Natural Products as Gastroprotective and Antiulcer Agents: Recent Developments

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Peptic ulcer, one of the most common gastrointestinal diseases, is a chronic inflammatory disease characterized by ulceration in the regions of the upper gastrointestinal tract where parietal cells are found and where they secrete hydrochloric acid and pepsin. The anatomical sites where ulcer occurs commonly are stomach and duodenum, causing gastric and duodenal ulcer, respectively. Physiopathology of ulcer is due to an imbalance between aggressive factors, such as acid, pepsin, *Helicobacter pylori* and non-steroidal anti-inflammatory agents, and local mucosal defensive factors, such as mucus bicarbonate, blood flow and prostaglandins. Several drugs are widely used to prevent or treat gastro-duodenal ulcers. These include H_2-receptor antagonists, proton pump inhibitors and cytoprotectives. Due to problems associated with recurrence after treatment, there is therefore the need to seek alternative drug sources against ulcers. In recent years, a widespread search has been launched to identify new gastroprotective drugs from natural sources. The aim of the present review is to highlight the recent advances in current knowledge on natural products as gastroprotective and antiulcer agents and consider the future perspectives for the use of these compounds.

Keywords: gastroprotective agents, plant extracts, terpenes, flavonoids, xanthones.

Peptic ulcer disease is a problem of the gastrointestinal tract characterized by mucosal damage secondary to pepsin and gastric acid secretion. It usually occurs in the stomach and proximal duodenum; less commonly, it occurs in the lower esophagus, the distal duodenum or the jejunum, as in hypersecretory states, hiatal hernias or ectopic gastric mucosa. *Helicobacter pylori* infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs) are the predominant causes of peptic ulcer disease in the United States [1].

H. pylori infection leads to gastroduodenal inflammation, peptic ulceration, gastric lymphoma, and gastric cancer, which has been proven with animal studies and human epidemiological report. *H. pylori* may induce inflammatory-associated gene expression in gastric epithelial cells, including activation of nuclear factor kappa B (NF-κB), enhance expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), and production of interleukin-8 (IL-8). *H. pylori* bacteria adhere to the gastric mucosa; the presence of another inflammatory protein and a functional cytotoxin-associated gene island in the bacterial chromosome increases virulence and probably ulcerogenic potential [2]. NSAIDs can cause damage to the gastro-duodenal mucosa *via* several mechanisms, including their topical irritant effect on the epithelium, impairment of the mucosal barrier function, suppression of gastric prostaglandin synthesis, reduction of gastric mucosal blood flow, and interference with the repair of superficial injury. The presence of acid in the lumen of the stomach also contributes to the pathogenesis of NSAIDs-induced ulcers and bleeding by impairing the restitution process, interfering with hemostasis and inactivating several growth factors that are important in mucosal

defense and repair [3]. A variety of other infections and co-morbidities are associated with a greater risk of peptic ulcer disease, such as Crohn's disease, hepatic cirrhosis, cytomegalovirus, tuberculosis, chronic renal failure, sarcoidosis and myeloproliferative disorder.

Most of the available gastroprotective drugs act on the offensive factors neutralizing acid secretion, like antacids, H_2 receptor blockers, like ranitidine, anticholinergics, like pirenzepin, proton pump inhibitors, like omeprazole, and lansoprazole, which interfere with acid secretion. However, the use of these antisecretory drugs may be associated with adverse events and ulcer relapse [4]. Thus, there is a need for more effective, less toxic and cost-effective anti-ulcer agents.

Herbal medicines have been used since the dawn of civilization to maintain health and to treat diseases. The World Health Organization estimates that about three quarters of the world's population currently use herbs and other forms of traditional medicines to treat their diseases because the use of these compounds are considered as safe [5,6].

In recent years, a widespread search has been launched to identify new anti-ulcer drugs from natural sources. In traditional medicine, for example, several plants have been used to treat gastrointestinal disorders, including gastric ulcers [7-9].

The potential use of plants has been successfully demonstrated in the field of gastroprotection in a recent article that reviewed the studies on extracts and pure compounds as gastroprotective agents reported in the literature up to 2005 [10].

The purpose of the present review article is to highlight the more recent data in current knowledge on natural products as gastroprotective and antiulcer agents. The mechanism of action and the structure-activity relationships are also discussed where it is possible.

1.   Extracts

Several studies on the gastroprotective effects of plant extracts have been recently undertaken. In a recent study, de Andrade *et al.* [11] evaluated the effects of *Maytenus robusta* extract, a plant used in folk medicine for the treatment of stomach ulcers, using the NSAIDs-induced ulcer, ethanol-induced ulcer and stress-induced ulcer protocols.

In the ethanol-induced ulcer model, it was observed that the treatment with *M. robusta* extract (50, 250 and 500 mg/kg) and positive control omeprazole (30 mg/kg) significantly reduced the lesion index, the total lesion area and the percentage of lesion, in comparison with the negative control group. The percentages of inhibition of ulcers were 75.1, 85.0, 86.6 and 75.5 for the treated groups with 50, 250 and 500 mg/kg of *M. robusta* and omeprazole, respectively. Significant inhibition was also observed in the lesion index in the indomethacin-induced ulcer model, the decrease being 62.5, 62.5, 63.6 and 96.2 for groups treated with 50, 250 and 500 mg/kg of *Maytenus robusta* and positive control (cimetidine), respectively. Similar results were observed in the stress-induced ulcer model, where the inhibition of ulcer lesions was 71.3, 72.7, 76.5 and 92.3 for the groups treated with 50, 250 and 500 mg/kg of plant extract. Regarding the model of gastric secretion, a reduction in the volume of gastric juice volume and total acidity was observed, as well as an increase in gastric pH.

At 200 mg/kg body weight (b.w.) the aqueous extract of *Decalepis hamiltonii* protected swim stress-induced ulcer lesions by 77%, similar to that of ranitidine (79%), a known antiulcer drug, at 30 mg/kg b.w. [12]. Reactive oxygen species (ROS) have been implicated in the pathogenesis of a wide variety of clinical disorders and gastric damage. Preventive antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) are the first line of defence against ROS. Administration of *D. hamiltonii* extract resulted in a significant increase in the SOD, catalase and reduced glutathione (GSH) levels, similar to those of control animals, suggesting the efficacy of *D. hamiltonii* extract in preventing free radical-induced damage during ulceration. The extract also normalized the approximately3.1 and 2.4 folds of increased H^+-K^+-ATPase and gastric mucin, respectively, in ulcerous animals, to levels similar to those found in healthy controls.

The gastroprotective effects of an aqueous suspension of the ethanolic extract of leaves and flowers of *Guazuma ulmifolia* was assessed in a model of acute gastric ulcer induced by diclofenac, using the proton pump inhibitor omeprazole as a protection reference [13]. Pretreatment with *G. ulmifolia* decreased the ulcerated area by diclofenac in a dose-dependent way. Myeloperoxidase activity, as a marker of neutrophil infiltration, was slightly reduced *in vivo*, whereas *in vitro* anti-inflammatory

activity was clearly inhibited in a dose-dependent manner. The lowest doses of the extract significantly decreased the levels of lipoperoxides, and superoxide dismuthase activity increased to a similar extent as with omeprazole. Examination of glutathione metabolism reflected a significant rise in glutathione peroxidase (GPx) activity at the highest dose of *G. ulmifolia*. These results showed that the aerial parts of *G. ulmifolia* had demonstrated protection of the gastric mucosa against the injurious effect of NSAIDs, mainly by anti-inflammatory and radical scavenging mechanisms.

