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Plants and Phytochemicals for Peptic Ulcer: An Overview

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ABSTRACT
World is rich in medical lore. Plants are the basis of life on earth and are central to people's livelihoods. The use of plants in religious ceremonies as well as for magic and medicinal purposes is very commonplace and widespread. Plants and phyto-constituents are better choice to treat diseases than the allopathic drugs. Most of the drugs used in primitive medicine were originated from plants and are the earliest and principal natural source of medicines. The drugs from plants are fairly innocuous and relatively free from toxic effects. The nature has provided us various medicinal plants which became the storehouse of remedies to cure all ailments of mankind. In modern era many plant-derived compounds have been used as drugs, either in their original or semi-synthetic form. Peptic ulcer is widespread and common health problem now a day. Generation of free radicals, decrease in mucosal defensive factor or increase in mucosal injurious factor causes peptic ulcer. In this review attempts have been made to know about some plants and their constituents which may be used in treatment or prevention of peptic ulcer. Various plants like *Anogeissus latifolia, Alchornea castaneaefolia, Utleria salicifolia, Solanum nigrum, Ocimum sanctum*, *Asparagus racemosus, Scoparia dulcis, Byrsonima crassa* etc. and their phyto-constituents proved active in antiulcer therapy.
KEY WORDS: Plants, Phytoconstituents, Peptic ulcer, Antioxidants, Cytoprotective.

List of Abbreviations Used :
NSAIDs, *Non steroidal anti-inflammatory drugs*; ROS, *Reactive oxygen species*; HCl, *Hydrochloric acid*; SOD, *Superoxide dismutase*; SH, *Sulfhydryl*; DPPH, *1,1-diphenyl-2-picrylhydrazyl.*

INTRODUCTION

Peptic ulcer is one of the most common, chronic gastrointestinal disorder in modern era. Now it has become a common global health problem affecting a large number of people world wide and also still a major cause of morbidity and mortality (1). Peptic ulcer disease can be characterized by inflamed lesions or excavations of the mucosa and tissue that protect the gastrointestinal tract. Damage of mucus membrane which normally protects the oesophagus, stomach and duodenum from gastric acid and pepsin causes peptic ulcer (2). The pathophysiology of this gastro-intestinal disorder is viewed as an imbalance between mucosal defensive factors such as bicarbonate, prostaglandin, nitric oxide, peptides, growth factors and injurious factors like acid, pepsin (3, 4). The modern approach is to control gastric ulceration by inhibiting gastric acid secretion, to increase gastroprotection, to increase epithelial cell proliferation or to stop apoptosis for effective ulcer healing process (5). Though different classes of drugs are used in the treatment of peptic ulcer but most of the drugs are exhibits serious side effects like arrhythmias, impotence, gynaecomastia, arthralgia, hypergastrinemia and haemopoeitic changes (6). Alternative approach in recent days is the research of medicaments from ayurvedic or traditional medicinal system. The use of phyto-constituents as drug therapy to treat major ailments has proved to be clinically effective and less relatively toxic than the existing drugs and also reduces the offensive factors serving as a tool in the prevention of peptic ulcer (7). In this modern era also 75-80% of the world populations still use herbal medicine mainly in developing countries, for primary health care because of better cultural acceptability, better compatibility with the human body and lesser side effects. The chemical constituents present in the herbal medicine or plant are a part of the physiological functions of living flora and hence they are believed to have better compatibility with human body (8). Natural products from plants are a rich resource used for centuries to cure various ailments. The use of natural medicine in the treatment of various diseases like peptic ulcer is an absolute requirement of our time (9). Therefore, alternative approach in recent days is the research of medicaments from traditional medicine. The use of phyto-constituents as drug therapy to treat major ailments has proved to be clinically effective and relatively less toxic than the existing drugs and also reduces the offensive factors serving as a tool in the prevention of peptic ulcer.

Factors Causing Peptic Ulceration

Gastric injury induced by NSAIDs

Non steroidal anti-inflammatory drugs (NSAIDs) are used widely in the treatment of pain, fever, inflammation, rheumatic and cardiovascular disease. Chronic administration of these drugs may cause various adverse gastrointestinal effects such as gastric erosions, gastric or duodenal ulceration and severe complications such as gastrointestinal hemorrhage and perforation. NSAIDs like aspirin, indomethacin is induce ulcer by inhibition of cyclooxygenase enzyme and by suppress the prostaglandin mediated effects on mucosal protection. NSAIDs also causes generation of free radicals, produce activation of neutrophils and their adherence to the vascular endothelium causes blocking of capillaries, reduction of local

gastric blood flow, reduces the hydrophobicity of the mucus gel layer and increase in acid and pepsinogen secretion (10-12).

Helicobacter pylori

Helicobacter pylori a gram negative rod, is one of the major causes of gastritis and subsequent development of gastric and duodenal ulcers, gastric adenocarcinoma and gastric B-cell lymphoma. *H. pylori* cause gastroduodenal diseases which is associated with infiltration of gastric mucosa by neutrophil, lymphocyte, monocytes and plasma cell (13, 14).

