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REVIEW ARTICLE

Antiulcer activity of natural compounds: A review

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ABSTRACT:
Peptic ulcer is a break in the lining of the stomach, first part of the small intestine, or duodenum. The duodenum is the first part of the small intestine. Contrary to popular belief, ulcers are not caused by spicy food or stress but instead are most commonly due to either an infection or long-term use of certain medications. The main goals for treating a peptic ulcer include eliminating the underlying cause (particularly H. pylori infection or use of NSAIDs), preventing further damage and complications, and reducing the risk of recurrence. Peptic ulcer which is mainly caused by bacterial attack or excess of acid secretion can be cured effectively by these isolated plant compounds. A number of drugs including proton pump inhibitors and H2 receptor antagonists are available for the treatment of peptic ulcer, but clinical evaluation of these drugs has shown incidence of relapses, side effects, and drug interactions. This has been the rationale for the development of new antiulcer drugs and the search for novel molecules has been extended to herbal drugs that offer better protection and decreased relapse. Craving for herbal medicines are still importance due lesser chance of adverse effects and easily available in surrounding place with low cost. In this review attempts have been made to summarize medicinal plants and their constituents used for peptic ulcer by the people of rural area which may be beneficial for the modern science.

KEYWORDS: Antiulcer, Isolated compounds, Alkaloids, flavonoids, Terpenoids.

INTRODUCTION:
A history of heartburn, gastroesophageal reflux disease (GERD) and use of certain forms of medication can raise the suspicion for peptic ulcer. Medicines associated with peptic ulcer include NSAIDs (non-steroid anti-inflammatory drugs) that inhibit cyclooxygenase, and most glucocorticoids (e.g. dexamethasone and prednisolone). A major causative factor (60% of gastric and up to 50-75% of duodenal ulcers) is chronic inflammation due to Helicobacter pylori that colonizes the antral mucosa. The immune system is unable to clear the infection, despite the appearance of antibodies. Thus, the bacterium can cause a chronic active gastritis (type B gastritis). Gastrin stimulates the production of gastric acid by parietal cells. In H. pylori colonization responses to increased gastrin, the increase in acid can contribute to the erosion of the mucosa and therefore ulcer formation. In Western countries the percentage of people with Helicobacter pylori infections roughly matches age (i.e., 20% at age 20, 30% at age 30, 80% at age 80 etc.) [1].

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Prevalence is higher in third world countries where it is estimated at about 70% of the population, whereas developed countries show a maximum of 40% ratio.

Ulcers are an open sore of the skin or mucus membrane characterized by sloughing of inflamed dead tissue. A gastric ulcer would give epigastric pain during the meal, as gastric acid production is increased as food enters the stomach. Symptoms of duodenal ulcers would initially be relieved by a meal, as the pyloric sphincter closes to concentrate the stomach contents; therefore acid is not reaching the duodenum [2]. Peptic ulcer disease (PUD) is an illness that affects a considerable number of people worldwide. It develops when there is an imbalance between the ‘‘aggressive’’ and ‘‘protective’’ factors at the luminal surface of the epithelial cells. Aggressive factors include Helicobacter pylori, HCl, pepsins, nonsteroidal anti-inflammatory drugs (NSAIDs), bile acids, ischemia, hypoxia, smoking and alcohol. While defensive factors include bicarbonate, mucus layer, mucosal blood flow, PGs and growth factors. [3] Burning or gnawing feeling in the stomach area lasting

between 30 minutes and 3 hours commonly accompanies ulcers [4].

In order to achieve this aim, various sources like ancient traditional books, journals, libraries and internet were explored for each of the medicinal plants for peptic ulcers and all retrieved articles were evaluated to achieve any in vitro, in vivo, or clinical evidence for their efficacy and possible mechanisms.

Etiology and Pathogenesis

Peptic ulcer occurs in that part of the gastrointestinal tract (GIT) which is exposed to gastric acid and pepsin i.e. the stomach and duodenum. The etiology of peptic ulcer is not clearly known. It results probably due to an imbalance between the aggressive (acid, pepsin, bile and *Helicobacter pylori*) and the defensive (gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide, innate resistance of the mucosal cells) factors [5].

A variety of psychosomatic, humoral and vascular derangements have been implicated and importance of *Helicobacter pylori* infection as a contributor to ulcer formation and recurrence has been recognized [6].

In gastric ulcer; acid secretion is normal or low. In duodenal ulcer; acid secretion is high in half of the patients but normal in the rest. Notwithstanding whether production of acid is normal or high, it does contribute to ulceration as an aggressive factor, reduction of which is the main approach to ulcer treatment.