A crude hydroalcoholic extract of *Polygala paniculata* administered orally was able to protect the gastric mucosa against lesions induced by ethanol 70% [14]. In this study the extract was given by two routes (oral and intraperitoneal) to evaluate whether the observed effect was related to an adherent property of the extract on the gastric mucosa by forming a protective barrier against the aggressive effects of ethanol. The results showed that, when given by the intraperitoneal route, *P. paniculata* extract exhibited an important cytoprotective effect similar to the one seen when the extract was given orally. This suggested that the pharmacological mechanism did not have any relationship with an adherent property of the extract. In addition, the extract partially protected the mucosa against indomethacin-induced lesions. The extract did not change the volume and acidity of gastric secretion and exerted an antioxidant activity. The gastroprotective effects of *P. paniculata* extract may have involved prostaglandins and be related to cytoprotective factors, such as antioxidant activity and maintenance of mucus production.

The methanol extract of the bark of *Terminalia arjuna* showed marked antiulcer and ulcer healing activity against 80% ethanol, diclofenac sodium and dexamethasone induced ulcer models dose-dependently [15]. Pre-, post and co-administration of extract showed 100% protection to the gastric mucosa against ethanol, diclofenac and dexamethasone induced ulcers. *T. arjuna* increased the levels of GSH in gastric mucosa, which were reduced upon ulcer induction with dexamethasone. These results suggest that GSH depletion has a role to play in the ulcerogenesis induced by dexamethasone. The restoration of GSH levels by the extract provides evidence for the involvement of GSH in the antiulcer activity of *T. arjuna*. *T. arjuna* also increased significantly the glycoprotein content of the mucosal

cells. The results indicate that the gastroprotective effect of *T. arjuna* extract is probably related to its ability to maintain the membrane integrity by its antilipid peroxidative activity that protects the gastric mucosa against oxidative damage and its ability to strengthen the mucosal barrier, the first line of defense against exogenous and endogenous ulcerogenic agents.

Some spices, namely black pepper, ginger, and turmeric have been shown to possess significant gastroprotective activities [16-18]. Recently, Al Mofleh *et al.* [19] provided substantial evidence for anti-ulcer and anti-secretory effects of an aqueous suspension of anise (*Pimpinella anisum*). Anise suspension significantly inhibited the ulcerative lesions in all animals treated with necrotizing agents. Chemical studies demonstrated that *P. anisum* and its major constituents, anethol, eugenol, anisaldehyde, methylchanicol, other terpenes and coumarins, were free radicals or active oxygen scavengers. In addition, the ability of anise suspension to protect gastric mucosa against lesions induced by chemical irritants is likely by maintaining the structural integrity of the gastric epithelium and a balance between aggressive factors and inherent protective mechanisms. Previously, the same research group evaluated the anti-ulcerogenic property of an aqueous suspension of *Mentha piperita* in different ulcer models *in vivo* [20]. The suspension at 250 and 500 mg/kg b.w., orally (i.p. in Shay rat model), had a significant effect in pyloric ligation induced basal gastric secretion, in indomethacin and noxious chemical (80% ethanol, 0.2 M NaOH and 25% NaCl) induced gastric ulceration. The aqueous suspension showed significant protection in all models used. These findings were supported by histopathological assessment of gastric tissue and by the determination of non-protein sulfhydryl (NP-SH) contents of the stomach, as these parameters showed protection of various indices and replenishment of the depleted NP-SH level by the suspension treatment, respectively. The ulcer protective effect of *M. piperita* may possibly be due to its anti-secretory effect, along with antioxidative and cytoprotective properties through a prostaglandins mediated mechanism.

The effect of *Carum carvi* pretreatment on gastric mucosal injuries caused by NaCl, NaOH, ethanol and pylorus ligation accumulated gastric acid secretions was investigated in rats [21]. Pretreatment at oral doses of 250 and 500 mg/kg b.w. was found to

provide a dose-dependent protection against the ulcerogenic effects of different necrotizing agents, ethanol-induced histopathological lesions, depletion of stomach wall mucus and NP-SH groups and pylorous ligated accumulation of gastric acid secretions. The protective effect of *C. carvi* against ethanol-induced damage of the gastric tissue appears to be related to the free-radical scavenging property of its constituents. The exact mechanism of action of the gastroprotective activity is not known. However, it might be due to flavonoid related suppression of cytochrome P450 1A1 (CYP1A1), which is known to convert xenobiotics and endogenous compounds to toxic metabolites.

Another spice, *Coriandrum sativum*, was evaluated for its gastroprotective activity [22]. Pretreatment at oral doses of 250 and 500 mg/kg b.w. was found to provide a dose-dependent protection against the ulcerogenic effects of different necrotizing agents, ethanol-induced histopathological lesions, pylorus ligated accumulation of gastric acid secretions and ethanol related decrease of NP-SH. Results obtained from the study of gastric mucus and indomethacin-induced ulcers demonstrated that the gastroprotective activity of *C. sativum* might not be mediated by gastric mucus and/or endogenous stimulation of prostaglandins, but might be related to the free-radical scavenging property of different antioxidant constituents (coumarins, catechins, terpenes and polyphenolic compounds) present in *C. sativum*. The inhibition of ulcers might be due to the formation of a protective layer of either one or more than one of these compounds by hydrophobic interactions.

An aqueous suspension of *Crocus sativus* was evaluated in rats for its gastric antiulcer activity induced by pylorus ligation, indomethacin and various necrotizing agents, including 80% ethanol, 0.2 M NaOH and 25% NaCl [23]. Gastric wall mucus and NP-SH contents were also estimated in rats. Histopathological assessment of the stomach was carried out. The *C. sativus* aqueous suspension at doses of 250 and 500 mg/kg exhibited decreases in basal gastric secretion and ulcer index in Shay rats and indomethacin treated groups. Gastric wall mucus elevation was observed, but no significant histopathological changes were noted. *C. sativus* exhibited significant antisecretory and antiulcer activities without causing any deleterious effects on acute and chronic toxicity in rodents.

In the ethanol-induced stress gastric ulcer test in rats, it was shown that the *Carlina acanthifolia* essential oil, traditionally used in the treatment of various disorders, including stomach diseases, produced significant dose-dependent gastroprotective activity [24]. This was particularly noticeable when the essential oil was given as a "pure oil" in a dose of 1.0 mL/kg. The free radical scavenging activity of the essential oil tested might be considered as one of the possible mechanisms of the gastroprotective effect observed [25].

The effect of San-Huang-Xie-Xin-Tang (a traditional oriental medicinal formula containing *Coptis chinesis*, *Scutellaria baicalensis* and *Rheum officinale*) and its main component baicalin was recently evaluated on *H. pylori*-infected human gastric epithelial AGS cells [26]. It is widely accepted that most peptic ulcers are associated with *H. pylori* infection and eradication of the organism leads to enhanced ulcer healing and reduces the chance of ulcer recurrence. NF-κB activation plays an important role in *H. pylori*-induced inflammation and apoptosis in gastric epithelial cells [27]. Treatment with San-Huang-Xie-Xin-Tang and baicalin significantly inhibited IκBα degradation and NF-κB activation in *H. pylori*-infected AGS cells. Previously, *H. pylori*-induced inflammation has been shown to be associated with COX-2 expression in experimental animals and human patients [28]. Furthermore, in early gastric cancer and intestinal metaplasia the expression of COX-2 in patients infected by *H. pylori* is increased [29]. Thus, chronic expression of COX-2 may play an important role in *H. pylori*-associated gastric carcinogenesis, in addition to propagation of gastric inflammation [30]. San-Huang-Xie-Xin-Tang and baicalin decreased *H. pylori*-induced COX-2 expression in human gastric epithelial cells. Thereby, they might inhibit COX-2 associated gastric inflammation.