Stress

Stress plays an important role in etiopathology of gastro-duodenal ulceration. Stress causes increase in gastric motility, vagal over activity, mast cell degranulation, decreased gastric mucosal blood flow and decreased prostaglandin synthesis results ulcers. Stress produces ulceration probably by release of histamine with enhanced acid secretion and reduced mucus production (15, 16).

Smoking

Smoking slows the healing of existing ulcer and increase the chance of ulcer reoccurrence. Cigarette smoking also increases the chance of getting an ulcer (17, 18).

Blood group

The peptic ulcer occurs higher in the people having blood group 'O' than those of blood groups 'A' and 'B' (19).

Sex

Gastric ulcer occurs to an equal extent in man and women but duodenal ulcer more commonly seen in man than in women (20).

Dietary factors

Various dietary factors involved in the peptic ulceration also. Caffeine stimulates acid secretion in stomach and can aggravate an existing ulcer. Though there is a little evidence of an association between alcohol use and peptic ulcer but ulcers are common in people who have cirrhosis of the liver, a disease which linked to heavy alcohol consumption. The amount of dietary salt consumption liked with the occurrence of gastric ulcer. The more salt consumption can induce gastritis of experimental animals (21, 22).

Free radicals

Oxygen derived free radical reactions have been implicated in the pathogenesis of many human diseases like neurodegenerative disorder, ischemic heart disease, inflammation, diabetes and also peptic ulcer (23, 24). Reactive oxygen species (ROS) may causes gastric damage by altering physical, chemical, psychological factors which results gastric ulceration in human and experimental animals. Increase in ROS and/or a decrease in antioxidant levels causes oxidative stress, which plays an important role in the pathogenesis of gastric ulcer (25). The metabolism of arachidonic acid, platelets, macrophages and smooth muscle cells generates the ROS, this may contribute to gastric mucosal damage. Oxygen free radicals are detrimental to the integrity of biological tissue and mediate their injury. The mechanism of damage involves lipid peroxidation, which destroys cell membranes and also release of intracellular components such as lysosomal enzymes which are responsible for further tissue damage. The radicals also promote degradation of the epithelial basement membrane components, complete alteration of the cell metabolism leads to mucosal damage (26-30).

PLANT EXTRACTS AND PHYTOCONSTITUENTS IN PEPTIC ULCER

Various medicinal plants are used traditionally in the treatment of peptic ulcer. Plants and phytomedicines exhibit their action by various mechanisms like antioxidant, cytoprotective, antisecretory action. Some of the plants and their phytoconstituents showing antiulcerogenic activity are tabulated in Table 1.

Table 1: Some Medicinal plants having antiulcerogenic activity

Botanical name	Traditional uses	Plant parts used	Chemical constituents in plant extract	Model for antiulcer study
Jasminum grandiflorum Family: Oleaceae	skin diseases, ulcers, wounds, otalgia, leprosy, ottorrhoea, dysmenorrhoea	leaves	alkaloids, saponins, phenolics, flavonoids, carotenoids, glycosides and carbohydrates	aspirin+pylorus ligation, absolute alcohol and acetic acid induced ulcer
Anogeissus latifolia Family: Combretaceae	skin diseases, snake and scorpion bite, stomach diseases, colic, cough and diarrhea	bark	(+) leucocyanidin, ellagic acid, glycosides of ellagic, flavellagic acid and gallic acid	aspirin, cold resistant stress, pylorus ligated and ethanol induced ulcer
Alchornea castaneaefolia Family: Euphorbiaceae	gastric pain, gastritis, ulcer, rheumatism, arthritis, flu and muscular pain	leaves and bark	quercetin-3-*O*-β-D-galactopyranoside, quercetin-3-*O*-α-L-arabinopyranoside, myricetin-3-*O*- α-L-arabinopyranoside, quercetin, gallic acid, amentoflavone, glycolipids and free sugars	HCl/ethanol, hypothermic restraint stress, pylorus ligated, acetic acid and indomethacin induced gastric ulcers in cholinomimetic treated mice
Utleria salicifolia Family: Periplocaceae	In colic and bleeding due to ulcer	rhizome	steroids, alkaloids, terpenoids, saponins and tannins	aspirin, ethanol, cold restraint stress, pylorus ligated, acetic acid and cysteamine

