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REVIEW ARTICLE

The Plant Kingdom as a Source of Anti-ulcer Remedies

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Phytogenic agents have traditionally been used by herbalists and indigenous healers for the prevention and treatment of peptic ulcer. This article reviews the anti-acid/anti-peptic, gastro-protective and/or anti-ulcer properties of the most commonly employed herbal medicines and their identified active constituents. Botanical compounds with anti-ulcer activity include flavonoids (i.e. quercetin, naringin, silymarin, anthocyanosides, sophoradin derivatives) saponins (i.e. from *Panax japonicus* and *Kochia scoparia*), tannins (i.e. from *Linderae umbellatae*), gums and mucilages (i.e. gum guar and myrrh). Among herbal drugs, liquorice, aloe gel and capsicum (chilli) have been used extensively and their clinical efficacy documented. Also, ethnomedical systems employ several plant extracts for the treatment of peptic ulcer. Despite progress in conventional chemistry and pharmacology in producing effective drugs, the plant kingdom might provide a useful source of new anti-ulcer compounds for development as pharmaceutical entities or, alternatively, as simple dietary adjuncts to existing therapies.

Keywords: gastric ulcer; gastro-protective effect; flavonoids; saponins; tannins; gum and mucilages.

INTRODUCTION

There is a balance in the stomach between the aggressive digestive capabilities of acid plus pepsin and the mucosal barrier. Ulceration occurs when there is a disturbance of the normal equilibrium caused by either enhanced aggression or diminished mucosal resistance. Several factors are implicated in the pathogenesis of gastric ulcer. These include increased acid–pepsin secretion, impaired bicarbonate neutralization, impaired mucus secretion and precipitate lesions on the mucosal layer (Kent Lloyd and Debas, 1994). Acid and pepsin secretion must be considered together because in practice it is difficult to distinguish the effects of each alone (Hersey, 1994). Drug treatment of peptic ulcers is targeted at either counteracting aggressive factors (acid plus pepsin, active oxidants, PAF, leukotrienes, endothelins, bile or exogenous factors including NSAIDs) or stimulating the mucosal defences (mucus, bicarbonate, normal blood flow, prostaglandins, nitric oxide) (Tepperman and Jacobson, 1994). The ideal aims of treatment of peptic ulcer disease are to relieve pain, heal the ulcer and delay ulcer recurrence. To date, no drug meets all the goals of therapy.

In recent years, gastric ulcer has also been associated with infection of gastrointestinal mucosal tissue by *Helicobacter pylori* (Tepperman and Jacobson, 1994). About 70% of patients with peptic ulcer disease are infected by *Helicobacter pylori* and eradication of this microorganism seems to be curative for this disease (Blaser, 1998).

This article reviews drugs derived from botanical sources more commonly used (or extensively studied) in the world for peptic ulcer and, if reported, the anti-ulcer mechanism postulated. While there are other actions on the stomach (e.g. emesis, motility) of the substances reviewed, this article will be concerned only with the anti-ulcer and gastro-protective effects.

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ACTIVE PRINCIPLES WITH ANTI-ULCER ACTIVITY

Flavonoids

Flavonoids are a group of about 4000 naturally occurring compounds with a wide range of biological effects, including anti-ulcer activity. They are important constituents of the human diet (a daily diet contains approximately 1 g of flavonoids per day) and are also found in several medicinal plants used in folk medicine around the world (Di Carlo *et al.*, 1999). Several mechanisms have been proposed to explain the gastroprotective effect of flavonoids; these include increase of mucosal prostaglandin content (Alcaraz and Hoult, 1985), decrease of histamine secretion from mast cells by inhibition of histidine decarboxylase (Bronner and Landry, 1985) and inhibition of *Helicobacter pylori* growth (Beil *et al.*, 1995). In addition, flavonoids have been found to be free radical scavengers (Baumann *et al.*, 1980; Cavallini *et al.*, 1978; Salvayre *et al.*, 1982); free radicals play an important role in ulcerative and erosive

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Table 1. Flavonoids with anti-ulcer activity

Flavonoid	Ulcer model	Reference
Anthocyanosides	Pylorus-ligated, reserpine, phenylbutazone	Magistretti *et al.*, 1998; Cristoni and Magistretti, 1987
Catechin	Stress	Lorenz *et al.*, 1975
Genistin	Phenylbutazone, serotonin pylorus-ligated, stress, reserpine	Rainova *et al.*, 1988
Hypolaetin-8-glucoside	Stress, ethanol, acetylsalicylic acid	Alcaraz and Hoult, 1985; Villar *et al.*, 1984
Kaempferol	Ethanol	Izzo *et al.*, 1994
Leucocyanidin	Aspirin	Lewis *et al.*, 1999
Luteolin-7-glycoside,	Pylorus-ligated, stress, reserpine, phenylbutazone, serotonin	Rainova *et al.*, 1988
5-Methoxyflavone	Indomethacin	Blank *et al.*, 1997
Myricetin 3-O-D-galactoside	Stress, pylorus-ligated, ethanol	Reyes *et al.*, 1996
Naringin	Ethanol, stress, pylorus-ligated	Martin *et al.*, 1993; Motilva *et al.*, 1993
Quercetin	Stress, ethanol, reserpine	Izzo *et al.*, 1994; Di Carlo *et al.*, 1994; Martin *et al.*, 1993
Rutin	Ethanol	Izzo *et al.*, 1994
Silymarin	Stress	Alarcon de la Lastra, 1992
Ternatin	Ethanol, indomethacin, stress	Rao *et al.*, 1997
Vexibinol	HCl, ethanol	Yamahara *et al.*, 1990