Recent studies also demonstrated that *H. pylori* acts through TLR2/TLR9 to activate both the PI-PLCγ/PKCα/c-Src/IKKα/β and NIK/IKKα/β pathways, resulting in the phosphorylation and degradation of IκBα, which in turn leads to the stimulation of NF-κB and COX-2 gene expression [31]. Thus, it was suggested that San-Huang-Xie-Xin-Tang and baicalin suppression of COX-2 expression might be mediated via inhibition of degradation of IκBα.

IL-8 secreted by gastric epithelial cells is likely to be an important host mediator inducing neutrophil migration to the site of infection and, therefore, may be important in the regulation of inflammatory and immune processes in response to *H. pylori* [32]. San-Huang-Xie-Xin-Tang and its major component also inhibit *H. pylori*-induced IL-8 production and, therefore, increase the benefit on gastric mucosal protection.

Alchornea glandulosa (Euphorbiaceae) is a plant used in folk medicine as an antiulcer agent. Rats pretreated with a methanolic extract of the leaves showed a significant, dose-dependent reduction of gastric ulcers induced by absolute ethanol. Pretreatment of mice with *A. glandulosa* extract (500, 1000 mg/kg, p.o.) showed significant, dose-dependent decreases in the severity of lesions caused by HCl/ethanol and by NSAID-induced gastric lesions. Pretreatment with the extract also induced antisecretory action *via* local and systemic routes and a significant decrease in the total gastric acid content. The gastroprotective effects of *A. glandulosa* involved the participation of nitric oxide (NO) and increased levels of endogenous sulfhydryl compounds, which are defensive mechanisms of the gastrointestinal mucosa against aggressive factors. The results showed that single oral administrations of *A. glandulosa* (250 mg/kg/once daily) potently stimulates gastric epithelial cell proliferation that contributes to the accelerated healing of gastric ulcers induced by acetic acid. In addition, no sub-acute toxicity (body weight gain, vital organs and serum biochemical parameters) was observed during treatment with the extract. Phytochemical investigation led to the isolation of gallic acid, methyl gallate, pterogynidine and different flavonoids. These compounds may contribute to the observed antiulcerogenic effects of *A. glandulosa* [33].

The gastroprotective potential of the 50% aqueous alcoholic extract of *Anogeissus latifolia* (100 and 200 mg/kg b.w.) was studied on aspirin, cold-resistant stress, pylorus ligated and ethanol-induced ulcers. The status of the antioxidant enzymes SOD and CAT, along with lipid peroxidation (LPO), was also studied in cold-resistant stress-induced ulcers [34]. Synthetic NSAIDs, like aspirin, cause mucosal damage by interfering with prostaglandin synthesis, increasing acid secretion and back diffusion of H^+ ions, resulting in overproduction of leukotrienes and other products of the 5-lipoxygenase pathway [35]. Hence, the protective action of *A. latifolia* extract (65.6% at

200 mg/kg) against aspirin-induced gastric lesions could possibly be due to its 5-lipoxygenase inhibitory effect. Ethanol-induced depletion of gastric wall mucus has been significantly prevented by *A. latifolia* extract. Pylorus ligation-induced ulcers are due to auto-digestion of the gastric mucosa and breakdown of the gastric mucosal barrier [36]. *A. latifolia* extract also protected against the cold-resistant stress-induced ulcers and pylorus ligation at 200 mg/kg. Stress-induced ulcers are probably mediated by histamine release with enhancement in acid secretion and a reduction in mucous production. Increase in gastric motility, vagal overactivity, mast cell degranulation decreased gastric mucosal blood flow, and decreased prostaglandin synthesis is involved in genesis of stress-induced ulcers [37-39]. Accordingly, the protective action of *A. latifolia* extract against stress-induced ulceration could be due to its histamine antagonistic, anticholinergic and antisecretory effects.

Stachytarpheta cayennensis is an herbaceous plant popularly known as gervão-roxo, gervão-do-campo or vassourinha-de-botão in Brazil and used in traditional medicine for the treatment of gastritis and ulcers [40]. Two hydroalcoholic extracts obtained respectively with ethanol/water 70:30 and ethanol/water 96:4 were prepared and tested. The oral pretreatment with the second ethanolic extract significantly inhibited the generation of gastric lesions induced by diclofenac, whereas the first extract induced a slight, but not statistically significant inhibition of mucosa damage.

Mouriri pusa is another medicinal plant commonly used in Brazil against gastric ulcer. The methanol and dichloromethane extracts obtained by sequential extraction from the leaves of *M. pusa* were evaluated for their ability to protect the gastric mucosa against injuries caused by necrotizing agents (0.3M HCl/60% EtOH, absolute ethanol, NSAIDs, stress and pylorus ligature) in mice and rats [41]. The best results were obtained after pretreatment with methanol extract, whereas the dichloromethane extract did not show the same significant antiulcerogenic activity. The mechanism involving the antiulcerogenic action of the methanol extract seemed to be related to NO generation and also suggested the effective participation of endogenous sulfhydryl groups in the gastroprotective action. Phytochemical investigation of the methanol extract of *M. pusa* yielded tannins and flavonoids. The presence of these phenolic compounds probably would explain the

antiulcerogenic effect of the polar extract of *M. pusa* leaves.

Recently, Berenguer *et al.* [42] evaluated the gastroprotective effect of *Rhizophora mangle* in a model of diclofenac-induced ulcers in rats and studied the mechanisms involved, using the proton pump inhibitor omeprazole for comparison. The major active principles are polyphenols [43]. These compounds have shown cytoprotective properties [44] and have been associated with antiulcerogenic activity in other plants [45,46]. The topical action of the aqueous extract of *R. mangle* in accelerating wound healing has been previously explained by several mechanisms, such as coating the wound, forming complexes with proteins of the microorganism cell wall, chelating free radicals and reactive oxygen species, stimulating the contraction of the wound and increasing the formation of new capillaries and fibroblasts [47]. Berenguer *et al.* [42] found a thick coating of *R. mangle* extract macroscopically adherent to the gastric mucosa, which suggests that in addition to antioxidant mechanisms, the formation of a physical barrier with similar properties as observed in topical wounds may contribute to the gastroprotective action of the drug.

A methanolic extract, the essential oil, light petroleum soluble and insoluble fractions of the methanolic extract of *Elettaria cardamomum* were studied in rats at doses of 100-500, 12.5-50, 12.5-150 and 450 mg/kg, respectively, for their ability to inhibit the gastric lesions induced by aspirin, ethanol and pylorous ligature [48]. In addition, effects on wall mucus and gastric acid output were recorded.

All fractions significantly inhibited gastric lesions induced by ethanol and aspirin, but not those induced by pylorus ligation. The methanolic extract proved to be active, reducing lesions by about 70% in the ethanol-induced ulcer model at 500 mg/kg. The light petroleum soluble fraction reduced the lesions by 50% at 50 and 100 mg/kg, with similar effect to that of the insoluble fraction of the methanol extract at 450 mg/kg. In the aspirin-induced gastric ulcer, the best gastroprotective effect was found in the light petroleum soluble fraction, which inhibited lesions by nearly 100% at 12.5 mg/kg.

Oral administration of *Kaempferia parviflora* ethanolic extract (30-120 mg/kg) inhibited gastric ulcer formation induced by indomethacin, HCl/EtOH and water immersion restraint stress [49]. It was found that pretreatment with *K. parviflora* at doses of 60 and 120 mg/kg significantly increased the amount of gastric mucus content in HCl/EtOH-ulcerated rats. The finding that *K. parviflora* failed to increase the gastric pH and decrease the gastric volume and acidity in pylorus-ligated rats suggests that the anti-secretory action is unlikely to be ascribed to the anti-gastric ulcer effect of the *K. parviflora*. The gastric wall mucus is thought to play an important role as a defensive factor against gastrointestinal damage. The gastric wall mucus was used as an indicator for gastric mucus secretion. The finding that pretreatment with *K. parviflora* at doses of 60 and 120 mg/kg significantly increased gastric mucus content in HCl/EtOH ulcerated rats suggests that the gastroprotective effect of *K. parviflora* is mediated only partly by preservation of gastric mucus secretion.