				induced ulcer
Solanum nigrum Family: Solanaceae	liver disorders, skin disease, fevers, inflammatory conditions, painful periods, diarrhoea, eye diseases, ulcer	fruits	tannins, alkaloids, carbohydrates, saponins, volatile oil and anthocyanins	cold restraint stress, indomethacin, pyloric ligation and ethanol induced ulcer
Ocimum sanctum Family: Labiatae	asthma, chronic fever, cold, cough, malaria, dysentery, convulsions, diabetes, diarrhea, arthritis, emetic syndrome etc.	leaves	eugenol, carvacrol, caryophyllene, apigenin, luteolin, apigenin-7-*O*-glucuronide, orientin, molludistin and ursolic acid	cold restraint stress, aspirin, alcohol, pylorus ligation, histamine and acetic acid induced ulcer
Scoparia dulcis Family: Scrophulariaceae	respiratory, gastric, hepatic disturbances, anti-inflammatory, diabetes and hypertension	aerial parts	cirsitakaoside (5-hydroxy-6,7-dimethoxyflavone 4- *O*-β-D-glucopyranoside) and quercetin	pylorus ligated, histamine and bethanechol stimulated gastric secretion
Byrsonima crassa Family: Malpighiaceae	antiemetic, diuretic, febrifuge, ulcer and in gastritis and diarrhea	leaves	quercetin-3-*O*-β-d-galactopyranoside, quercetin-3-*O*-α-l-arabinopyranoside, amentoflavone, catechin and epicatechin.	HCl/ethanol-induced ulcer
Asparagus racemosus Family: Liliaceae	antispasmodic, astringent, antidiarrhoeatic, antidysentric, useful in tumours, throat infection, leprosy etc.	root	Total saponins like shatavarin I–IV	cold restraint stress, pyloric ligation, aspirin +pyloric ligation, aspirin, ethanol, cysteamine induced ulcer
Centaurea solstitialis Family: Asteraceae	ulcer and in gastritis	spiny flowers	sesquiterpene lactones chlorojanerin, 13-acetyl solstitialin A and solstitialin A	Ethanol, indomethacin, indomethacin + HCl/ethanol, *N*Gnitro-l-arginine methyl ester +ethanol, *N*-ethylmaleimide + ethanol, water restraint stress, and serotonin induced ulcer
Anacardium occidentale Family: Anacardiaceae	antimicrobial, antidiarrhoeal, antihypertensive, antidiabetic, increase urination, antiinflamatory etc.	leaves	glycosylated quercetin, glycosylated myricitin, catechin, a tetramer of proanthocyanidin and biflavonoid amentoflavone.	HCl/ethanol induced gastric lesions
Calophyllum brasiliense Family: Clusiaceae	rheumatism, varicose, haemorrhoids and chronic ulcers	stem bark	flavones, flavonols, triterpenoids, xanthones and steroids	ethanol, indomethacin, hypothermic restraint stress, pyloric ligation and bethanechol induced ulcer

Rhizophora mangle Family: Rhizophoraceae	antiseptic, astringent, haemostatic, dyspepsia, antifungal, antidiarrheal, inflammations etc.	bark	polyphenols, catechin, epicathechin, gallic and elagic acids, Chlorogenic, gallotannins, elagitannins and condensed tannins	diclofenac induced ulcer
Larrea divaricata Family: Zygophyllaceae	anti-inflammatory and anti-rheumatic	leaves	Dihydrogualaretic acid	absolute ethanol and 0.6N HCl induced ulcer
Hemidesmus indicus Family Asclepiadaceae	In blood diseases, diarrhea, syphilis, fever and skin, eye, respiratory, kidney disorders etc.	root	alkaloids, tannins and phenols, saponins	pyloric ligated, aspirin + pyloric ligated, cyteamine induced duodenal ulcer
Spartium junceum Family: Fabaceae	mild sedative and diuretic, peptic ulcer	flower	alkaloids and saponin, main chemical constituent is spartitrioside	water immersion restraint, ethanol, pyloric ligation induced ulcer
Amomum subulatum Family: Zingiberaceae	In gastrointestinal disorders, digestive, stomachic, antiemetic and carminative	fruit	essential oils, anthocyanins, aurone and flavanone	aspirin, ethanol and pylorus ligature induced ulcer

Jasminum grandiflorum

Jasminum grandiflorum L. is a folk medicine. Antiulcer activity of *Jasminum grandiflorum* L. was investigated using 70% ethanolic extract of leaves. It also produces *in vitro* antioxidant activity (31). Ethanolic extract of leaves produces antisecretory activity which is observed by the significant ($P<0.01$) reduction of the gastric juice volume, free acidity and total acidity and increase in gastric juice pH when compared to ulcer control in aspirin plus pylorus ligation-induced ulcer model. Extract also produce significant ($P<0.01$) reduction in ulcer index in ethanol induced ulcer may be due to its antioxidant activity. In acetic acid induced chronic ulcer model gastric lesions occur due to the release of histamine, which increases the capillary permeability and back diffusion of hydrochloric acid (HCl). Pretreatment with the extract showed complete regeneration of mucosal glandular structure. Thus antisecretory and antioxidant activities of the extract may responsible for its antiulcer activity.