Regulation of Acid Secretion by Parietal Cells

The regulation of acid secretion by parietal cells is especially important in the pathogenesis of peptic ulcer, and constitutes a particular target for drug action. The secretion of the parietal cells is an isotonic solution of HCl (150 m mol/l) with a pH less than 1, the concentration of hydrogen ions being more than a million times higher than that of the plasma. The Cl-is actively transported into canaliculi in the cells that communicate with the lumen of the gastric glands and thus with the stomach itself. This Cl- secretion is accompanied by K+, which is then exchanged for H+ from within the cell by a K+/H+ ATPase (+ and bicarbonate ions [7]. The later exchanges across the basal membrane of the parietal cell for Cl-. The principal stimuli acting on the parietal cells are:

Gastric: Gastrin is a peptide hormone synthesized in endocrine cells of the mucosa of the gastric antrum and duodenum, and secreted into the portal blood. Its main action is stimulation of the secretion of acid by the parietal cells. Gastrin also indirectly increases pepsinogen secretion, stimulates blood flow and increases gastric motility. Release of this hormone is controlled both by neuronal transmitters and blood-borne mediators, as well as the chemistry of the stomach contents. Amino acids and small peptides directly stimulate the gastrin-secreting cells.

Acetylcholine: Acetylcholine is released from (e.g.vagal) neurons and stimulates specific muscarinic receptors on the surface of the parietal cells and on the surface of histamine-containing cells.

Histamine: Within the stomach, mast cells (or histamine-containing cells similar to mast cells) lying close to the parietal cell release a steady basal release of histamine, which is further increased by gastrin and acetylcholine. The hormone acts on parietal cell H2 receptors, which are responsive to histamine concentrations that are below the threshold required for vascular H2 receptor activation.

Prostaglandins: Prostaglandins (mainly E2 and I2), synthesised in the gastric mucosa mainly by cyclo-oxygenase-1, stimulate mucus and bicarbonate secretion, decrease acid secretion and cause vasodilatation, all of which serve to protect the stomach against damage (Figure-1).

Animal Models Used in the Screening of Antiulcer Activity

Various screening models are used for the screening of the anti ulcer activity it helps to understanding the etiology of the ulcer and screening of anti ulcer agents.

Cold restrain stress induced ulcer: Animal of different groups were subjected to cold stress after 45 min of the formulation and OMZ treatment. Rats were deprived of food, but not water, for about 18 h before the experiment. Rats were immobilized by strapping the fore and hind limbs in restraint cage and kept for 2 hr, at a temperature of 4°C. After 2 hr, animals were sacrificed, the stomach was incised along the lesser curvature and ulcer was scored as: Red coloration (0.5), Spot ulcer (1), hemorrhagic streak (1.5), Ulcers (2), Perforation (3). Mean ulcer score for each animal was expressed as ulcer index. The percentage of ulcer protection was calculated as- Mean ulcer index of control-mean ulcer index of test / mean ulcer index of control x 100. [8]

Aspirin induced ulcers: The above sections. After 45 min of formulations (6 ml/kg, p.o.) or ranitidine (50 mg/kg, p.o.) treatment to different groups, the animals were administered with aspirin in dose of 500 mg/kg. The animals were sacrificed after 4 h and the stomach was then excised and cut along the greater curvature, rinsed gently with saline to remove the gastric contents and blood clots. Ulcer index was then calculated by adding the total number of ulcers and calculate ulcer index. [9]