Sannomiya *et al.* [50] evaluated the potential antiulcerogenic effect of three different extracts obtained from the leaves of *Byrsonima crassa*, namely hydromethanolic (80% MeOH), methanolic and chloroform extracts. The oral administration of all the extracts reduced the formation of lesions associated with HCl/ethanol administration in mice. The 80% MeOH extract significantly reduced the incidence of gastric lesions by 74, 78 and 92% at doses of 250, 500 and 1000 mg/kg, respectively. The methanolic extract reduced the ulceration only at doses of 500 and 1000 mg/kg. Phytochemical investigation of *B. crassa* revealed the presence of phenolic compounds that may probably explain the antiulcerogenic effect of the extracts of *B. crassa*.

In the HCl/EtOH-induced gastric ulcer model, an hydroalcoholic extract obtained from *Pradosia huberi* barks demonstrated significant inhibition of the ulcerative lesion index by 73% (500 mg/kg) and 88% (1000 mg/kg), respectively [51]. The gastric damage induced by absolute ethanol in rats was effectively reduced by 84, 88 and 81% (250, 500 and 1000 mg/kg). In the NSAID-induced lesion model, *P. huberi* extract also showed an antiulcerogenic effect with decrease in gastric lesions. *P. huberi* administered either orally or intraduodenally was able to change gastric juice parameters as well as those treated with cimetidine. The treatment with *P. huberi* extract significantly increased gastric volume, the pH values and promoted reduced acid output. By comparison of the effects produced by the intraduodenal and oral routes, it was observed that *P. huberi* was better for local activity in gastric

mucosa than in systemic action. The hydroalcoholic extract of *P. huberi* was also shown to be an inhibitor of intestinal motility. The mechanism of action of the.extract did not seem to be related to the NO-inhibitor, but showed the participation of endogenous sulphydryl groups in the gastroprotective action.

In order to establish the pharmacological basis for their ethnomedicinal use in gastric disorders, studies were made of the effects of ethanol extracts and fractions from root tubers of *Cynanchum auriculatum*, *C. bungei* and *Cynoctonum wilfordii* on ethanol- and indomethacin-induced gastric lesions, and histamine-induced gastric acid secretion in rats [52]. Oral administration of the ethanol extract and chloroform fraction of *C. wilfordii* at doses of 150 and 68 mg/kg, respectively, significantly inhibited the development of ethanol- and indomethacin-induced gastric lesions and also caused a significant decrease of gastric acid secretion after histamine-induced gastric lesion. Oral administration of ethanol extract and the chloroform fraction of *C. auriculatum* at doses of 300 and 69 mg/kg, respectively, significantly inhibited ethanol- and indomethacin-induced gastric lesions.

Cissus quadrangularis is well known for the treatment of gastric disorders owing to it being a rich source of carotenoids, triterpenoids and ascorbic acid. Jainu *et al.* [53] evaluated an ethanol extract of *C. quadrangularis* against the gastric toxicity induced by aspirin in rats with an optimum protective dose of 500 mg/kg of extract in the aspirin model. In addition, administration of aspirin increases lipid peroxidation status, xanthine oxidase (XO), and myeloperoxidase, and decreases selenium-GPx activities in the gastric mucosa, resulting in mucosal damage at both cellular and subcellular level. Pretreatment with *C. quadrangularis* ameliorated the observed effects significantly in the gastric mucosa of ulcerated rats. These findings suggest that the gastroprotective activity of *C. quadrangularis* could be mediated possibly through its antioxidant effect, as well as by the attenuation of the oxidative mechanism and neutrophil infiltration.

Administration of a 70% methanolic extract of *Punica granatum* fruit rind showed inhibition in aspirin- and ethanol-induced gastric ulceration [54]. In treated groups of animals, the SOD, CAT, GSH and GPx levels were increased and found more or less equal to the normal values. The tissue lipid peroxidation level was found to be decreased in

treated groups of animals as compared with the control group. Histopathological examination of the stomach of the ulcerated animals showed severe erosion of the gastric mucosa, sub-mucosal edema and neutrophil infiltration. All of these symptoms were found to be normal in the treated groups. In general, the results of this investigation revealed the gastroprotective activity of the extract through an antioxidant mechanism.

Al-Qarawi *et al.* [55] evaluated, in a rat model of ethanol-induced gastric ulceration, the beneficial effects on gastric ulcers of a plant used in folk medicine, *Phoenix dactylifera*. Aqueous and ethanolic undialyzed and dialyzed extracts from date fruits and pits were given orally to rats at a dose of 4 mL/kg for 14 consecutive days. On the last day of treatment, rats were fasted for 24 h and were then given 80% ethanol (1 mL/rat) by gastric intubation to induce gastric ulcer. Rats were killed after 1 h of ethanol exposure and the incidence and severity of the ulceration were estimated, as well as the concentrations of gastrin in plasma, and histamine and mucus in the gastric mucosa. As a positive control, a single group of rats that were fasted for 24 h was administered orally with lansoprazole and was given 80% ethanol, as above, 8 h thereafter. The results indicated that the aqueous and ethanolic extracts of the date fruit and, to a lesser extent, date pits, were effective in ameliorating the severity of gastric ulceration and mitigating the ethanol-induced increase in histamine and gastrin concentrations, and the decrease in mucin gastric levels. The ethanolic undialyzed extract was more effective than the other extracts used. It is postulated that the basis of the gastroprotective action of *P. dactylifera* extracts may be multi-factorial, but may include an antioxidant action.

The tissue lipid peroxidation level was found to be decreased in the treated groups of animals as compared with the control group. Histopathological examination of the stomach of the ulcerated animals showed severe erosion of the gastric mucosa, sub-mucosal edema and neutrophil infiltration.

Portulaca oleracea, commonly used in Iranian folk medicine, has been demonstrated to protect mice from gastric aggressive factors and its administration reduced total gastric acidity and increased pH of gastric juice [56]. On induction of gastric ulceration by using HCl, pretreatment with the aqueous and ethanolic extracts showed a dose-dependent reduction

in the severity of ulcers. The dose of 0.8 g/kg of the aqueous extract and 1.4 g/kg of the ethanolic extract had similar activity to sucralfate (0.1 g/kg). In lesions induced by ethanol, the dose of 0.56 g/kg, and 0.8 g/kg of the aqueous extract, and 0.8 and 1.4 g/kg of the ethanolic extract showed significant inhibition of lesions. The oral and intraperitoneal doses of both extracts inhibited the total gastric acidity in the pylorus-ligated mice in a dose-dependent manner. The highest dose of extracts had antisecretory activity, which was comparable to cimetidine.