Anogeissus latifolia

Bark of *Anogeissus latifolia* (Roxb. ex DC.) Wall. ex Guill. & Perr. important for its ethnobotanical uses. Gastroprotective effect of 50% aqueous alcoholic extract of the bark of *Anogeissus latifolia* was studied (32). The plant has also been reported for its wound healing and radical scavenging activity (33, 34). In aspirin induced ulcer *Anogeissus latifolia* bark extract (200 mg/kg) protects gastric mucosa 66% and the protective action may be due to its 5-lipoxygenase inhibitory effect. Extract produces gastroprotective effect on ethanol induced ulcer as dose dependent manner. *Anogeissus latifolia* extract also active against the cold resistant stress induced ulcers (84.16%) and pylorus ligation (67.64%) at 200 mg/kg may be due to its histamine antagonistic, anticholinergic, antisecretory and antioxidant effect. Extract contain high percentage of the gallic acid and ellagic acid (0.95% w/w and 0.25% w/w respectively). Thus high percentage of the gallic acid and ellagic acid in the extract justifies the potent antioxidant activity of the plant and which may be important for its antiulcer activity.

Alchornea castaneaefolia

The hydroethanolic extract of the leaves and bark obtained from *Alchornea castaneaefolia* A. Juss. showed significant ulcer preventive effect (35). Leaves and bark extract at dose of 1000 mg/kg orally significantly inhibit ulcer formation 88% and 86% respectively in HCl/ethanol induced ulcer on mice and 62% and 60% respectively in indomethacin/bethanechol induced ulcer models. Pre-treatment with leaf extract protect gastric mucosa 55% in hypothermic restraint stress-induced ulcers in mice and 34% in pylorus ligated mice, but it does not produce any anti secretory effect in shay model. Leaf extract also decreased the mean area of chronic ulcer and proved effective in promoting the healing process in chronic gastric ulcer induced by acetic acid in rats. Enriched flavanoidic

fraction was isolated from hydroethanolic extract of leaf and administration separately, it (100 mg/kg) produced 52% and 79% gastroprotection against HCl/ethanol and NSAIDs induced gastric lesions respectively. But it did not show any significant increase in mucoprotective effect in pylorus ligated animals. Pretreatment with enriched flavanoidic fraction shows drastic increase of prostaglandin E_2 levels which is markedly reduced on indomethacin treatment. Enriched flavanoidic fraction also produce marked decrease in the serum gastrin level and almost three times increase in serum level of somatostatin hormone when compared to the negative control. Gastrin is a gastrointestinal hormone stimulates of the gastric acid secretion (36) and somatostatin is a regulatory peptide produce potent inhibitory effects on gastric acid, pepsin and gastrin secretion (37). Phytochemical investigation shows presence of various flavonoids glycosides in extract. So *Alchornea castaneaefolia* produced its action by strengthen defensive factors like prostaglandin synthesis, in addition to other gastroprotective actions, like a stimulant effect on somatostatin synthesis and an inhibitory effect on gastrin secretion.

Utleria salicifolia

Utleria salicifolia Bedd. Ex. Hook. F. is one of the ethnobotanical plant found in south western ghats of India. The 50% ethanolic extract of *Utleria salicifolia* rhizome posses antiulcer activity in dose dependent manner (38). It produces 14.48–51.03%, 28.80–56.52%, 13.22–60.74%, 21.22–77.14% and 20.0–84.37% protection in pylorus ligation, aspirin, ethanol, cold-restraint stress and acetic acid induced ulcer respectively. Mucus secretion and bicarbonate secretion are the first line of defense against potential ulcerogens. *Utleria salicifolia* extract significantly (P<0.001) increased gastric wall mucus in ethanol induced ulcer, proved its cytopotective activity. Rhizome extract of *Utleria salicifolia* (100 and 200 mg/kg) also protect ulcer by 68% and 90% against cysteamine induced duodenal ulcer in rats. Lipid peroxidation level is an indicator for the generation of ROS in the tissue (39). Free radicals induce cell degeneration via peroxidation of membrane lipids, breaking of DNA strands and denaturing cellular proteins result injury in cell (40). Antioxidant activity of the extract observed against cold-restraint stress induce ulcer with increased superoxide dismutase (SOD) and decreased lipid peroxidation level when compare to ulcer control. It also decreased elevated level of plasma corticosterone. Thus antiulcer effect of extract of *Utleria salicifolia* may be due to its increase in first line of defense system, free radical scavenging activity and provide close relationship between free radical scavenging activity and the involvement of endocrinological (plasma corticosterone) responses.

Solanum nigrum –

Solanum nigrum Linn. is a traditional medicine and recommended in ayurveda for the treatment of gastric ulcers. Antiulcer effect of *Solanum nigrum* fruits extracts was investigated in various ulcer induced model in rodents (41). The aerial parts of *Solanum nigrum* extract show antisecretory action (42). *Solanum nigrum* fruit also posses antioxidant, hepatoprotective and antitumor activity (43-45). Pre-treatment with *Solanum nigrum* fruits extracts at higher dose significantly inhibited the gastric lesions induced by cold restraint stress (76.6%), indomethacin (73.8%), pyloric ligation (80.1%) and ethanol (70.6%). *Solanum nigrum* fruits extracts healed acetic acid induced chronic ulcer also. Extract decrease the volume of gastric acid, acid concentration, acid output, pepsin concentration and pepsin output in pyrolus ligated animals. Significant increase in plasma concentrations of the gastric hormone, gastrin and an increase in the gastric mucosal H^+K^+ATPase activity were observed in ethanol induced ulcerated rats. Increased acid secretion, generation of free radicals and hyperoxidation of lipid causes ulcer in stress and ethanol induced ulcer. Gastrin hormone significantly reduced with pretreatment with extract which regulates gastric acid secretion, releases of histamine and gastric endocrine cell proliferation (46). Thus anti-secretary activity of *Solanum nigrum* mainly related to the inhibition of H^+K^+ATPase and suppression of gastrin release, while its ulcer protective and ulcer healing activities may be primarily related to an antisecretory and antioxidant activity.