lesions of the gastrointestinal tract. In relation to their low toxicity and to the properties reported, flavonoids could have a therapeutic potential ideal for treatment of gastrointestinal diseases associated with *Helicobacter pylori* infection, i.e. type B gastritis and duodenal ulcer (Di Carlo *et al.*, 1999).

Anti-ulcer flavonoids are shown in Table 1. The most studied are naringin, quercetin, silymarin, anthocyanosides and sophoradin derivatives. Moreover, several extracts containing flavonoids have been found to exert gastro-protective activity (Di Carlo *et al.*, 1999), although the precise chemical composition, in many cases, is unknown.

Quercetin. Quercetin is the most abundant of the flavonoid molecules and it is found in many medicinal botanicals, including *Thea sinensis*, *Glycyrrhiza glabra*, *Hypericum perforatum*, *Ginkgo biloba* and many others. It has been reported to prevent gastric mucosal lesions produced by cold-restraint stress and pylorus-ligation (Martin *et al.*, 1988; 1993), reserpine (Manicheva and Barnaulov, 1984) and ethanol or acidified ethanol (Alcarcon de la Lastra *et al.*, 1992; Izzo *et al.*, 1994; Di Carlo *et al.*, 1994). Quercetin increases the amount of neutral glycoproteins in the gastric mucosa (Di Carlo *et al.*, 1999). As these proteins are the most abundant and possibly the most important in the gastric mucosa (Marti-Bonmati *et al.*, 1980), it can be assumed that their quantitative replacement is a return to normality of the mucosa, and thus a recovery of the defensive capacity against aggression from absolute ethanol.

Stimulation of local prostaglandin production is possibly one protective mechanism as quercetin stimulates the enzyme cyclooxygenase (Moroney *et al.*, 1988) and, in addition, the cyclooxygenase inhibitor, indomethacin, reverses the protective effect of quercetin on ethanol-induced ulceration (Robak and Gryglewski, 1988). The increase in prostaglandin synthesis may explain the increase in the amount of mucus observed and its participation in ulcer prevention. Other possible mechanisms include inhibition of the gastric proton pump (Di Carlo *et al.*, 1999), inhibition of the lipoxygenase pathway (Moroney *et al.*, 1988), inhibition of platelet activating factor synthesis (Izzo *et al.*, 1994), inhibition of lipid peroxidation (Alarcon de la Lastra *et al.*, 1994) and scavenging of free radicals associated with a significant enhancement in glutathione peroxidase activity (Martin *et al.*, 1998). An interesting aspect of the anti-ulcer effect of quercetin is that it has been shown to inhibit the growth of *Helicobacter pylori* in a dose-dependent manner *in vitro* (Beil *et al.*, 1995).

Naringin. Naringin has been shown to prevent gastric mucosal ulceration in several animal models, including restraint stress, pyloric occlusion and ethanol-induced chronic ulcer (Parmar, 1983; Martin *et al.*, 1993; Motilva *et al.*, 1992;1993).

In ethanol-treated rats, naringin significantly reduced the ulcer index and increased the hexosamine content of the gastric mucus without affecting prostaglandin E_2 and the total protein content (Martin *et al.*, 1994). Thus, the gastro-protective action of naringin could be explained, at least in part, through a complex non-prostaglandin-dependent mechanism that involves an increase in the glycoprotein content and viscosity of the gastric mucosa. Naringin also possesses antioxidant and superoxide anion scavenger properties (Robak *et al.*, 1988; Martin *et al.*, 1994) which could contribute to its gastro-protective effect.

Silymarin. Silymarin is a flavonolignan complex which can be extracted from the fruit (*Cardui marie fructus*) of the milk thistle, *Silybum marianum* (Samuelsson, 1999)

Silymarin has been found effective in some types of experimentally induced gastric ulcers. Treatment with silymarin prevents, in a highly significant way, the ulceration induced by cold-restraint stress and histamine output in pylorus-ligated rats but does not prevent the formation of ethanol-induced gastric lesions (Alarcon de la Lastra *et al.*, 1992). The anti-ulcerogenic effect of silymarin could be related to its inhibitory mechanism on the lipoxygenase pathway, avoiding leukotriene synthesis (Bindoli *et al.*, 1977; Alarcon de la Lastra *et al.*, 1992).