Lavandula hybrida Reverchon "Grosso" exerted gastroprotective effects [57]. Interestingly, the principal constituents of the oil, linalool and linalyl acetate, were demonstrated to contribute to the gastroprotective effect of lavender oil which, orally administered, caused a dramatic reduction in ethanol-induced gastric injury to rats. The lack of a protective effect against gastric mucosal damage caused by indomethacin led to the hypothesis that gastroprotection afforded by *L. hybrida* oil cannot be attributed to interference with the arachidonic acid metabolic cascade.
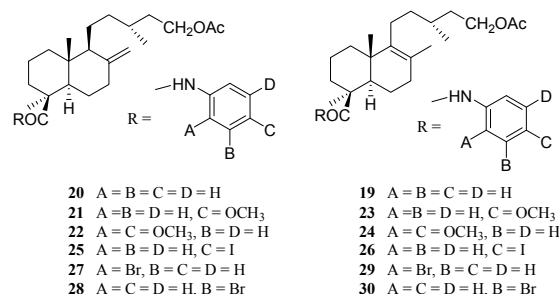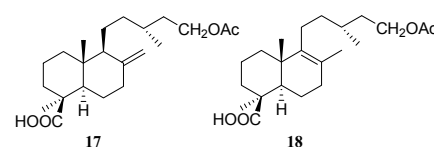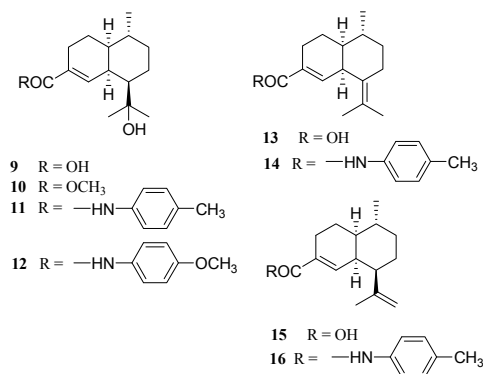
2. Pure compounds

2.1. Terpenes: Several plant terpenoids, including sesquiterpenes, diterpenes and triterpenes, have been shown to protect the gastric mucosa against the damage caused by different ulcerogens [58]. Recently the gastroprotective effect of the sesquiterpene cyperenoic acid and seven semi-synthetic derivatives was assessed in the HCl/ethanol-induced gastric ulcer model in mice [59]. At doses of 25, 50 and 100 mg/kg, cyperenoic acid (**3**) showed a dose-dependent gastroprotective effect, reducing the ulcers by 45 and 75% at 50 and 100 mg/kg, respectively, compared with the untreated controls.

Of the sesquiterpenes **1-8**, assessed at a single oral dose of 50 mg/kg, the best gastroprotective effect was observed for derivative **8**, obtained as a diasteromeric mixture by reduction of the 4,5-double bond of cyperenoic acid (**3**). Compound **8** reduced the lesion index by 86%, being the most active of the sesquiterpenes evaluated in this work and more active than lansoprazole at 20 mg/kg. The products **1** and **3-8** did not show significant differences in gastroprotective activity. Cyperenol (**1**) and cyperenoic acid methyl ester (**4**), however, were more cytotoxic with IC$_{50}$ values of 44 and 75, and 48 and 75 mM against AGS cells and fibroblasts, respectively. The best gastroprotective effect with a
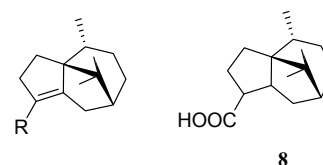
1	R = CH$_2$OH
2	R = CH$_2$OCOCH$_3$
3	R = COOH
4	R = COOCH$_3$
5	R = CONHCH$_2$CH$_3$
6	R = CONHCH$_2$CH$_2$CH$_2$CH$_3$
7	R = CONHPhOCH$_3$

8

9 R = OH
10 R = OCH$_3$
11 R = —HN—⬡—CH$_3$
12 R = —HN—⬡—OCH$_3$

13 R = OH
14 R = —HN—⬡—CH$_3$

15 R = OH
16 R = —HN—⬡—CH$_3$

17 CH$_2$OAc

18 CH$_2$OAc

20 A = B = C = D = H
21 A = B = D = H, C = OCH$_3$
22 A = C = OCH$_3$, B = D = H
25 A = B = D = H, C = I
27 A = Br, B = C = D = H
28 A = C = D = H, B = Br

19 A = B = C = D = H
23 A = B = D = H, C = OCH$_3$
24 A = C = OCH$_3$, B = D = H
26 A = B = D = H, C = I
29 A = Br, B = C = D = H
30 A = C = D = H, B = Br

lower cytotoxicity was found for compound **8**, cyperenoic acid (**3**) and the *p*-anisidyl derivative **7**.
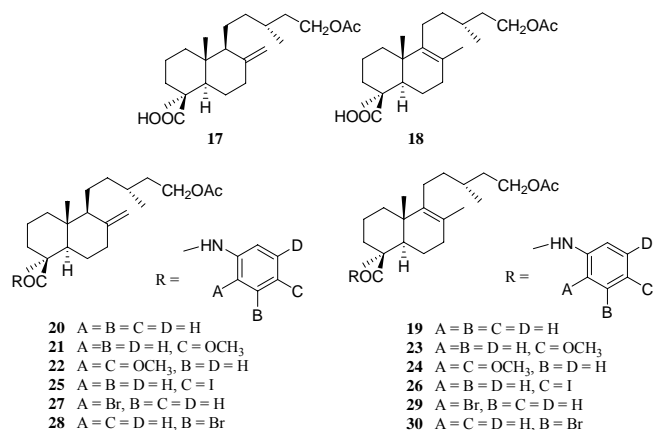
The main sesquiterpene of *Fabiana imbricata*, 11-hydroxy-4-amorphen-15-oic acid (**9**), at doses of 25, 50 and 100 mg/kg showed a dose-dependent gastroprotective effect in HCl/EtOH-induced gastric lesions in mice, reducing the lesions by 68% at 100 mg/kg [60]. Seven derivatives of this terpene were prepared and their gastroprotective effects were assessed in HCl/EtOH-induced gastric lesions in mice. Compounds **9**, **10** and **12** reduced the lesion index by 60-65%, while the mixture of compounds **13** and **15**, as well as **14** and **16** presented values of 71% and 51%, respectively. The most active compound proved to be the amide derivative **11**,

which reduced the lesion index by 80%. At 20 mg/kg, lansoprazole reduced the lesion index by 70%. Compounds **13** and **15**, lacking the alcohol function at C-11, had a better gastroprotective activity than **9**. In the case of compounds **14** and **16**, where the alcohol function at C-11 is absent and the acid group is substituted by an amide function, the gastroprotective activity was reduced when compared with compound **11**. The alcohol function at C-11 is required for a better gastroprotective effect when there is a substitution of the acid for an amide. At doses of up to 1000 mg/kg, oral administration of **9** did not show any observable symptoms of toxicity or mortality in mice. Therefore, the intraperitoneal LD_{50} for this compound in mice is higher than 1000 mg/kg and it can be regarded as 'not harmful'. The cytotoxicity study revealed that compound **9**, as well as the mixtures of **13** and **15** and compounds **14** and **16** presented low toxicity towards AGS cells and fibroblasts. In the compound series **9-12**, when the acid function at C-15 is substituted forming an amide (**11** and **12**), the cytotoxicity increased significantly. A comparison of the acids **9**, **13** and **15** indicated a comparable low cytotoxicity, thus suggesting that the presence of the alcohol function at C-11 did not contribute to this effect.

When the corresponding amides were prepared (i.e. **11-12** and **14-16**), the presence of the hydroxy group at C-11 determined the cytotoxicity of the products. The labdane diterpenes 15-acetoxyimbricatolic acid (**17**) and 15-acetoxylabd-8(9)-en-19-oic acid (**18**) isolated from *Araucaria araucana* exhibited significant gastroprotective activity at 50 and 100 mg/kg in mice, respectively.

From these compounds, some aromatic amides were prepared and assessed for their gastroprotective effect in the HCl/EtOH-induced gastric lesion model in mice [61]. The analysis of the gastroprotective activity of the benzylamides belonging to the series 8(9)- and 8(17)-ene was undertaken at doses of 12.5, 25 and 50 mg/kg in the HClI/EtOH-induced gastric lesion model in mice.