Ocimum sanctum

Ocimum sanctum Linn. (Tulsi) one of the important medicinal plant in ayurveda reported for anti-carcinogenic, anthelmintic, anti-rheumatic, anti-stress, anti-bacterial, anti-septic, antioxidant, anti-stress and antifertility activity (47-51). The ethanolic extract of leaves of *Ocimum sanctum* shows anti-ulcerogenic activity (52). Extract of *Ocimum sanctum* (100 mg/kg) produced protection index 65.07%, 63.49%, 53.87%, 62.06% and 61.76% in cold restraint, aspirin, alcohol, pyrolus ligation and histamine induced ulcer respectively. Accumulation of gastric acid and pepsin which leads to auto-digestion of gastric mucosa and generation of free radicals causes ulcer in pyrolus ligated model (53, 54). *Ocimum sanctum* found to reduce free and total acidity, peptic activity and increased mucus secretion of gastric juice in pylorus ligation induced ulcer model. Incidence of ulcer in different ulcer model due to increased acid secretion, decrease in mucosal defense factor and generation of free radicals. So anti-ulcerogenic activity of *Ocimum sanctum* either due to the effect on acid secretion or on cytoprotection or on both. *Ocimum sanctum* also found effective in acetic acid induced chronic ulcer model. Healing of ulcer depends on regeneration of mucosal glandular structure and migration of epithelial cells to cover ulcer crater. So the ulcer healing property of *Ocimum sanctum* may be due to its cytoprotective activity coupled with antisecretory effect. The antiulcer effect of fixed oil of *Ocimum sanctum* was also investigated (55). Fixed oil of dried seeds produce antiulcer potential on various ulcer models like aspirin, indomethacin, alcohol, histamine, reserpine, serotonin, stress and aspirin plus pylorus ligated induced ulcer models. Significant reduction of ulcer index was observed in dose dependent manner. Results proved that, *Ocimum sanctum* and its active constituents are effective therapeutic agent to treat gastric ulcer.

Scoparia dulcis

Freeze-dried aqueous extract of the aerial parts of *Scoparia dulcis* L. produced reduction gastric hypersecretion and ulcer in rodents (56). Aqueous freeze-dried extract of *Scoparia dulcis* mixed up with water and extracted with n-butanol. The antiulcerogenic activity of the resulting aqueous phase and butanolic phase which is flavonoid-rich were also investigated. Pre-treatment with the aqueous extract of *Scoparia dulcis* (0.5-1 g/kg, p.o.) produce significant reduction in ulcer in dose dependent manner against indomethacin and ethanol induced ulcer. Aqueous extract and flavonoid-rich fraction produce antiulcer effect by decreasing volume of gastric juice, total acidity and by increases in pH in pyrolus ligated induced ulcer. But the water phase was found inactive. Flavonoid-rich fraction found 4–8 times more active than the aqueous extract in the pylorus ligature model. Both histamine and bethanechol stimulated gastric acid secretion but potently inhibited by aqueous extract of *Scoparia dulcis*. So it may due to blockade or inhibition of a common target in the cascade of events that leads to gastric acid secretion such as the H^+K^+ATPase. Flavonoid-rich fraction inhibit H^+K^+ATPase, it (0.01–1 mg/ml) prevented the hydrolysis of Mg^+-ATP by the isolated rabbit gastric H^+K^+ATPase with IC_{50} = 500 μg/ml. Cirsitakaoside and quercetin active principle of flavonoid-rich fraction produces inhibition of the gastric H^+K^+ATPase activity *in vitro* (57, 58). Inhibition of gastric secretion by the aqueous extract of *Scoparia dulcis* may be due to the inhibition of the H^+K^+ATPase enzyme.