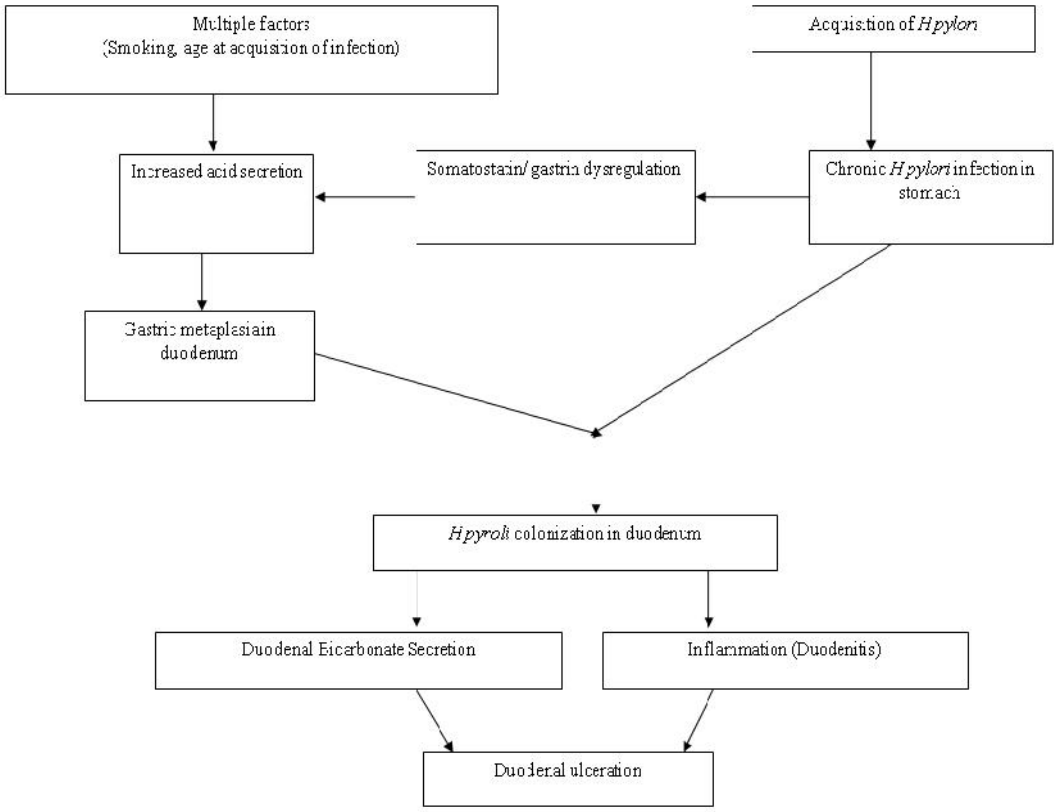

Figure 1-Formation of ulcer

Ethanol induced ulcer: The animals were divided into five groups as described above except that catechin (200 mg/kg, p.o.) was used as standard. The gastric ulcers were induced in rats by administrating absolute ethanol (99%) (1 ml/200 g) orally, after 45 min of formulations. They were kept in specially constructed cages to prevent coprophagia during and after the experiment. The animals were anaesthetized one hour later with anesthetic ether and stomach was incised along the greater curvature and ulceration was scored. The percentage of ulcer protection was calculated as mean ulcer index of control-mean ulcer index of test / mean ulcer index of control x 100. [10]

Pylorus Ligation Induced Ulcer: After 1 hr of treatment to different groups, the animals were anaesthetized using thiopentone sodium (35 mg/kg, i.p.), the abdomen was opened and pylorus ligation was done without causing any damage in its blood supply. After 4 hr their stomachs were dissected and its contents were collected into tubes for analysis of volume of gastric juice, pH, total and free acidity. The ulcers were scored as described under cold stress induced ulcers. The gastric juice was collected after 4 hr of Pylorus ligation induced ulcers and centrifuged for 5 min at 2000 rpm. The supernatant was collected and the volume of gastric juice was expressed as ml/100 g body weight. Total acidity was determined in the supernatant by titrating against 0.01 N NaOH, using 2-3 drops of topfers reagent as indicator until canary yellow color was observed. Volume of NaOH required was noted and this corresponds to free acidity. Further 2-3 drops of phenolphthalein was added and titrated with 0.01 N NaOH until pink color was restored and this gives total acidity. Free acidity and total acidity is expressed in terms of 0.1 N HCL per 100 g of gastric contents. [11]

Water immersion stress induced ulcers: Stress induced ulcers were induced by force swimming in the glass cylinder (height 45cm diameter 35cm) containing water up to 35cm maintained at 35oc for 3 hrs. Animals were fasted 24 hrs prior to the experiment. After the drug treatment (standard/test) animals were allowed to swim for 3hrs then animal were dissected stomachs were removed. All stomachs were opened along the greater curvature ulcer index and % inhibition was calculated and Histopathological studies conducted. [12]

Indomethacin induced ulcers: All the animals were fasted 36 hours before administration of Indomethacin. The animals were divided into groups. Each rat was administered with the 20mg/kg Indomethacin orally.30 min prior to the administration of the Indomethacin standard/test drug was administered. The rats were anaesthetized with ether 1 hour latter the stomach was incised through the greater curvature and examined for the number of lesion under the dissecting microscope by titrating with 0.01N NaOH using phenolphthalein as an indicator. gastric juice estimated for pepsin. Ulcer index and % inhibition were calculated and histopathological studies conducted for the stomach tissues. [13]