A significant gastroprotective effect was observed for 15-acetoxylabd-8(9)-en-19-oic acid benzylamide (**19**) starting at 12.5 mg/kg, reducing the gastric lesions by 50%, while 15-acetoxylabd-8(17)-en-19-oic acid benzylamide (**20**) reduced lesions by 66% at 25 mg/kg. At 25 mg/kg, the highest gastroprotective effect was observed for the benzyl- and 3-bromo phenylamides from **17**, as well as for the benzyl- and

20	A = B = C = D = H
21	A = B = D = H, C = OCH₃
22	A = C = OCH₃, B = D = H
25	A = B = D = H, C = I
27	A = Br, B = C = D = H
28	A = C = D = H, B = Br

19	A = B = C = D = H
23	A = B = D = H, C = OCH₃
24	A = C = OCH₃, B = D = H
26	A = B = D = H, C = I
29	A = Br, B = C = D = H
30	A = C = D = H, B = Br

p-toluidylamides from **18**, these being as active as lansoprazole at 20 mg/kg. The presence of a 4'-methoxy or a 2',4'-dimethoxy functionality did not result in significant differences in the gastroprotective effects of **21** and **22**, but a strong effect was observed for **23**, while the activity of **24** was lower. The effect of a halogen in the aromatic ring on the gastroprotective activity can be assessed by comparing **25** and **26**, which bear iodine. While the gastroprotective activity of **27** and **28** was strong and comparable to that of **20**, there was a substantial decrease in the gastroprotective effect of **29** and **30** compared with **19**. The results suggest a relevant role of the exomethylene function in the gastroprotective effect of the brominated derivatives, with higher activity for **28**. The effect, however, is not statistically different from that of **27**. The structural modifications undertaken led to labdane derivatives with an increased gastroprotective effect compared with the parent compounds.

The gastroprotective effect of the diterpenes jatropholone A (**31**), jatropholone B (**32**) and sixteen semisynthetic derivatives was assessed in the HCl/ethanol-induced gastric lesion model in mice and the cytotoxicity was determined towards fibroblasts and AGS cells [62]. In a dose-response study, **32** reduced gastric lesions by 65% at 6 mg/kg and **31** by 54% at 100 mg/kg. The jatropholone B derivatives **33-38** and the compounds **39-42** were compared at a single oral dose of 25 mg/kg, while the jatropholone A derivatives **43-48** were assessed at 100 mg/kg. A decrease in gastroprotective activity was observed for the ether as well as for the ester derivatives of **32**. The methyl and propyl ethers of **31** were more gastroprotective than the natural product The placement of an additional methyl group at C-2 in the jatropholone B derivatives led to a loss of selectivity; the methyl and propyl ethers lack a

gastroprotective effect. At the dose of 25 mg/kg compound **32** reduced the lesions by 83%, while compound **31** inhibited them by only 36%. At 100 mg/kg, all the derivatives of **31** were active. Compounds **45-47** showed a similar activity to that of their parent **31**, while derivatives **43**, **44** and **48** were the most active. Considering the derivatives of **32**, at 25 mg/kg, compounds **34**, **41** and **42** showed the best gastroprotective effect, while compounds **38** and **39** were the less active.

The gastroprotective mechanism of the natural diterpene ferruginol (**49**) was assessed *in vivo*. The involvement of gastric prostaglandins PGE(2), reduced GSH, NO or capsaicin receptors was evaluated in mice either treated or untreated with indomethacin, *N*-ethylmaleimide (NEM), *N*-nitro-L-arginine methyl ester (L-NAME) or ruthenium red, respectively, and then orally treated with **49** or vehicle. Gastric lesions were induced by oral administration of ethanol. The effects of ferruginol (**49**) on the parameters of gastric secretion were assessed in pylorus-ligated rats. Gastric PGE(2) content was determined in rats treated with **49** and/or indomethacin.

The reduction of gastric GSH content was determined in rats treated with ethanol after oral administration of ferruginol (**49**), lansoprazole or vehicle. Finally, the acute oral toxicity was assessed in mice. Indomethacin reversed the gastroprotective effect of ferruginol (**49**) (25 mg/kg), but not NEM, ruthenium red or L-NAME. The diterpene (25 mg/kg) increased the gastric juice volume and its pH value, and reduced the titrable acidity, but was devoid of effect on the gastric mucus content. Ferruginol (**49**) increased gastric PGE(2) content in a dose-dependent manner and prevented the reduction in GSH observed due to ethanol-induced gastric lesions in rats. Single oral doses up to 3 g/kg **49** did not elicit mortality or acute toxic effects in mice. The results showed that ferruginol (**49**) acted as a gastroprotective agent stimulating gastric PGE(2) synthesis, reducing gastric acid output and improving the antioxidant capacity of the gastric mucosa by maintaining GSH levels [63].

The principal 28-noroleanane-type triterpene oligoglycosides camelliosides A (**50**) and B (**51**), isolated from the flowers buds of *Camellia japonica*, showed protective effects on both ethanol- and indomethacin-induced gastric lesions and their gastroprotective effects were either equivalent or
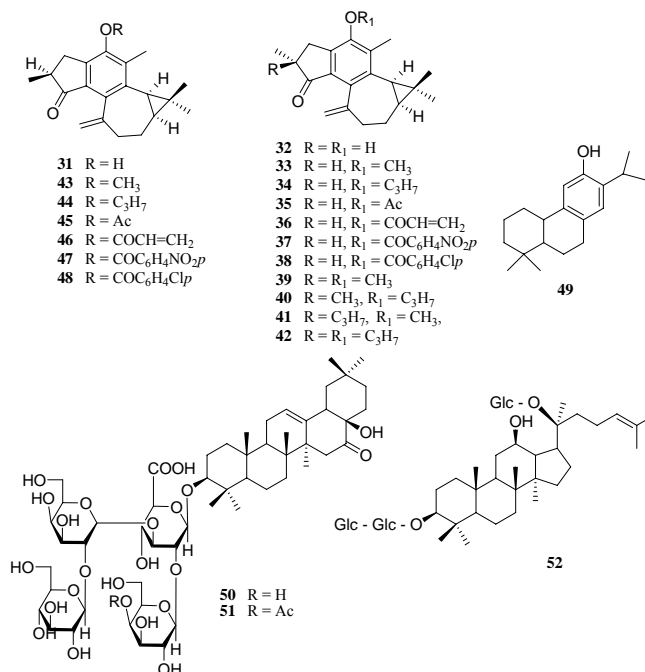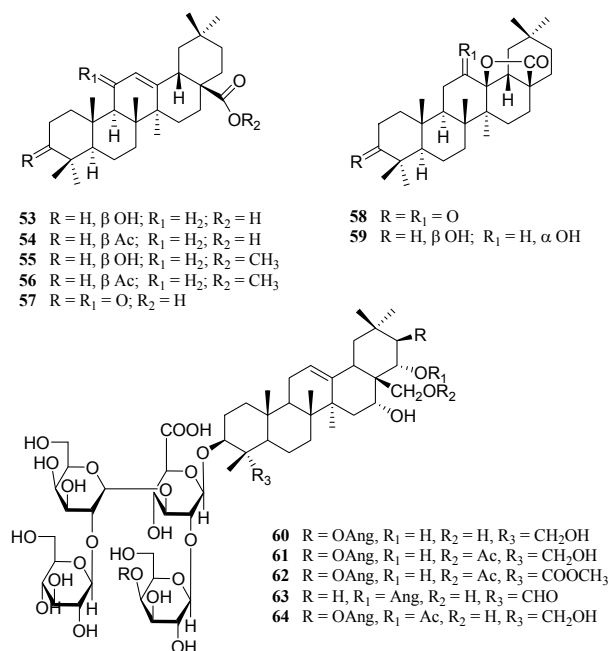

stronger than those of the reference compounds, omeprazole and cimetidine [64].