Table 2. Plants containing saponins with anti-ulcer activity

Botanical name	Part plant	Ulcer model	Reference
Calendula officinalis	Rhizome	Caffeine-arsenic, butadione, pylorus-ligated	Iatsyno *et al.*, 1978
Calliandra portoticensis	Leaves	Stress, pylorus-ligated, *E. coli*	Aguwa and Lawal, 1988
Glycyrrhiza glabra	Root	Acetic acid, pylorus ligated	Ottenjann and Rosh, 1970
Kochia scoparia	Fruit	Ethanol, indomethacin	Matsuda *et al.*, 1998
Panax binnatifidus	Rhizome	Psychological stress	Nguyen *et al.*, 1996; Houng *et al.*, 1998
Panax japonicus	Rhizome	Stress, HCl	Yamahara *et al.*, 1987
Pyrenacantha staudtii	Leaves	Indomethacin, serotonin, stress	Aguwa and Okunji, 1986
Rhigiocarya racemifera	Leaves	Indomethacin, reserpine, serotonin	Aguwa, 1985; 1986
Spartium junceum	Flowers	Ethanol	Yesilada and Takaishi, 1999
Veronica officinalis	Aerial parts	Indomethacin, reserpine	Scarlat *et al.*, 1985

Anthocyanosides. Anthocyanosides, extracts from *Vaccinium myrtillus*, exert a significant preventive and curative anti-ulcer activity. Protective effects have been observed not only on ulcer induced by ligature of the pylorus, by reserpine and by phenylbutazone, in which oral treatment was given before or simultaneously with ulcer formation, but also in ulcer induced by restraint or by acetic acid, in which the animal received treatment when the lesions were already established (Magistretti *et al.*, 1988). The anti-ulcer activity is not exerted through a blockade of gastric secretion but it is, in part, attributed to the increase in the mucus of the stomach wall. Anthocyanosides are thought to act by influencing the biosynthesis of the mucopolysaccharides, thus improving the efficiency of the mucus barrier at the gastric level (Cristoni and Magistretti, 1987; Magistretti *et al.*, 1988).

Sophoradin derivatives. Sophoradin has been isolated from the root of the ancient Chinese medical plant *Sophora subprostrata*, a plant used in China for the treatment of digestive diseases (Kyogoku *et al.*, 1979). Flavonoids derived from sophoradin are known to exhibit gastro-protective and ulcer healing properties. Solon, a synthetic flavonoid derived from sophoradin, has been shown to have anti-ulcer and gastro-protective effects by influencing the formation and metabolism of prostaglandins in the gastric mucosa (Konturek *et al.*, 1986).

Recently, Brzozowski *et al.* (1998) have reported that SU-840, a novel synthetic flavonoid derivative of sophoradin reduced gastric acid and pepsin secretion and gastric lesions induced by ethanol, acidified aspirin or restraint stress, an effect due in part to nitric oxide and prostaglandin production.

Saponins

Saponins are widely distributed in plants and are a particular form of glycosides. They are so-called because of their soap-like effect, which is due to their surfactant properties. They also have haemolytic properties and, when injected into the blood stream, are highly toxic. When taken by mouth saponins are comparatively harmless. According to the structure of the aglycone or sapogenin two kinds of saponin are recognized, the steroidal and triterpenoid type (Samuelsson, 1999).

Plant materials often contain triterpenoid saponins in considerable amounts. With regard to plants with anti-ulcer activity, liquorice root contains about 2%–12% of glycyrrhizic acid and the seeds of the horse-chestnut up to 13% of aescin (Newall *et al.*, 1996). Several plants containing high amounts of saponins have been shown to possess anti-ulcer activity in several experimental ulcer models (Table 2). Among these, saponins isolated from the rhizome of *Panax japonicus* and the fruit of *Kochia scoparia* (which contain approximately 20% of saponins) have been demonstrated to possess gastro-protective properties (Matsuda *et al.*, 1998). The same authors reported that some oleanolic acid oligoglycosides, extracted from *P. japonicus* and *K. scoparia*, showed protective effects on ethanol- and indomethacin-induced gastric damage. Moreover, a methanol extract of *P. japonicus* rhizome was demonstrated to possess protective activity also on stress- or HCl-induced ulcers (Yamahara *et al.*, 1987). The protective activities of all these active saponins are not due to inhibition of gastric acid secretion but probably due to activation of mucous membrane protective factors (Saito *et al.*, 1977).