Histamine induced ulcers: Guinea pigs weighing (300-400 gm) were divided into groups of six each and the animals were fasted for 36 hours (water allowed) before experiment. One ml of histamine acid phosphate (50 mg base) was administered intraperitoneally. Promethazine hydrochloride 5 mg was injected intraperitoneally 15 min before and 15 min after histamine administration. The standard/test drugs were administered by gavage 45 minutes before histamine. Four hours after administration of histamine, the guinea pigs were sacrificed by stunning. The anterior abdominal wall was opened and the stomach dissected out. Stomach was opened along the greater curvature ulcers were identified. Severity scores were calculated. Histopathological studies were conducted on the stomach tissues. [14]

Reserpine induced ulcers: Adult albino rats weighing 150-180gms were fasted for 24 hr. Animals were divided into different groups following water ad libitum. Reserpine (5mg/kg) administered intramuscularly rats. 30 min after the administration of the standard or test drug or control vehicle (Distilled water) intraperitoneally. All the animals were sacrificed after 18 hr, their stomachs were removed, opened along the greater curvature and sum of lengths (mm) of all lesions for each rat was used as ulcer index and percentage protection of ulcers were calculated. Histopathological studies were performed on the stomachs tissues. [15]

Serotonin induced ulcers: Rats weighing 120-150gms were taken and they were randomly divided into groups. Animals kept fasting for 24hrs and water withdrawn 2hr before the experiment. Serotonin creatinine sulphate (20mg/kg) was administered subcutaneously to rats. The standard drug/test drug/ control vehicle (Distilled water) was administered intraperitoneally after 30 min prior to the serotonin injection. The animals were sacrificed after 18 hr, their stomachs were removed and opened along the greater curvature, and the ulcer index was determined. Percentage protection of the ulcers calculated. Histopathological studies were conducted. [16]

Acetic acid induced ulcers: Rats were anaesthetized with pentobarbitone (35 mg/kg, ip). The abdomen was opened and the stomach was visualized. A cylindrical glass tube (6 mm in diameter) was tightly placed upon the anterior serosal surface of the glandular portion of stomach 1 cm away from the pyloric end. 50% acetic acid (0.06 ml/animal) was instilled into the tube and allowed to remain for 60 sec on the gastric wall . After removal of acid solution, the abdomen was closed in two layers and animals were caged and fed normally. Standard and test drug administered orally 4 h after the application of acetic acid and continued up to 9 days after induction of ulcer. The animals were then sacrificed after 18 h of the last dose of drug on 10th day of experiment to assess the ulcer size and healing. Ulcer index was calculated based upon the product of length and width (mm2/ rat) of ulcers. [17]

Hydrochloric acid induced ulcers: Rats weighing 150-180gms are taken and they were divided into groups. Thirty minutes after the test or reference drug or the control vehicle treatment, 0.6 M HCl was orally administered to each rat. After 1 h the rats were anaesthetised with excess of anaesthetic ether and stomach was cut open along the greater curvature, cleared of residual matter with saline and the inner surface was examined for ulceration. Ulcer index and % ulcer protection. Histopathological were conducted by Gastric tissue samples from each group were fixed in 10% formalin for 24 h. The formalin fixed specimens are embedded in paraffin and section (3-5µm) and stained with haematoxylin and eosin dye. The histochemical sections are evaluated by light microscopy. [18]

Active Principles with Antiulcer Activity

Chemical constituents of plants are responsible for various pharmacological activities. These constituents may be alkaloids, trepenoids, flavonoids, glycosides, terpens and resins. The list of biological sources provided which gives active compounds with antiulcer activity (Table-1).