Byrsonima crassa

Byrsonima crassa Niedenzu (IK) is a folk medicine, bark and leaves are used in antiemetic, diuretic, febrifuge, ulcer, gastritis and diarrhea (59). Antiulcerogenic effect of hydromethanolic, methanolic and chloroform extracts of the leaves of *Byrsonima crassa* (60) investigated against HCl/ethanol-induced gastric ulcer. Ethanol treatment causes solubilization of mucus with a concomitant fall in the transmucosa potential difference and increase Na^+ and K^+ flow into the lumen, pepsin secretion, the loss of H^+ ions and the histamine content in the lumen. DNA, RNA and protein level also depressed by ethanol leading to flow stasis and injured areas (61). Generation of free radicals also play important role in pathogenesis of ethanol induced peptic ulcer. Choloform extract (250, 500 and 1000 mg/kg) inhibited ulcer formation by 59%, 57% and 69% respectively, hydromethanolic extract (250, 500 and 1000 mg/kg) reduced the incidence of gastric lesions by 74%, 78% and 92% respectively and the methanolic extract reduced the ulceration by 93% and 99% at the doses of 500 mg/kg and 1000 mg/kg. Phytochemical investigation methanolic extract shows the presence different flavanoids. Science the catachol and flavonoids possessing antioxidant ant antiulcer activity so extract may be involved in the scavenging of the reactive oxygen species on the surface of gastric mucosa, thus protecting cells from gastric injury.

Asparagus racemosus

Antiulcer effect of methanolic extract of fresh roots of *Asparagus racemosus* Willd. was investigated (62). Extract showed protective effect against gastric ulcers induced by cold restraint stress, pyloric ligation, aspirin plus pyloric ligation, acetic acid and cysteamine induced duodenal ulcers but it was found ineffective against aspirin and ethanol induced ulcer. In pylorus ligated ulcers extract produce increased individual mucopolysacharide leading to increase in total carbohydrates but did not decrease acid, pepsin secretion and did not produce any effect on cell proliferation. So, protective effect of *Asparagus racemosus* against pylorus ligated ulcers may be due to its cytoprotective nature without influencing acid secretion or neutralising intra-gastric acidity. *Asparagus racemosus* was found ineffective against aspirin induced ulcers because extract may not able to overcome the loss of protective effect caused by decrease in prostaglandins and absence of effect on cell proliferation, as damage caused by aspirin. Activity of *Asparagus racemosus* against aspirin plus pylorus ligated ulcer may due to its cytoprotective activity apart from prostaglandins synthesis. Free radicals are one of the important factors that contributed in stress induced ulcer. Treatment with extract significantly decreases the lipid peroxidation level which can correlate with its antioxidant activity. The polysaccharide fraction of plant has been reported to possess significant antioxidant activity *in vitro* (63). Thus antiulcer effect of *Asparagus racemosus* against stress induced ulcer may due to its antioxidant activity. *Asparagus racemosus* healed chronic gastric ulcers produced by 50% acetic acid. The increase in defensive mucosal factors may have a beneficial role in protecting ulcers induced by acetic acid. Therefore, ulcer healing and gastroduodenal ulcer protecting effect of *Asparagus racemosus* may be due its mucosal defensive factors rather than offensive factors.

Centaurea solstitialis

Crude extracts from the spiny flowers of *Centaurea solstitialis* L. ssp. showed antiulcer effect against water immersion and immobilization induced ulcers in rats (64). Sesquiterpene lactones have been isolated and identified as the active constituents of the chloroform extract of the flowering aerial parts of the plant which produce antiulcer activity against ethanol induced ulcer in rats (65). Three guaianolide type sesquiterpene lactones like chlorojanerin, 13-acetyl solstitialin A and solstitialin A were isolated from the extract found that chlorojanerin and 13-acetyl solstitialin A are the active constituents. Antiulcer effects chlorojanerin and a mixture of 13-acetyl solstitialin A (95%) and solstitialin A (5%) were investigated which significantly produce antiulcer effect on indomethacin, indomethacin plus HCl/ethanol, *N*Gnitro-l-arginine methyl ester plus ethanol, *N*-ethylmaleimide plus ethanol, water immersion restraint stress and serotonin induced ulcer but found ineffective against ulcer induced by pyloric ligation and diethyldithiocarbamate (66). Mixture found effective against cysteamine induced duodenal and ethanol induced (oral administration) gastric lesions, but was ineffective when ethanol administered subcutaneously. Chlorojanerin found active against ethanol induced ulcer (oral and subcutaneously induced) but inactive against cysteamine induced ulcer. Chlorojanerin and mixture does not produce any effect on gastric secretion and pH but significantly decrease titratable acidity and titratable acid output. So antiulcer effect may due to their neutralizing effect on gastric

acid not because of antisecretory effect. Compounds do not produce antioxidant activity as it ineffective against diethyldithiocarbamate induced ulcer. The cytoprotection may be the major reason for there ulcer protective effect.