Aescin is a mixture of saponins obtained from the seeds of *Aesculus hippocastanum* (horse-chestnut). Aescin has been shown to posses anti-ulcer activity in various ulcer models (cold restraint and pylorus-ligated) (Marhuenda *et al.*, 1993), an effect which is, in part, due to inhibition of gastric acid and pepsinogen secretion. However, aescin also prevents gastric lesions due to absolute ethanol (Marhuenda *et al.*, 1994), a model of gastric ulceration in which acid and pepsin do not play a significant role; thus, the protective effect of aescin involves other mechanisms, such as improvement of blood flow (Marhuenda *et al.*, 1994). It is unlikely that prostaglandins or the maintenance of surface mucus gel could play a role in aescin-induced gastro-protection as this saponin does not enhance prostaglandin E_2 levels nor does it increase the amount (or the composition) of mucus in ethanol-induced gastric ulceration (Marhuenda *et al.*, 1994).

Tannins

Tannins are used in medicine primarily because of their astringent properties, which are due to the fact that they react with the proteins of the layers of tissue with which they come into contact (Samuelsson, 1999). Tannins are known to ‘tan’ the outermost layer of the mucosa and to render it less permeable and more resistant to chemical and mechanical injury or irritation (Asuzu and Onu, 1990); however, the correlation between the molecular

Table 3. Plants containing tannins with anti-ulcer activity

Botanical name	Part plant	Ulcer model	Reference
Calliandra portoticensis	Leaves	Stress, pylorus-ligated, *E. coli*	Aguwa and Lawal, 1988
Entandrophragma utile	Bark	Ethanol	John and Onabanjo, 1990
Linderae umbellatae	Stem	Stress	Ezaki *et al.*, 1985
Mallotus japonicus	Bark	(Clinical study)	Saijo *et al.*, 1989
Rhigiocarya racemifera	Leaves	Indomethacin, reserpine, serotonin	Aguwa, 1985; 1986
Veronica officinalis	Aerial parts	Indomethacin, reserpine	Scarlat *et al.*, 1985

structures of tannins and the astringent/anti-ulcer activity is not known.

When a low concentration of tannins is applied to the mucosa, only the outermost layer is tanned, becoming less permeable and affording an increased protection to the subjacent layers against the action of bacteria, chemical irritation, and, to a certain extent, against mechanical irritation. High concentrations of tannins cause coagulation of the proteins of the deeper layer of the mucosa, resulting in inflammation, diarrhoea and vomiting.

Several plants with anti-ulcer activity which contain tannins have been reported (Table 3). A crude extract of *Linderae umbellatae* exhibited anti-peptic and anti-ulcerogenic activity, and these effects were considered ascribable to the presence of tannins or related compounds (Ezaki *et al.*, 1985). Nine condensed tannins (monomers, dimers, trimers and tetramers) have been isolated and their anti-peptic and anti-ulcer activity confirmed experimentally (pylorus-ligated in rats and stress-induced gastric lesions in mice) (Ezaki *et al.*, 1985). Marked differences were observed among monomers, dimers, trimers and tetramers. Monomers and dimers, did not inhibit peptic activity *in vitro*, while trimers displayed higher inhibition of peptic activity than tetramers (though tetramers showed higher astringency than trimers). In pylorus-ligated mice, trimers and tetramers clearly suppressed the peptic activity of gastric juice and also monomers and dimers slightly suppressed the peptic activity of mouse gastric juice *in vivo* (Ezaki *et al.*, 1985). As monomers and dimers are inactive *in vitro* it is possible that their activity *in vivo* is not related to the direct inhibition of pepsin, but related to influence on the secretion mechanism of pepsin.

Gums and mucilages

Gums and mucilages are usually brittle, amorphous, transparent or translucent substances, which readily absorb water to form gelatinous masses or viscous colloidal solutions. The colloidal character of gums, mucilages and other mucoids accounts largely for their use as therapeutic agents. Mucilaginous drugs have the property of covering and protecting the mucosa of the stomach and are used in the treatment of gastric ulcer. Plants containing mucilages traditionally used in several countries in the treatment of gastric ulcer include *Althaea officinalis, Cetraria islandica, Malva sylvestris, Matricaria chamomilla* and *Aloe* species (Capasso and Grandolini, 1999)

Guar gum is obtained from the endosperm of the seed of *Cyamopsis tetragonolobus*, a plant long cultivated in India and Pakistan and nowadays also grown in the United States (Samuelsson, 1999). The main constituent is a galactomannan, a β-1,4-linked D-mannose linear polysaccharide with an α-1,6-linked D-galactose residue attached to every other D-mannose unit. Gum guar increased the healing rate of stress-induced gastric ulcers in the rat. Proposed mechanisms are reduced acidity, increased local mucosal supply of energy and mechanical protection (Harju and Sajanti, 1987;1991). Moreover, guar gum, in duodenal ulcer patients, decreases gastric acidity and the rate of emptying of gastric contents, probably because of its effects on viscosity and neutralization of gastric acidity (Harju and Larmi, 1985; Harju, 1984; 1985).