The oligoglycoside fraction from the flower buds of *Panax ginseng* was found to show protective effects on ethanol-induced gastric mucosal lesions in rats. From this fraction, ginsenoside Rd (protopanaxadiol 3,20-*O*-bisdesmoside) (**52**) was isolated, together with new dammarane-type triterpene tetraglycosides. Ginsenoside Rd (**52**) exhibited inhibitory effects on ethanol- and indomethacin-induced gastric mucosal lesions in rats. The effect of **52** on ethanol-induced gastric lesions was equipollent to that of a reference compound, cetraxate hydrochloride [65].

The triterpene oleanolic acid (**53**) and its semisynthetic derivatives **54-59** were studied for gastroprotective and ulcer-healing effect using AGS cells and human lung fibroblasts (MRC-5) [66]. The assessment of the effect of the oleanolic acid derivatives on the PGE(2) content showed a significant increase of this prostaglandin when the AGS cell cultures were treated with compounds **53**, **54**, **56** and **58**.

The gastroprotective effect of oleanolic acid derivatives was assessed also in the HCl/EtOH-induced gastric lesions in mice. All the assayed compounds exhibited gastroprotective activity at the dose of 50 mg/kg, reducing the gastric lesions to different degrees ranging from 38% for compound **54**

53 R = H, β OH; R₁ = H₂; R₂ = H
54 R = H, β Ac; R₁ = H₂; R₂ = H
55 R = H, β OH; R₁ = H₂; R₂ = CH₃
56 R = H, β Ac; R₁ = H₂; R₂ = CH₃
57 R = R₁ = O; R₂ = H

58 R = R₁ = O
59 R = H, β OH; R₁ = H, α OH

60 R = OAng, R₁ = H, R₂ = H, R₃ = CH₂OH
61 R = OAng, R₁ = H, R₂ = Ac, R₃ = CH₂OH
62 R = OAng, R₁ = H, R₂ = Ac, R₃ = COOCH₃
63 R = H, R₁ = Ang, R₂ = H, R₃ = CHO
64 R = OAng, R₁ = Ac, R₂ = H, R₃ = CH₂OH

65 R = OH
66 R = H

67

68 R = OH, R₁ = H
69 R = OH, R₁ = OH
70 R = OCH₃, R₁ = OH

71 . H₂O

and up to 76% for compound **57**. The most active products were compounds **57** and **59**. In the compound group **53-56**, differing in the free or esterified hydroxyl group at C-3 and the free or methylated carboxylic acid function at C-28, acetylation of the hydroxyl group at C-3 with a free COOH at C-28 reduced the gastroprotective activity, as can be observed for compound **54**. Methylation of the COOH at C-28 in compound **57** significantly lowered the gastroprotective effect. Therefore, the effect should be related to the presence of a free carboxylic acid at C-28 when there is an oxo group at C-3 and C-11. In compounds **58** and **59**, the free hydroxyl groups at C-3 and C-12 increased the gastroprotective effect, the activity of compound **58** being in the same range as that of oleanolic acid (**53**).

The triterpene saponins theasaponins A1 (**60**), A2 (**61**), F3 (**62**), assamsaponin A (**63**) and assamsaponin D (**64**), isolated from the seeds of *Camellia sinensis*, were tested for their gastroprotective effects. Theasaponin A2 (**61**) showed an inhibitory effect on ethanol-induced gastric mucosal lesions in rats at a dose of 5.0 mg/kg, p.o. and its activity was more potent than that of omeprazole. Structure-activity relationships for theasaponins on ethanol-induced gastroprotective activities may suggest that (a) the 28-acetyl moiety enhances activity and (b) theasaponins having a 23-aldehyde group exhibit more potent activities than those with either a 23-hydroxymethyl group or a 23-methoxycarbonyl group [67].
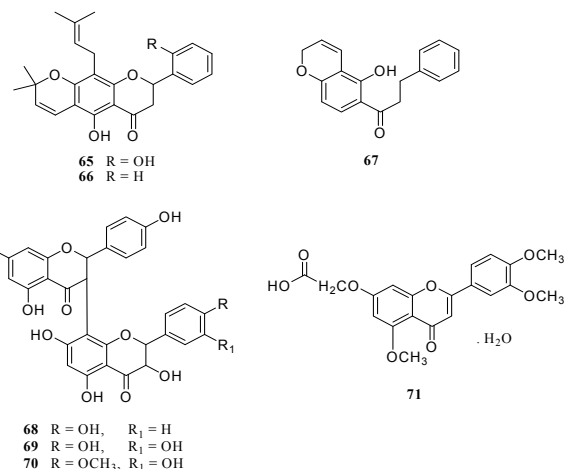
2.2. Flavonoids: The flavonoids minimiflorin (**65**) and mundulin (**66**) and the chalcone lonchocarpin (**67**), isolated from *Lonchocarpus oaxacensis* and *L. guatemalensis*, respectively, were tested on H⁺,K⁺-ATPase isolated from dog stomach [68].

The flavanone minimiflorin (**65**) was the most potent inhibitor, while mundulin (**66**) was 7.3-fold less potent than **65**. Hydroxylation at C-2' accounts for this difference in potency. Thus, hydroxylation plays an important role in conferring inhibitory activity of the gastric H⁺,K⁺-ATPase to the flavanones. Lonchocarpin (**67**), which has only one hydroxyl group in its molecule showed only moderate inhibition of ATPase (about 18-fold less potent than **65**). A comparison of the relative potencies of these active compounds with omeprazole shows that many of these isolated compounds have higher inhibitory activity of H⁺,K⁺-ATPase than the reference compound, from 2 to 44 times higher for the most potent inhibitor of H⁺,K⁺-ATPase tested here, mundulin (**66**).

Kolaviron is a mixture of three compounds, *Garcinia* biflavonoid GB1 (**68**), GB2 (**69**) and kolaflavanone (**70**) and has been extensively studied for its anti-inflammatory property in various experimental models [69-72]. The antioxidant and scavenging properties of kolaviron have also been demonstrated [73]. Recently, it was demonstrated also that treatments with kolaviron significantly inhibited gastric lesions produced by indomethacin and acidified ethanol [74]. The effects of kolaviron on both indomethacin and ethanol-induced hemorrhagic erosion may be associated with an increase in gastric mucosal blood flow and gastric mucus secretion.
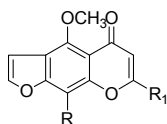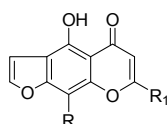
OCH₃

72 R = H
73 R = OCH₃

74 R = —N O (morpholine)
75 R = —N N—CH₃ (N-methylpiperazine)
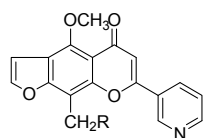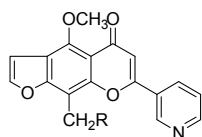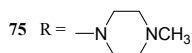
76 R = H, R₁ = C₆H₅
77 R = H, R₁ = p-ClC₆H₄
78 R = H, R₁ = p-CH₃C₆H₄
79 R = —H₂CN O , R₁ = C₆H₅
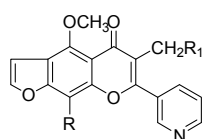80 R = , R₁ = p-ClC₆H₄

81 R = H, R₁ = C₆H₅
82 R = H, R₁ = p-ClC₆H₄
83 R = —N O , R₁ = C₆H₅
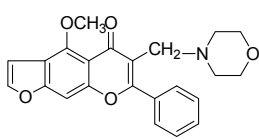84 R = , R₁ = p-ClC₆H₄

