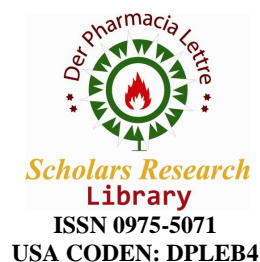




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### A review on medicinal plants for peptic ulcer

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#### ABSTRACT

Peptic ulcer is the most common gastrointestinal disorder in clinical practice. A number of drugs including proton pump inhibitors and H<sub>2</sub> receptor antagonists are available for the treatment of peptic ulcer, but these drugs have shown incidence of relapses, side effects, and drug interactions. Thus 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. Medicinal plants provide an effective and safer way in disease management. Many medicinal plants exhibit antiulcer activity and found useful in the treatment of peptic ulcer. In this review attempts have been made to know about some plants which may be used in treatment or prevention of peptic ulcer. Various plants like *Amomum subulatum*, *Scoparia dulcis*, *Jasminum grandiflorum*, *Davilla rugosa*, *Kielmeyera coriacea*, *Larrea divaricata*, *Qualer grandiflora*, *Mammea Americana*, *Anacardium occidentale*, *Ocimum sanctum*, *Azadirachta indica* proved active in antiulcer therapy.

**Keywords:** Peptic ulcer, Medicinal plants, Antiulcer activity.

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#### INTRODUCTION

Peptic ulcer is an excoriated area of the gastric or duodenal mucosa caused by action of the gastric juice. It is a chronic and recurrent disease, and is the most predominant of the gastrointestinal diseases [1]. It is generally recognized that peptic ulcer is caused by a lack of equilibrium between the gastric aggressive factors and the mucosal defensive factors [2]. Gastric ulcer is among the most serious diseases in the world. It is a major health problem with multifactorial etiology. The development of gastric ulcer occurs with acid and the breakdown of mucosal defense. Local mechanisms implicated in mucosal defense are; mucus-like alkaline secretions, mucosal hydrophilicity, rapid epithelial cell renewal, rich mucosal blood flow, mucosal sulphhydryls and increased resistance of gland cells in deep mucosa to acid and peptic activity [3].

Peptic ulcer is a sore on the lining of the gastrointestinal tract caused due to mucosal erosions [4]. It can be classified mainly into four types they are gastric, duodenal, esophageal and Meckel's Diverticulum ulcers [5]. Gastric ulcer is a peptic ulcer that develops in the stomach. Duodenal and esophageal ulcers occur in the duodenum and esophagus respectively. Meckel's Diverticulum ulcer is a less common type of ulcer that develops in the Meckel's Diverticulum (a vestigial remnant in the form of a small bulge in the small intestine).

The predominant causes of peptic ulcer are infection with the bacterium called *Helicobacter pylori* (*H. pylori*) and the use of Non Steroidal Anti-Inflammatory Drugs (NSAIDs) such as aspirin and ibuprofen [6]. Pepsin is the one of the proteolytic enzymes that is secreted along with hydrochloric acid in the stomach. These substances are essential for food digestion but at the same time have the ability to erode the cell linings of the digestive system if secreted in excess amount. The stomach defends itself from hydrochloric acid and pepsin by creating a mucus coating and producing bicarbonates. *H. pylori* infection and NSAIDs can impair these protective functions. This makes the cell linings of the G.I. tract susceptible to hydrochloric acid and pepsin and leads to the formation of ulcer. *H. pylori* infection alone is the major causative factor (95% of the duodenal ulcer and 80% of gastric ulcers). Factors related with lifestyle such as smoking, alcohol, spicy foods and stress are also associated with peptic ulcer formation.

Different classes of drugs are used in the treatment of peptic ulcer but most of these drugs exhibits serious side effects like arrhythmias, gynaecomastia, impotence, arthralgia, hypergastrinemia and haemopoietic changes [7]. Alternative approach in recent days is the research of medicaments from ayurvedic or traditional medicinal system. The use of phytoconstituents 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 [8]. 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 [9]. This paper outlines the properties of some medicinal plants that exhibit antiulcer activity. Although extensive research has been conducted in this area, recent studies with significant findings involving *Amomum subulatum*, *Scoparia dulcis*, *Jasminum grandiflorum*, *Davilla rugosa*, *Kielmeyera coriacea*, *Larrea divaricata*, *Qualer grandiflora*, *Mammea Americana*, *Anacardium occidentale*, *Ocimum sanctum*, *Azadirachta indica* are emphasized here.

### ***Amomum subulatum***

*Amomum subulatum* Roxb. (Large cardamom) commonly used as a spice. Methanolic extract of fruits of large cardamom shows antiulcer activity [10]. 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 [11]. 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. Antiulcer

effect may be 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, auronones 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 [12]. 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.