Myrrh, an oleo-gum-resin obtained from *Commiphora molmol*, contains up to 60% gum and up to 40% resin (Newall *et al.*, 1996). Myrrh pre-treatment produced a dose-dependent protection against the ulcerogenic effects of different necrotizing agents such as ethanol, indomethacin, sodium hydroxide or hypertonic sodium chloride (Al-Harbi *et al.*, 1997). The protective effect of myrrh is attributed to its effect on mucus production or increase in nucleic acid and non-protein sulphydryl concentration, which appears to be mediated through its free-radical scavenging, thyroid-stimulating and prostaglandin-inducing properties.

HERBAL DRUGS WITH ANTI-ULCER ACTIVITY

Liquorice

Liquorice, the root and rhizome of different varieties of *Glycyrrhiza glabra* (Leguminosae), has been extensively used in medicine for its anti-ulcer activity (Ottenjann and Rosch, 1970). The principal constituent of liquorice is glycyrrhizinic acid, a triterpenoid saponin. This chemical class is known to offer protection against ulcers. Takagi *et al.* (1969) showed that glycyrrhizin (the potassium or calcium salt of glycyrrhizinic acid) inhibited ulcer in Shay rats and also prevented experimental gastric ulcers caused by acetic acid administration. To avoid the side-effects of glycyrrhizin in liquorice preparations, a glycyrrhizin-free fraction of liquorice extracts was studied (Takagi and Ishii, 1967). The glycyrrhizin-free fraction, called FM 100 fraction, was found to be effective for gastric ulcers in rats by inhibiting gastric juice secretion. The protective effect of FM 100 fraction has been confirmed by clinical observation (Takagi *et al.*, 1969). Saitoh *et al.* (1976) isolated new isoflavonoids and chalcones from the fraction FM 100, which could

contribute to the anti-ulcer activity of liquorice. Simple derivatives of glycyrrhetinic acid (the genin of glycyrrhizinic acid) such as carbenoxolone (an ester derivative) and deglycyrrhizinized liquorice (DGL), have been used extensively in gastric ulcer treatment (Habib *et al.*, 1979; Bennett *et al.*, 1980).

Carbenoxolone derives from the hydrolysis of glycyrrhizinic acid after its extraction from liquorice root. Carbenoxolone was the first drug found to accelerate peptic ulcer healing by a mechanism not involving the inhibition of acid secretion (Baron, 1977). Several mechanisms of action have been proposed to explain the pharmacological activity of carbenoxolone. Thus, carbenoxolone stimulates gastric mucus production (Bickel and Kauffman, 1981), enhances the rate of incorporation of various sugars into gastric mucosal glycoproteins (Johnston *et al.*, 1975), promotes mucosal cell proliferation (Van Huis and Kramer, 1981), inhibits mucosal cell exfoliation (Domschke *et al.*, 1977), inhibits prostaglandin degradation (Peskar, 1980), increases the release of PGE_2 and reduces the formation of thromboxane B_2 (Aguwa and Okunji, 1986) and regulates DNA and protein synthesis rates in gastric mucosa (Van Huis and Kramer, 1981). More recently nitric oxide has been claimed to contribute to the anti-ulcer effect of carbenoxolone (Peskar *et al.*, 1991; Franco *et al.*, 1993). In view of the wide range of alternative therapies now available and of the numerous side effects, carbenoxolone use has been limited; indeed carbenoxolone produces effects similar to those of aldosterone excess (sodium retention and hypokalaemia leading to hypertension, oedema and cardiac failure) (Newall *et al.*, 1996).

DGL is an effective anti-ulcer agent and, unlike carbenoxolone, it does not have fluid retaining properties. DGL protected against gastric ulceration in rats induced by pyloric ligation and increased healing of peptic ulcer in patients (Rees *et al.*, 1979). Moreover, DGL reduced bile acid-induced hydrogen ion back-diffusion across the canine gastric mucosa and diminished acute gastric mucosal damage due to aspirin or aspirin plus taurodeoxycholic acid (Morgan *et al.*, 1983).

Aloe gel

Two distinct preparations of *Aloe* plants are most used medicinally. The resinous leaf exudate (named aloe) is used as a laxative, and the mucilaginous gel (named aloe vera or aloe gel) from the leaf parenchyma is used as a remedy against a variety of skin disorders (Reynolds and Dweck, 1999). Aloe gel had a prophylactic effect and was also curative if given as a treatment for stress-induced gastric ulceration in rats (Galal *et al.*, 1975; Parmar *et al.*, 1986). A lectin fraction (glycoprotein) from *Aloe arborescens*, Aloctin A, had anti-ulcer effect in rats (Saito *et al.*, 1989), while another high molecular weight fraction, not containing glycoprotein, was very effective in healing ulcer induced by mechanical or chemical stimuli but not those induced by stress (Teradaira *et al.*, 1993). This fraction contained substances with molecular weights between 5000 and 50 000 Da, which were considered to both suppress peptic ulcers and to heal chronic gastric ulcers. In addition, a component from Cape Aloe exudate, named aloe ulcin, suppressed ulcer growth and L-histidine decarboxylase in rats (Yamamoto, 1973). An early clinical study found that oral administration of aloe gel was effective in the treatment of peptic ulcer (Blitz *et al.*, 1963). By contrast, in a more recent study, it has been shown that a health product containing aloe vera gel did not prevent lesion formation associated with cold-restraint or ethanol administration in animals (Koo, 1994).