85 R = H, R₁ = N(CH₃)₂
86 R = OCH₃, R₁ = —N O
87 R = OCH₃, R₁ = —N N—CH₃

88

The gastroprotective activity of DA-6034 (**71**), a new flavonoid derivative, against various ulcerogens including ethanol, aspirin, indomethacin, stress, and acetic acid was evaluated [75]. The basic mechanisms of DA-6034 (**71**) as a defensive factor, such as mucus secretion and endogenous PGE(2) synthesis were determined. Rats with gastric lesions induced by ethanol-HCl, aspirin, indomethacin, and stress that had been pretreated with **71** orally showed either a statistically significant decrease or decreasing tendency of the gastric lesion. In acetic acid-induced gastric lesions, repeated oral administration of **71** exhibited a U-shape activity in ulcer healing, with the maximum and minimum inhibition being observed at 30 and 10 mg/kg/day, respectively. DA-6034 (**71**) also increased the mucus content in the gel layer, as well as endogenous PGE(2) synthesis. These results suggest that **71** prevents gastric mucosal injury, and these gastroprotective activities appear to be due to the increase in the gastric defensive systems. The therapeutic limitations of **71** caused by its low solubility in acidic conditions were overcome by using the effervescent floating matrix system (EFMS), which was recently designed to cause

tablets to float in gastric fluid and release the drug continuously. The release of DA-6034 (**71**) from tablets in acidic media was significantly improved by using EFMS, which is attributed to the effect of the solubilizers and the alkalizing agent, such as sodium bicarbonate used as a gas generating agent. DA-6034 EFMS tablets showed enhanced gastroprotective effects in gastric ulcer-induced beagle dogs, indicating the therapeutic potential of EFMS tablets for the treatment of gastritis [76].

Some furoflavones (**74-88**), synthesized from the naturally occurring chromones visnagin (**72**) and khellin (**73**), exhibited gastroprotective activity in the ethanol damage model [77].

In the benzopyrone portion of the furoflavone system, the type of aromatic substitution at the 7-position affected the gastroprotective effect. The *p*-methoxyphenyl derivative **78** was more active than the *p*-chlorophenyl **77**, which was more active than the phenyl derivative **76**.

The presence of a 9-alkylaminomethyl substituent in these compounds decreased the activity of **79** and **80**, while the presence of a 6-alkylaminomethyl substituent increased the activity (compound **86** showed more activity than **76**). When the aromatic group in position 7 was pyridinyl, the activity was slightly decreased (compounds **74** and **85**), except in the case of the 9-*N*-methylpiperazinomethyl derivative **75**, which showed promising gastroprotective activity. It was found that the presence of a methoxy group showed great effect on the activity.

Substitution at the 4-position with a methoxy group (compounds **76-80**) enhanced the gastroprotective activity, in contrast to 4-hydroxy derivatives **81-83**, which showed a marked decrease in activity. Substitution with another methoxy group (**87**) produced a potent level of gastroprotection.

In summary, furoflavones exhibited good gastroprotective activity in the ethanol damage model when there was a methoxy group (either in the 4, 9 or 7-position as methoxyphenyl) and an appropriate substitution in the 6-position with an alkylaminomethyl group.

2.3. Xanthones: Four xanthones, 6-desoxyjacareubin (**89**), jacareubin (**90**), 1,3,5,6-tetra-hydroxy-2-(3-hydroxy-3-methylbutyl)-xanthone (**91**) and 1-

89 R = H
90 R = OH

91

92

93
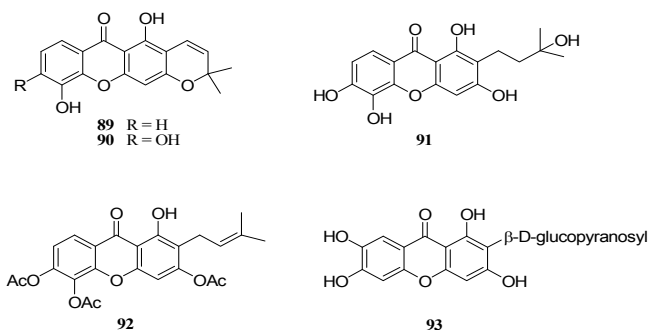
hydroxy-3,5,6-tri-*O*-acetyl-2(3,3-dimethylallyl) xanthone (**92**), isolated from *Calophyllum brasilienses* were tested on H^+,K^+-ATPase isolated from dog stomach [68].

The compounds showed IC_{50} values ranging from 47 μM to 1.6 mM. Steric hindrance by the substituents at C-6 and C-3 appears to influence the potency of inhibition of H^+,K^+-ATPase activity of these compounds. The presence of a hydroxyl group at C-6 seems to play a prime role in the activity of xanthones on gastric ATPase. In accord with this, groups at C-6 in xanthone **89** reduced the potency of H^+,K^+-ATPase inhibition by 34-fold. In addition, acetylation at this position (xanthone **91**) also reduced the activity of the enzyme by a similar amount. Also, the presence of a bulky substituent at C-3 significantly reduced the potency of inhibition of gastric H^+,K^+-ATPase activity by xanthone **91**.

In search of novel gastroprotective agents, mangiferin (**93**), a naturally occurring glucosylxanthone from *Mangifera indica*, was evaluated in mice suffering gastric injury induced by ethanol and indomethacin. The effects of **93** on gastric mucosal damage were assessed by determination of changes in either mean gastric lesion area or ulcer score in mice and on gastric secretory volume and total acidity in 4 hour pylorus-ligated rats. Mangiferin (**93**) (3, 10 and 30 mg/kg p.o.) significantly attenuated the gastric damage induced by ethanol and indomethacin. *N*-Acetylcysteine (750 mg/kg, i.p.) and lansoprazole (30 mg/kg, p.o.), used as positive controls in these ulcerogenic models, resulted in 50% and 76% suppression of gastric injury, respectively. In 4 hour-pylorus-ligated rats, intraduodenally applied **93** (30 mg/kg) caused significant diminutions in gastric secretory volume and total acidity. In addition, like *N*-acetylcysteine, a donor of sulfhydryls, mangiferin (**93**) effectively prevented the ethanol-associated depletion of gastric mucosal non-protein sulfhydryl

content in mice, suggesting an antioxidant action. These findings provide evidence that mangiferin (**93**) affords gastroprotection against gastric injury induced by ethanol and indomethacin, most possibly through the antisecretory and antioxidant mechanisms of action [78].

Conclusions: The development of safe and effective drugs capable of preventing stomach damage induced by NSAIDs or other gastric-damaging substances represents an important goal of medicinal research considering the large use of these drugs and the increased healthcare costs when peptic ulcer disease becomes a chronic condition. It is well established that natural products are an excellent source of chemical structures with a wide variety of biological activity, including gastroprotective properties. The large number of compounds derived from natural sources that are currently undergoing evaluation in clinical trials is another positive indicator that natural product discovery provides good value for human medicine.

This paper gives an up-to-date review of plant extracts, natural compounds and their derivatives as gastroprotective agents. This knowledge should encourage further *in vitro* and *in vivo* pharmacological studies and help to provide leads to the ultimate goal of developing novel gastroprotective drugs.

List of abbreviations

AGS	=	Human gastric epithelial cells
CAT	=	Catalase
COX-2	=	Cyclooxygenase-2
CYP1A1	=	Cytochrome P450 1A1
EFMS	=	Effervescent floating matrix system
GPx	=	Glutathione peroxidase
GSH	=	Glutathione
IC_{50}	=	Inhibitory concentration 50%
IL-8	=	Interleukin-8
iNOS	=	Inducible nitric oxide synthase
LD_{50}	=	Lethal dose 50%
L-NAME	=	*N*-nitro-L-arginine methyl ester
LPO	=	Lipid peroxidation
MRC-5	=	Human lung fibroblasts
NEM	=	*N*-ethylmaleimide
NF-κB	=	Nuclear factor kappa B
NO	=	Nitric oxide
NP-SH	=	Non-protein sulfhydryl
NSAIDs	=	Nonsteroidal anti-inflammatory drugs
PGE	=	Prostaglandin
ROS	=	Reactive oxygen species
SOD	=	Superoxide dismutase
XO	=	Xanthine oxidase

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