Anacardium occidentale

Antiulcerogenic effect of a 70% ethanolic extract of cashew (*Anacardium occidentale* L.) leaves was investigated against HCl/ethanol induced ulcer and found that extract inhibit gastric lesions significantly in dose dependent manner (67). Freeze-dried hydroethanolic extract was washed with petroleum ether first and then extracted with dichloromethane and methanol. The dichloromethane (3.92 mg/kg) and methanol fractions (257.12 mg/kg) considered as 400 mg/kg of hydroethanolic extract and were tested for their anti-ulcer activity. Methanol fractions produce significant ulcer protection but dichloromethane fraction did not produce ulcer protection against HCl/ethanol induced ulcer. Anti *H. pylori* effect of fruits of cashew also investigated (68). Phytochemical investigation shows the presence of various flavonoids, mainly quercetin glycosides and saponins in ethanol extract. Flavonoid are free radical scavengers, plays important role in gastric ulcer also an increase mucosal prostaglandin content and decrease in histamine secretion from mast cells by the inhibition of histidine descarboxylase (69). Quercetin was also found to prevent gastric mucosal lesions (70). Various saponins also found to possess antiulcer activity (71, 72). Since methanol is a bad solvent for tannins so the active component of the methanolic fraction is a substance other than tannin. Therefore, flvanoids and saponin are mainly responsible for antiulcer activity of *Anacardium occidentale.*

Calophyllum brasiliense

Stem bark of *Calophyllum brasiliense* Camb. used in peptic ulcer traditionally. Dichloromethane fraction obtained from the hexane extract of stem bark of *Calophyllum brasiliense* produce significant inhibition of gastric ulcer in dose dependent manner against various ulcer models (73). Dichloromethane fraction (250 mg/kg) shows 97% and fraction (200 mg/kg) produces 96% and 99% protection against ethanol, indomethacin and hypothermic restraint-stress induced gastric lesions respectively. Ethanol produce ulcer by generating oxygen free radicals, reduce gastric mucosal non-protein sulfhydryl (SH) levels and stimulate the formation of leukotriene. Dichloromethane fraction showed a significant increase in nonprotein sulfhydryls concentration, indicates that the gastroprotective effect of fraction at least partly involves the sulfhydryl mechanism. Hypothermic restraint stress produces hyperacidity and decreases mucosal pH but does not produce any effect on gastric mucosal sulfhydryl levels (74). Thus protective effect of fraction in this model is independent of sulfhydryl mechanism. Bark fraction produce significant inhibition of gastric fluid volume, total acidity and increase in gastric pH in both pylorus ligated and 2 hrs bethanechol stimulated animals. Therefore increase in gastric mucus and/or an increased prostaglandin generation may be due to the enhanced gastric pH in fraction treated animals. So, gastroprotection effect of bark extract may due to stimulation of gastric mucus, preventing sulfhydryl depletion, by elevation of gastric pH and antisecretory property.

Rhizophora mangle - Gastroprotective effect of the aqueous bark extract of *Rhizophora mangle* L. investigated against diclofenac induced gastric ulcer in comparison with omeprazole as a standard drug (75). Pretreatment with extract reduce ulcerated area in dose dependent manner. *Rhizophora mangle* increase prostaglandin production though NSAIDs induced depletion. Polyphenolic compounds found in *Rhizophora mangle* may be stimulate prostaglandin formation and responsible for its effect. Antioxidant property of the extract also evaluated, it increases superoxide dimutase and glutathione peroxidase level which depleted in diclofenac treated group. Extract also prevent lipid peroxidation *in vitro* prove its potential use as a drug for free radical pathologies. Polyphenolic compounds have cytoprotective property and produce antiulcerogenic activity in other plants. Antiulcerogenic activity of tannins may due to their protein precipitating and vasoconstricting effects (76). Their astringent action also can help to prevent ulcer formation. Microscopically it was found that *Rhizophora mangle* extract form a thick coating adherent to the gastric mucosa which is beneficial to protect gastric mucosa. Results indicate that the ulcer protective effects of *Rhizophora mangle* may because of its antioxidant and cytoprotective properties.

Larrea divaricata

Anti-ulcerogenic effect of the methanolic extract of *Larrea divaricata* Cav. leaves was investigated against absolute ethanol and 0.6N HCl induced ulcer in rats (77). Dose dependent ulcer protection found in case of pretreatment with the extract. Extract inhibit ulcer by 97% and 100% against 0.6N HCl induced ulcer at a dose of 300 mg/kg and 400 mg/kg and produce 96%, 96% ulcer protection in ethanol induced ulcer at a dose of 300 mg/kg and 400 mg/kg. Effect of extract on blocking endogenous sulfhydryl (SH) groups with *N*-ethylmaleimide was also studied in ethanol induced ulcer animals. Because ethanol produce of free radicals and decrease of the levels of nonprotein SH compounds in the gastric mucosa leads gastric ulcer. But antiulcer effect of extract was not decreased when endogenous SH groups were blocked by *N*-ethylmaleimide. Thus, SH groups are not involved in the anti-ulcerogenic activity of the *Larrea divaricata*. *In vitro* antioxidant activity of the extract also studied using 1,1-diphenyl-2-picrylhydrazyl (DPPH) test method. So, antiulcerogenic activity of methanolic extract of *Larrea divaricata* may due to its antioxidant activity.