Capsicum (chilli)

Capsicum, also known as chilli or paprika, is the fruit of various *Capsicum* species (Samuelsson, 1999). It is widely used as a spice and, traditionally, it has been used internally for colic, flatulent dyspepsia, chronic laryngitis, insufficiency of peripheral circulation and externally for neuralgia (Newall *et al.*, 1996). Capsaicin (the active pungent ingredient) has been used extensively as a probe to elucidate the function of sensory neurons in various organs and systems (including the stomach), because of its ability to excite and later defunctionalize a subset of primary afferent neurons (Abdel-Salam *et al.*, 1997b).

Chilli, as well as capsaicin, has a protective effect on ethanol- or aspirin-induced lesion formation in the rat gastric mucosa (Kang *et al.*, 1995a); in addition capsaicin and long-term chilli intake (360 mg daily for 4 weeks) protects against haemorrhagic shock-induced gastric mucosal injury in the rat, an effect which may be mediated by capsaicin-sensitive afferent neurons (Teng *et al.*, 1998). The pathophysiological basis of gastric protection by chilli (capsaicin) remains unclear. An increase in gastric mucosal blood flow has been described and this may be related to the release of calcitonin gene-related peptide and nitric oxide rather than to the production of prostaglandins (Lambrecht *et al.*, 1993). The protective effect of capsicum could also involve vanilloid receptors because resiniferatoxin, an ultrapotent analogue of capsaicin present in the latex of *Euphorbia resinifera* (Euphorbium), also displays anti-ulcer activity (Abdel Salam *et al.*, 1997a) and both capsaicin and resiniferatoxin act on vanilloid (capsaicin) receptors (Szallasi and Blumberg, 1999).

Chilli causes dyspepsia in patients with and without ulcer, and ulcer patients are often advised to avoid its use (Kang *et al.*, 1992). Therefore, the peptic ulcer patients consume less chilli than controls (Kang *et al.*, 1995b). Nevertheless, epidemiological and clinical data suggest that chilli ingestion may have a beneficial effect on human peptic ulcer disease. For examples chilli has a gastro-protective effect on aspirin-induced gastric mucosal injury in humans (Yeoh *et al.*, 1995). In addition, Kumar *et al.* (1984) showed that chilli ingestion has no detrimental effect on the healing rates of duodenal ulcer patients on treatment and it does not cause macroscopic gastroduodenal mucosal injury in humans (Kang *et al.*, 1988). By contrast, others have shown that chilli increased DNA loss and microbleeding (Desai *et al.*, 1972; Myers *et al.*, 1987) suggesting the occurrence of cellular damage.

HERBAL FORMULATIONS

There are many plants used in anti-ulcer herbal formulations that have not yet been individually investigated for

