Ayurvedic complex herbal preparation used to rejuvenate or attain the complete potential of an individual in order to prevent disease and degenerative changes that lead to disease. Bafna et al., (71) tested Pepticare using various doses (125, 250, 500 and 1000mg/kg, p.o) for its antiulcer activity in pylorus ligated and ethanol induced gastric mucosal injury in rats. It is well known that pylorus ligature causes gastric hypersecretion, but the reasons are not yet completely explained. It is described that due to surgery, the stomach gets larger, and the pressure on sensitive receptors in the antral gastric mucosa increases and activates the vagus-vagal reflex, causing increased gastric secretion (72). Further, neutrophil migration in mucosa following pylorus ligation suggest that these cells might be involved in gastric mucosal injury, possibly by releasing free radicals that cause lipid peroxidation and damage to cell membrane (73). Antioxidant enzymes, such as Superoxide dismutase (SOD) and Catalase (CAT) are the first line of defense against reactive oxygen species. Reduced glutathione (GSH) is a major low molecular weight scavenger of free radical in the cytoplasm and an important inhibitor of free radical mediated lipid peroxidation (74). Pylorus ligation increased lipid peroxidation and decreased SOD, CAT and GSH in control groups, leading to oxidative stress. Pepticare was found more potent than *Glycyrrhiza glabra* alone against pylorus ligation; ethanol induced ulcers and showed significant reduction in ulcer index and total acidity in both the models. This activity was principally attributed to antioxidant mechanism of Pepticare (71).

The Indian traditional system of medicine has identified the *Piper betel* leaves with digestive and pancreatic lipase stimulating activities (75, 76). Bhattacharya et al., (9) evaluated the protective activity of allylpyrocaqtechol (APC), the major antioxidant constituent of *Piper betel*, against indomethacin induced stomach ulceration in rats. Gastrointestinal toxicity associated with NSAIDs is an important medical problem despite recent pharmaceutical advances (77). Besides being used as analgesics, the NSAIDs are being increasingly used for prevention of malignancies, stroke, preeclampsia, alzheimer's disease etc (78, 79). The percentage of gastric ulcer cases induced by NSAIDs is emerging day by day accounting for approximately 25% of gastric ulcers (80). Treatment with APC

for 7 days suppressed most of the biochemical adverse effects induced by indomethacin, a prototype of NSAIDs with concomitant increase in SOD and CAT levels (9).

It is well known that stress plays an important role in etiopathology of gastroduodenal ulceration and stress induced ulcer, a major type of ulcer is probably mediated by increase in gastric motility, vagal overactivity (81), mast cell degranulation (82), decreased gastric mucosal blood flow (83) and decreased prostaglandin synthesis (84). A study on gastroprotective potential of *Anogeissus latifolia* extract (ALE) (100 and 200mg/kg body weight) on aspirin, cold resistance stress (CRS), pylorus ligated (PL) and ethanol induced ulcers in rats suggested significant gastroprotective activity of ALE in CRS induced ulcers. ALE decreased lipid peroxidation (LPO) and superoxide dismutase (SOD) with concomitant increase in catalase (CAT) activity in CRS induced ulcers. Protective action of ALE (200mg/kg) against aspirin and stress induced ulceration was attributed to its 5-lipooxygenase inhibitory activity and histamine antagonistic, anticholinergic and antisecretory effects respectively. The study encourage towards possible use of ALE to control stress ulcers, incidence of which are increasing with the modernisation of life. (85).

Oral administration of *Gynostemma pentaphyllum* butanol fraction (GPB) at 200 and 400mg/kg body weight significantly inhibited gastric ulcer formation induced by indomethacin, HCl/Ethanol and water immersion restraint stress in rats (86). The water immersion stress induced ulcers are mediated by increase in gastric acid secretion (87) and decrease in mucosal microcirculation (88) and mucus content (89). The reduced microcirculation when coupled with enhanced acid secretion aggravates the condition at faster rate. Pretreatment with GPB increased gastric mucus in HCl/Ethanol ulcerated rats while in pylorus ligated rats, it had shown no effect on gastric volume, and pH or acidity output thus indicating lack of antisecretory effect. Results indicated that GPB possessed gastroprotective potential related to the preservation of gastric mucus synthesis and secretion which may be a value addition as an adjuvant therapy to current medication (86).

Casearia sylvestris (Flacourtiaceae) is a plant used in popular medicine in Brazil for treating traumas. There are some reports about its use for treating skin lesions and small ulcerations (90). Its pharmacological action has been referred to volatile oils, tannins and triterpenes content of the leaves (91). Esteves et al., (92) evaluated antiulcer activity of the essential oil from *Casearia sylvestris* (EOCS) using stress induced and pylorus ligated ulcers. EOCS inhibited 90% of stress induced ulcers while cimetidine inhibited 70% suggesting the potential alternative to the existing synthetic medication. Terpenic compound, bicyclogermaerene (sesquiterpene), detected in essential oil was attributed for its antiulcer activity (92).

Mauriri pusa Gardn. (Melastomataceae) is a medicinal plant traditionally used in the central region of Brazil against gastric ulcer. Andreo et al. (2006) evaluated gastroprotective activity of methanolic (MeOH) and dichloromethane (DCM) extracts obtained by sequential extraction from leaves of *Mouriri pusa* against injuries caused by necrotizing agents like 0.5% HCl / 60% EtOH, absolute ethanol, NSAIDs, stress and pylorus ligature in mice and rats. MeOH extract, 5mg/kg, p.o alone showed significant antiulcer activity (93).