Table 1- Chemical Constituents from medicinal plants with Antiulcer Activity

S. No.	Plants Name	Chemical Constituents	Family	Effect	Mode of Action	Reference
1.	*Cucumis sativus*	9-beta-methyl-19-norlanosta-5-ene (cucurbitane glycoside)	(Cucurbitaceae)	Active [78]	Reduction in gastric secretion [78]	19
2.	*Alchornea glandulosa*	Sulfhydryl	(Euphorbiaceae)	Active [79]	Defensive mechanisms of the gastrointestinal mucosa against aggressive factors	20
3.	*Annona squamosa*	one 1-(4-β-D-glucopyranosyloxyphenyl)-2-(β-D-glucopyranosyloxy)-ethane (Ehtanone)	(Annonaceae)	Active [80]	Inhibition of H(+) K(+)-ATPase activity	21
4.	*Tectona grandis*	Verbascoside (phenylethanoid)	(Verbenaceae)	Active [81]	Inhibition of H(+) K(+)-ATPase with corresponding decrease in plasma gastrin level	22
5.	*Sargassum micracanthum* [82]	Plastoquinones [82]	Sargassaceae	Active [82]	Increase of PGE2 levels [82]	23
6.	*Cinnamomum cassia* [83]	3-(2-hydroxyphenyl)-propanoic acid [83]	(Fabaceae)	Active [83]	Inhibited the secretion of gastric acid [83]	24
7.	*Xenorhabdus nematophila* [84]	Xenocoumacins (metabolic product) [84	Enterobacteriaceae	Active [84]	Inhibited the secretion of gastric acid [84]	25
8.	*Myracrodruon urundeuva* Allemão [85]	Tannin-enriched fraction (TEF) [85]	(Anacardiaceae)	Active [85]	Inhibited the secretion of gastric acid [85]	26
9.	*Maytenus ilicifolia* [86]	Heteroxylan (polysaccharides) [86]	(Celastraceae)	Active [86]	inhibited the secretion of gastric acid [86]	27
10.	Potent antiulcer Isolated product [87]	l-serine [87]		Active [87]	Inhibit gastric secretion [87]	28
11.	alpha-2 adrenoceptor agonist [88]	[1-(2,-dimethylphenyl)-3-isobutoxyamidinourea]hydrochloride (WHR1582A) [88]		Active [88]	Due to activation of alpha-2 adrenoceptors located presynapitcally on the vagus [88]	29
12.	Potent antiulcer Isolated product [89]	2-methyl-8-(phenylmethoxy)imidazol[1,2-a]pyridine-3-acetonitrile[(SCH 28080) Imidazole [89]		Active [89]	Inhibits histamine-stimulated gastric secretion [89]	30
13.	*Cochlospermum tinctorium*	Arabinogalactans type II (poly-saccharides)[90]	Cochlospermaceae	Active [90]]	Inhibition of Secretion of gastric juice and output of acid and pepsin activity [90]	31
14.	*Jasminum grandiflorum* [91]	Methyl jasmonate (volatile organic compounds) [91]	(Oleaceae)	Active [91]	Reduction in gastric fluid volume, total acidity and an increase in the pH of the gastric fluid [91]	32
15.	*Alpinia galangal* [92]	1′S-1′-Acetoxychavicol acetate [92]	(Zingiberaceae)	Active [92]	Increased the glutathione levels of gastric mucosa and increase of PGE2 levels [92]	33
16.	*Aralia elata* [93]	Araloside [93]	Araliaceae)	Active [93]	Inhibition of Secretion of gastric juice [93]	34
17.	*Qualea grandiflora* [94]	sitosterol [94]	(Vochysiaceae)	Active [94]	PGE2 stimulate the secretion of bicarbonate and mucus, maintain mucosal blood flow and regulate mucosal cell turnover and repair [94]	35

18.	*Ammania baccifera* [95]	Hentriacontane (alkane hydrocarbon) [95]	(Lytharaceae)	Active [95]	Increasing mucosal PGE2 content and by inhibiting histamine secretion from mast cell by inhibition of histidine decorboxylase [95]	36
19.	*Aesculus hippocastanum* L. [96]	Aescin[96]	(Sapindaceae)	Active [96]	induced ulcer(rats) [96]	37
20.	*Phyllanthus niruri* L	4-methoxy-securinine	(Euphorbiaceae)	Active [7]	enhancing mucosal protection possibly by mobilization of endogenous prosta-glandins [7]	38
21.	*Vinca minor* L	Vincamine[9]	. (Apocynaceae) [9]	Active[9]	prostaglandin-mediated mechanism [9]	39
22.	*Enantia chlorantha*	7,8,-dihydro-8-hydroxypalmatine (protoberberine-type alkaloid) [15]	(Annonaceae)	Active[15]	Enhanced mucus production [15]	40
23.	*Melaleuca bracteata* F [58]	3-hydroxyl-lup-20 (30)-ene-28-oic [58]	(Myrtaceae)	Active [58]	Inhibition of gastric acid [58]	41
24.	*Xylocarpus granatum* [67]	Photogedunin[67]	(Meliaceae)	Active[67]	Inhibition of H(+) K(+)-ATPase activity [67]	42

CONCLUSION:

This article provides a list of various isolated compounds used in the treatment of peptic ulcer with their chemical structure, experimental models and their mode of action. An understanding of the mechanism and control of gastric acid secretion of medicinal plants will elucidate new pathway for research and treatment of peptic ulcer.

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