Table 4. Plants with anti-ulcer activity from ethnopharmacological studies

Botanical name	Part plant	Extract type	Ulcer model	Reference
Alpinia galanga	Rhizome	Ethanol	Stress, pylorus-ligated, ethanol, HCl	Al-Yahya *et al.*, 1990
Amphipterygium adstringens	Stem bark	Methanol	Ethanol	Navarrete *et al.*, 1998
Anchusa strigosa	Root	Aqueous	Ethanol	Disi *et al.*, 1998
Artemisia herba-alba	Leaves	Aqueous	Ethanol	Gharzouli *et al.*, 1999
Astronium urundeuva	Bark	Aqueous	Aspirin, stress, histamine	Rao *et al.*, 1987
Atractylodis lancea	Rhizome	Acetone	Ethanol, HCl	Matsuda *et al.*, 1998
Azadirachta indica	Leaves	Aqueous	Stress, ethanol	Garg *et al.*, 1993
Baccharis triptera	Small branches	Aqueous	Pylorus-ligated, stress, indomethacin	Gamberini *et al.*, 1991
Bauhinia racemosa	Flower buds	Methanol	Aspirin	Akhtar and Ahmad, 1995
Bryophyllum pinnatum	Leaves	Methanol	Aspirin, indomethacin, serotonin, reserpine, stress, ethanol, pylorus-ligated, acetic acid	Pal and Nag Chaudhuri, 1991
Caesalpinia ferrea	Stem	Crude	Acetic acid	Bacchi *et al.*, 1995
Camellia sinensis	Leaves	Aqueous	Stress, ethanol, aspirin, indomethacin, reserpine, histamine, serotonin	Maity *et al.*, 1995
Cassia nigrans	Leaves	Ethanol	Aspirin, pylorus-ligated	Maity *et al.*, 1995; Akah *et al.*, 1998
Cistus incanus	Aerial part	Aqueous	HCl, ethanol, reserpine, serotonin	Attaguile *et al.*, 1995
Curcuma longa	Rhizome	Ethanol	Pylorus-ligated, cold-restraint stress, indomethacin, reserpine, ethanol, HCl	Rafatullah *et al.*, 1990
Diodia sarmentosa	Whole plant	Ethanol	Aspirin, pylorus-ligated	Akah *et al.*, 1998
Entandrophragma utile	Bark	Aqueous	Ethanol	John and Onabanjo, 1990
Eremomastax speciosa	Leaves	Aqueous	Ethanol, HCl, pylorus-ligated	Tan *et al.*, 1996
Ficus exasperata	Leaves	Ethanol	Aspirin, pylorus-ligated	Akah *et al.*, 1998
Laurus nobilis	Seeds	Aqueous, oil	Ethanol	Afifi *et al.*, 1997
Maytenus aquifolium, ilicifolia	Leaves	Aqueous	Indomethacin, cold-restraint stress	Souza-Formigoni *et al.*, 1991
Microgramma squamulosa	Rhizome	Crude, ethanol, water	Stress, ethanol, HCl, acetic acid	Suffredini *et al.*, 1999
Mikania cordata	Root	Methanol	Stress, ethanol, aspirin, phenylbutazone, pylorus-ligated	Bishayee and Chatterjee, 1994
Moringa pterygosperma	Flower buds	Methanol	Aspirin	Akhtar and Ahmad, 1995
Pistacia lentiscus	Resin from stem		Pylorus-ligated, aspirin, phenylbutazone Reserpine-restraint plus cold stress, ethanol	Al-Said *et al.*, 1986
Pluchea indica	Root	Methanol	Indomethacin, ethanol, aspirin, stress, reserpine	Sen *et al.*, 1992
Punica granatum	Fruit peel	Aqueous	Ethanol	Gharzouli *et al.*, 1999
Pyrenacantha staudtii	Leaves	Aqueous	Aspirin, indomethacin, serotonin, reserpine	Aguwa and Mittal, 1981
Quercus ilex	Root bark	Aqueous	Ethanol	Gharzouli *et al.*, 1999
Saussurea lappa	Root	Acetone	Stress	Yamahara *et al.*, 1985
Stachytarpheta cayennensis	Whole plant	Aqueous	Stress, ethanol, pylorus-ligated	Vela *et al.*, 1997
Stryphnodendron adstringens	Aerial parts	Total extract	Stress, ethanol, indomethacin	Audi *et al.*, 1999
Styrax camporum	Stem	Ethyl acetate	Acetic acid	Bacchi *et al.*, 1995
Swertia chirata	Whole plant	Ethanoll	Indomethacin, pylorus-ligated, ethanol	Rafatullah *et al.*, 1993
Synclisia scabrida	Leaves	Ethanol	Aspirin, pylorus-ligated	Akah *et al.*, 1998
Tanacetum vulgare	Aerial parts	Chloroform	Ethanol	Tournier *et al.*, 1999
Trianthema pentandra	Whole plant	Methanol	Aspirin	Akhtar and Ahmad, 1995
Trichosanthes kirilowii	Fruit	Ethanoll	Stress, histamine, serotonin, ethanol, HCl, pylorus-legated	Takano *et al.*, 1990
Vernonia kotschyana	Root	Aqueous	Stress, indomethacin, ethanol, pylorus-ligated	Sanogo *et al.*, 1996; Germanó *et al.*, 1996
Zingiber officinalis	Root	Methanol, acetone	HCl/ethanol	Yamahara *et al.*, 1988

their efficacy in this condition. Mitra *et al.*, (1996) reported the anti-ulcer effect of a herbal formulation, UL-409, consisting of six medicinal plants, namely *Glycyrrhiza glabra* L. (Papilionaceae; Root), *Saussurea lappa* C.B. Clarke (Compositae; Rott), *Aegle marmelos* Corr. (Rutaceae; Fruit), *Foeniculum vulgare* Mill. (Umbeliferae; Seed), *Rosa damascena* Mill. (Rosaceae; Flower Petals) and *Santalum album* L. (Santalaceae; Stem). This herbal formulation was found to increase the stomach mucus and decrease the acid volume, free and total acid content in rats. Moreover this formulation significantly prevented the occurrence of stress-induced ulceration, and significantly inhibited gastric ulceration induced by ethanol, aspirin, pylorus-ligation, histamine and indomethacin in rats and guinea-pigs (Mitra *et al.*, 1996; Kulkarni and Goel, 1996). On the basis of these observations, it was concluded that this formulation possesses anti-ulcer activity due to a modulation of defensive factors so improving gastric cytoprotection.