### ***Scoparia dulcis***

Freeze-dried aqueous extract of the aerial parts of *Scoparia dulcis* L. produced reduction gastric hypersecretion and ulcer in rodents [13]. 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 pylorus 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  $IC_{50} = 500 \mu g/ml$ . Cirsitakoaside and quercetin active principle of flavonoid-rich fraction produces inhibition of the gastric  $H^+ K^+$  ATPase activity *in vitro* [14],[15]. Inhibition of gastric secretion by the aqueous extract of *Scoparia dulcis* may be due to the inhibition of the  $H^+ K^+$  ATPase enzyme.

### ***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 [16]. 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.

### ***Davilla rugosa***

*Davilla rugosa* Poiré is a commonly used Brazilian folk medicine. Antiulcer action of the fractions of the hydroalcoholic extract of *D. rugosa* stems was studied in rats [17]. These extracts were shown to protect rats from developing gastric ulcers. Further, the daily oral dose of 800 mg/kg of the extract for 30 consecutive days was reported to produce no toxic effects.

***Kielmeyera coriacea***

*Kielmeyera coriacea* Mart. is a Brazilian cerrado plant belonging to family Guttiferae and is popularly known as "Pau Santo". Xanthone, triterpenes and a biphenyl from *Kielmeyera coriacea* had shown antifungal activity against *Cladosporium cucumerinum* and *Candida albicans* [18]. 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 [19]. 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 [20], resulting in release of mediators such as histamine [21]. 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 [22]. 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.

***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 [23]. 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.

***Qualer grandiflora***

*Qualer grandiflora* Mart (Vochysiaceae), popularly known as "Pau terra" is native to Brazilian cerrado. Antiulcer activity of hydroalcoholic extract of bark of *Qualer grandiflora* (500mg/kg) was evaluated [24]. 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 [25]. 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 [26],[27]. 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 [24].

***Mammea americana***

*Mammea americana* L. (Guttiferae) is a tree native to the West Indies and Northern South America have been used for its several medicinal properties[28],[29]. 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 [30].

#### ***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 [31]. 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 [32]. 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 decarboxylase [33]. Quercetin was also found to prevent gastric mucosal lesions [34]. Various saponins also found to possess antiulcer activity [35], [36]. Since methanol is a bad solvent for tannins so the active component of the methanolic fraction is a substance other than tannin. Therefore, flavonoids and saponin are mainly responsible for antiulcer activity of *Anacardium occidentale*.

#### ***Ocimum sanctum***

*Ocimum sanctum*, popularly known as Tulsi in Hindi, is a sacred plant that belongs to the family *Labiatae*. *Ocimum sanctum* contains a number of chemical constituents that interact in a complex way to elicit their pharmacodynamic responses. *Ocimum sanctum* is highly effective in a wide spectrum of diseases and reported to possess anticarcinogenic, anthelmintic, antiseptic, antirheumatic, antistress, and antibacterial properties [37]. Clinical trials have reported the usefulness of *Ocimum sanctum* in heart diseases [38] and diabetes[39]. *Ocimum sanctum* also possess anti-inflammatory and immunomodulatory properties, attributed to its potential to inhibit cyclooxygenase and lymphokines[40]. The fixed oil obtained from *Ocimum sanctum* L. showed significant antiulcer activity against aspirin, indomethacin, alcohol, histamine, reserpine, serotonin and stress induced ulceration in rats[41]. Significant inhibition of gastric secretion was observed in aspirin induced gastric ulceration in pylorus ligated rats.

#### ***Azadirachta indica***

*Azadirachta indica* A. Juss, commonly known as "Neem," has been extensively used in India as an ayurvedic medicine for the treatment of various diseases, such as, leprosy, intestinal helminthiasis, and respiratory disorders in children[42],[43],[44]. Antiulcer and cytoprotective potential of *Azadirachta indica* (neem) stem bark extract was evaluated in albino rats[45]. *A. indica* significantly inhibited gastric ulceration induced by indomethacin. This action was accompanied by a dose-dependent decrease in total gastric acidity. It was proposed that *A. indica* probably act via histamine H<sub>2</sub> receptor.



## CONCLUSION

From this study we can conclude that studies with new active principles obtained from plant sources can result in novel and effective pattern of treatment. Chemical substances derived from plants have been used to treat human diseases since the dawn of medicine. Many medicinal plants have shown significant anti ulcer activity. These plants provide leads to find therapeutically useful compounds, thus more efforts should be made towards isolation and characterization of the active principles and their structure activity relationship. The combination of traditional and modern knowledge can produce better drugs for the treatment of peptic ulcer with fewer side effects.

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