Hemidesmus indicus

Hemidesmus indicus var. *indicus* is a traditional medicine for gastric ailments widely distributed in India, consists essential oils and phytosterols like hemidesmol, hemidesterol and saponins. Antiulcerogenic activity of aqueous ethanolic extracts of the roots *Hemidesmus indicus* collected during flowering and vegetative periods were investigated. Extract decreased aggressive factors like pepsin and proteins and increases defensive factor like pH, hexose, hexosamine, fucose and sialic acid. As a result carbohydrate protein ratio is increased, which indicate the increase in mucin activity (79). This result suggests that increase in glycoprotein content of

the gastric mucosa. Increase in potassium and sodium ion concentration in extract treated group also observed indicates increase in bicarbonate ion concentration, which plays an important role in protecting the gastric mucosa against HCl. Flowering period root extract produce better antiulcer effect than the vegetative period root extract. This may be due to the change both in quality and quantity of the chemical composition, Antiulcer activity of the extracts may be due to the presence of saponins, terpenoids and amino acids which shows gastroprotective activity.

Spartium junceum

Flowers of *Spartium junceum* L. traditionally used in the treatment of peptic ulcer. Methanolic and aqueous extracts of the flower shows antiulcer activity. Anti-ulcerogenic activity of various fractions obtained from the methanolic extract of *S. junceum* flowers by successive solvent extraction also investigated (80). Aqueous fraction possesses very high and ethylacetate extract fraction showed weak antiulcerogenic activity. Significant anti-ulcerogenic activity of both butanol fraction and final-H_2O fraction-2 also investigated. As aqueous fraction shows highest activity, it was again fractionated by ion-exchange chromatography first on Amberlite-2 and then by molecular sieving on Sephadex LH-20. Fraction LH/Fr.2–9 possesses good ulcer inhibitory effect on oral administration, but showed a high toxicity when injected intraperitoneally. Active fractions LH/Fr.2–9 produce 100%, 94.6% and 83.9% ulcer protection against ethanol, stress and pylorus ligation induced ulcer respectively. Fraction inhibits gastric acid secretion, titratable acidity, acid output and possesses anti-peptic activity in pylorus-ligated rats. It increases gastric pH but did not produce any effect on the hexosamine content of the gastric mucosa. Through bioassay-guided fractionation process spartitrioside isolated as main active constituent. Antiulcrogenic activity of spartitrioside also investigated against ethanol induced ulcer. Active saponin fractions found ineffective against *Helicobacter pylori (*81). Result suggested that the inhibitory effect of fraction on stress-induced lesions may due to decreased acid secretion. Antiulcerogenic activity of active fraction and spartitrioside against ethanol induced gastric lesions may because of its cytoprotective activity.

Amomum subulatum

Amomum subulatum Roxb. (large cardamom) commonly used as a spice. Crude methanolic extract of fruits of large cardamom possess antiulcer activity (82). This extract again fractionized successively by petroleum ether (60–80°), ethyl acetate and finally with methanol. Essential oil obtained from the dried fruits of *Amomum subulatum* by steam distillation process. Antiulcerogenic activity of those fractions like petrol soluble fraction, ethyl acetate soluble fraction, methanol soluble fraction, methanol insoluble fraction and essential oil investigated. Ethanol reduces the secretion of bicarbonates and production of mucus results ulcer in gastric mucosa (83). Total methnolic fraction (860, 1720 mg/kg), petrol soluble fraction (262 mg/kg), ethyl acetate soluble fraction (196 mg/kg), methanol insoluble fraction (790 mg/kg) and essential oil (200 mg/kg) produce significant ulcer protection against ethanol induced ulcer but methanol soluble fraction (465 mg/kg) found ineffective. Petrol soluble, ethyl acetate soluble, methanol insoluble fraction also found to increase gastric wall mucus in ethanol induced ulcer. So antiulcer effect may due to cytoprotective and strengthening effect on gastric mucosa. Ethyl acetate soluble fraction produce highest activity and shows presence of phenolic compound. Thus phenolic compounds (flavanones, aurones or anthocyanins) present in this fraction, may be responsible for gastroprotection effect. Total methanolic extract of the fruit does not show any significant ulcer protection against aspirin induced ulcer. Aspirin causes ulcer by inhibition of cyclooxygenase pathway of arachidonic acid metabolism results overproduction of leukotriene and other products of 5-lipoxygenase pathway (84). So total methanolic extract may did not produce any effect on cyclooxygenase pathway. Histamine may be involved in the formation of pylorus ligated ulcers. No fraction found significantly effective against pylorus ligated ulcer. So ulcer protective effect of fraction is involved in direct protective effect of on gastric mucosa.

CONCLUSION

The plant and phytomedicine are important choice to treat the peptic ulcer. Most of the phyto-constituents showed better result than the modern medicine. Various phyto-chemicals like flavanoids, tannins, saponins, terpinoids showed their antiulcer activity due to their cytoprotection, antisecretory and antioxidant property. The plants are a reservoir of potentially useful chemical compounds which serve as drugs, are provided newer leads and clues for modern drug design by synthesis. Thus plant and phyto-medicine can be our source of drug with less toxic effect and better result to treat peptic ulcer in future.

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