Manonmani and co-workers (1994) reported the anti-ulcerogenic effect of an Ayurvedic formulation, Cauvery-100 (C-100). C-100 consists of dasamoolam (a preparation consisting of 10 medicinal plants) plus 13 other medicinal plants, namely *Emblica officinalis* L. (Euphorbiaceae, fruit), *Cuminum cyminum* L. (Umbelliferae, fruit), *Trema orientalis* L. Blume (Urticaceae, root), *Vitis vinifera* L. (Vitaceae, fruit), *Carum carvi* L. (Umbelliferae, fruit), *Withania somnifera* L. Dunal (Solanaceae, root), *Eclipta alba* L. Hassk (Compositae, whole plant), *Embelia ribes* Burm (Myrisinaceae, fruit), *Citrum limon* L. Burm (Rutaceae, fruit rind), *Picrorrhiza kurrooa* Benth (Scrophulariaceae, root), *Glycyrrhiza glabra* L. (Papillonace, weakstem), *Aegle marmelos* L. Corr. Serr (Rutaceae, root) and *Zingiber officinale* Roscoe (Zingiberaceae, rhizome). This formulation was found to decrease the number of lesions induced by indomethacin and to decrease the volume and total acidity of gastric juice in rats. It was also found that C-100 increased the levels of hexose, hexosamine and sialic acid (a substance normally decreased in the untreated ulcer group), while decreasing the protein level (normally raised in the untreated ulcer group). The authors concluded that C-100 could act both to decrease acidity and to increase mucosal defence in the gastric region.

ETHNOPHARMACOLOGICAL STUDIES

Gastrointestinal disorders are one of the most important causes of morbidity for the populations of non-industrialized countries. Many pharmaceutical products employed for the treatment of gastroduodenal ulcers and peptic diseases, have decreased the morbidity rates, but they can produce many adverse effects. Moreover, these pharmaceutical products are too expensive for poorer populations. The importance of ethnopharmacological studies is emphasized by the observation that the first drug effective against gastric ulcer was carbenoxolone, discovered as a result of research on a commonly used indigenous plant, *Glycyrrhiza glabra*. Also, studies on cabbage, previously employed as an anti-ulcer agent in folk medicine, has led to the development of gefarnate (Hossenbocus and Colin-Jones, 1974; Katoh *et al.*, 1998). Thus, a search among medicinal plants is still important, despite the progress in conventional chemistry and pharmacology in producing effective drugs. Countless plants known to indigenous medicine are used for the treatment of peptic ulcers; a rather conservative list is reported in Table 4. Among these, of particular interest are *Ptelopsis suberosa* and *Ocimum sanctum*.

The bark of *Pteleopsis suberosa* is commonly used in Mali for the treatment of gastric ulcers and was also claimed to be effective in a clinical trial (Mariko, 1989). Experimental studies have shown that a *Pteleopsis suberosa* decoction obtained from the bark of plants showed a protective action against ethanol- and indomethacin-induced gastric mucosa damage, an effect which is due in part to the stimulation of prostaglandin synthesis. A saponin fraction is most likely responsible for the biological activity (De Pasquale *et al.*, 1995; Germanò *et al.*, 1998).

Ocimum sanctum is commonly known as 'Tulsi' in Hindi and 'Holy basil' in English. The fixed oil of *Ocimum sanctum* has been shown to possess anti-ulcer activity against aspirin-, indomethacin-, alcohol-, histamine-, reserpine-, serotonin- and stress-induced ulceration in experimental animal models (Mandal *et al.*, 1993; Singh and Majumdar, 1999). Significant inhibition was also observed in gastric secretion and aspirin-induced gastric ulceration in pylorus-ligated rats. The anti-ulcer activity of the oil could be due to inhibition of the 5-lipoxygenase pathway or to leukotriene or histamine antagonistic properties (Singh and Majumdar, 1999).

CONCLUSIONS

A variety of botanical products have been reported to possess anti-ulcer activity (especially from ethnopharmacological studies) but the documented literature has centred primarily on pharmacological action in experimental animals. Except for a few phytogenic compounds (i.e. aloe, liquorice and chilli), limited clinical data are available to support the use of herbs as gastroprotective agents and thus, the data on efficacy and safety are limited. Despite this, there are several botanical products with potential therapeutic applications because of their high efficacy and low toxicity. Finally, it should be noted that substances such as flavonoids, aescin, aloe gel and many others, that possess both anti-inflammatory and anti-ulcer activity are of particular therapeutic importance as most of the anti-inflammatory drugs used in modern medicine are ulcerogenic.

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