In current clinical practice, many patients of ulcer exhibit complex pathophysiology indicating need of drug(s) with putative mechanism of action (94). It has also been demonstrated that many antiulcer drugs and formulation are effective in the similar way (7, 25). Furthermore, most of them possess antioxidant action (95, 96, 97). In light of this, ethanolic extract of leaves of *Jasminum grandiflorum* L. (JGLE) was screened for its antiulcer potential against aspirin plus pylorus ligation (APL) induced ulcers (4). APL induces ulcer due to pylorus obstruction followed by impaired mucosal digestion and thereby accumulation of acid-pepsin (98). The traditional claim regarding its use in ulcerative stomatitis made it ideal to validate against APL induced ulcers (99). The significant prevention of APL induced ulcer with the pretreatment (100, 200 mg/kg, p.o) of JGLE validated its traditional claim. The study attributed the effect for its antisecretory and antioxidant potential (4).

Mammea americana L. (Guttiferae) is a tree native to the West Indies and Northern South America have been used for its several medicinal properties (100, 101). The evaluation of antiulcer activity of ethanolic, methanolic and dichloromethane extract of *Mammea americana* against 0.3M HCl/60% EtOH, hypothermic restraint stress, indomethacin and pylorus ligation induced ulcers found significant prevention of these ulcers by ethanolic and dichloromethane extracts only. As the aforementioned models of ulcers involves different mechanisms of induction, hence study revealed complex mechanism of action of extracts. This may be possible due to presence of numerous phytochemicals that acts simultaneously and synergistically. The possible actions exhibited by the extracts pretreatment are synthesis of mucus, phospholipids, bicarbonates and prostaglandins as well as reduced acid and pepsin outputs (102).

Malairajan et al., (103) reported antiulcer activity of ethanolic extract of *Toona ciliate* Roemer (Meliaceae) (300mg/kg, p.o) against aspirin plus pylorus ligation induced gastric ulcer, HCl-ethanol induced ulcer and water immersion stress induced ulcer in rats employing ranitidine, sucralfate and omeprazole respectively as reference standard. HCl-ethanol induced gastric damage in mice is due to leukotriene production and involvement of 5-lipooxygenase. So the protective effect of extract against gastric damage might be due to protection against 5-lipooxygenase and leukotriene pathway. Water immersion provides both emotional as well as physiological stress to animal. Results demonstrated that *Toona ciliate* extract produced antiulcerogenic effects mediated by its antisecretory, cytoprotective and proton pump inhibition mechanism. In routine clinical investigation, it is not always possible to rule out exact cause of ulcers, and hence ability of agent to relieve ulcer is more important. In this regards, agent with multiple favorable actions is of great use. The present investigation suggests possible use of *Toona ciliate* extract for idiopathic type of ulcers. (103).

Ocimum sanctum L. (Labiatae) is a reputed drug in Indian traditional system of medicine. Extract of *Ocimum sanctum* (1, 2and 3 ml/kg, i.p) significantly suppressed the development of ulcers in dose dependent manner against aspirin, indomethacin, alcohol, histamine, serotonin, reserpine, stress induced ulceration and pylorus ligated ulceration in experimental animal models. The result indicate that it act probably via lipooxygenase inhibitory, histamine antagonistic and antisecretory effects, however exact mechanism of its action will be clear upon detailed phytochemical analysis (8).

Unani systems of medicine prescribed the fruits of *Amomum subulantum* for treatment of GI disorders and are used as muquavvi-e-meda (stomachic), hazim (digestive), maneqai (antiemetic) and kasir-e-riyah (carminative) (104, 105, 106, 107). Jafri et al., (108) studied the effect of crude methanolic extract and its different fractions viz essential oil, petroleum ether (PE) and ethyl acetate (EA) of fruits of *Amomum subulantum* Roxb. for their ability to inhibit gastric lesions induced by aspirin, ethanol, pylorus ligature and their effects on wall mucus, output of gastric acid and pepsin. It has been postulated that histamine may be involved in the formation of pylorus ligated ulcers and play a mediating role in the gastric secretion, stimulated by gastrin, vagal excitation and cholinergic agents (109-111). The aforementioned results suggested a direct protective effect of EA fraction on gastric mucosal barrier while gastroprotective effect of PE and essential oil was attributed to their lowering effect on gastric motility (108).

Qualer grandiflora Mart (Vochysiaceae), popularly known as "Pau terra" is native to Brazilian cerrado. Hiruma-Lima et al., (112) evaluated antiulcer activity of hydroalcoholic extract of bark of *Qualer grandiflora* (500mg/kg). It exhibited decrease in ulcer index induced by HCl/ethanol solution, indomethacin/bethanechol and stress in mice. It is well reported that the suppression of prostaglandin synthesis by NSAIDs (indomethacin) results in increased susceptibility to mucosal injury and gastroduodenal ulceration (113). Cholinomimetic agents (bethanechol) administered in association with NSAIDs have a synergistic effect on gastric injury induced by increased secretion of acid and pepsin in the stomach (114, 115). In pylorus ligated model, results suggested that *Qualer grandiflora* (p.o) reduced the severity of gastric lesion only without effect on pH, gastric acidity or volume. Furthermore, phytochemical investigation of *Qualer grandiflora* hydroalcoholic bark extract suggested probable involvement of terpene, steroid, saponin, phenolic compound and tannin for aforementioned activities (112).

CONCLUSION

Considering several existing theories on peptic ulcer and the number of preclinical reports mentioned in the review, we can conclude that studies with new active principles obtained from plant sources can results in novel and effective pattern of treatment. The studies regarding possible mechanisms 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. Moreover, the effectiveness of the herbal extracts towards majority of types of ulcers that coupled with comparatively lesser side effects and drug interactions compared to existing allopathic medication can leave a unique footmark in the therapy. The study also points that many claims made in traditional system of medicines across the globe have not been satisfactorily exploited. The scientific validation of these claims may come up with ideal polyherbal formulation to substitute modern medicine.

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