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EDITORIAL

Spices, herbal xenobiotics and the stomach: Friends or foes?

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Abstract

Spices and herbal remedies have been used since ancient times to treat a variety of disorders. It has been experimentally demonstrated that spices, herbs, and their extracts possess antimicrobial, anti-inflammatory, antirheumatic, lipid-lowering, hepatoprotective, nephroprotective, antimutagenic and anticancer activities, besides their gastroprotective and anti-ulcer activities. Despite a number of reports on the toxicity of herbs and spices, they are generally accepted as safer alternatives to conventional therapy against gastric ulcers. To this end, it is also believed, that excessive consumption of spices may favor the pathogenesis of gastric and duodenal ulcer and some studies have substantiated this common perception. Based on various *in vivo* experiments and clinical studies, on the effects of spices and herbs on gastric ulcers, it has indeed been shown that certain spices do possess remarkable anti-ulcer properties mediated by antisecretory, cytoprotective, antioxidant, and anti-*Helicobacter pylori* effects and mechanisms regulated by nitric oxide, prostaglandins, non-protein sulfhydryl molecules and epidermal growth factor expression. Accordingly, their consumption may attenuate and help prevent peptic ulcer disease. In the present review, the beneficial effects of spices and herbal nutritive components on the gastric mucosa are discussed against the paradigm of their deleterious potential.

Key words: Herbs; Spices; Stomach; Stomach ulcers; Anti-ulcer agents

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INTRODUCTION

Herbs and spices are considered as an important additive to food in several parts of the world. They enhance aroma, piquancy, and impart flavor to food. For long, they have been regarded as the essential component of eastern cuisine and have also been adopted into western diets. Since ancient times, spices and herbs have also been used in traditional treatment of a number of diseases. Nowadays, several experimental studies and, to a lesser extent, clinical trials have also emphasized the role of herbs in the treatment of a variety of disorders[1-4]. Several herbs and herbal extracts have been shown to possess antibacterial properties[5-7]. For instance, onion, garlic, ginger, pepper and mustard have demonstrated antimicrobial activity against several types of bacteria[8]. Tayel and El-Tras have recently reported a potent antibacterial activity of cinnamon and clove against several bacterial strains[9]. Some spices possess antifungal activity[10,11]. Beside their antifungal activity, herbs have also shown vermicidal, nematocidal and molluscicidal potential[12-15]. In addition, gingerol, the active ingredient of ginger, and eugenol have shown anti-inflammatory

and antirheumatic activity[16]. More recent studies have also demonstrated anti-inflammatory and antirheumatic properties of herbs[17-19]. Furthermore, gingerol and curcumin have also shown lipid-lowering potential in experimental animals[20-22] as well as in clinical trials[23,24].

In addition, many studies have especially endorsed the experimental evidence of folkloric utilization of spices to treat gastrointestinal disorders, without gastric mucosal toxicity. Also clinical, video-endoscopic studies conducted by Graham *et al*[25] have shown an adaptive cytoprotection. Furthermore, several experimental studies have also demonstrated cytoprotective activity of herbs[26-29].

On the other hand, some spices are considered to be toxic to the gastric mucosa and may potentiate or induce gastric injuries. Gastric mucosal toxicity induced by some spices in experimental animals is related to their oxidative constituents such as phenylpropenes, safroles, methyl eugenol, 1'-hydroxyestragole, myristicin and elemicin[30,31]. Meyers *et al*[32] have reported deleterious effect of red pepper and black pepper on the stomach. Both have induced a significant enhancement in parietal secretion, pepsin secretion, and potassium loss, as well as a dose-dependent gastric cell exfoliation and mucosal microbleeding, which are comparable to those induced by aspirin. Other studies have also reported epigastric pain and dyspepsia. The mechanism of epigastric pain and dyspepsia induced by red and black pepper is not well-defined. However, it is believed to be a consequence of inhibition of gastric surface hydrophobicity, enhancement of surface wettability and activation of intramucosal pain receptors[33]. Some spices may stimulate acid secretion and have deleterious effects on the gastric mucosal lining. Intragastric perfusion of albino rats with aqueous extracts of red pepper, fennel, omum/ajwain, cardamom, black pepper, cumin and coriander have stimulated a cholinergic response, and/or *via* other mechanism(s) have induced acid secretion with a respectively declining order. In injured stomach, cumin and coriander increase gastric secretion, and red pepper has an inhibitory effect[34].

Herbs in general are believed to be safe, and several studies have found them to be non-detrimental and beneficial to gastric mucosa and have cytoprotective properties[25,28]. In addition to their anti-ulcerogenic activity, it has been reported that spices contain protective factors that possess anticancer potential[35-37]. The ulcerogenic and/or anti-ulcerogenic activity of herbs is likely to be due to the oxidative and anti oxidative action of their different phytoconstituents. The prominent mechanism of protective action is mediated by their antioxidant activity and the ability to scavenge reactive oxygen species (ROS). A variety of herbs such as clove, cinnamon, oregano, black pepper, turmeric, ginger and polygonum species are known to contain phytoconstituents with anti-oxidative potential[38-46]. Antioxidative constituents of herbs are summarized in the Table 1.

The beneficial effects of herbs and plant extracts in the prevention of gastric injury have been indicated in several experimental studies. For example, various extracts of *Mammea americana* have significantly reduced the ulcer index and demonstrated a cytoprotective effect in experimentally induced ulcers[47]. Further pharmacological and histopathological studies have demonstrated significant protection against ethanol-induced ulcers in rats by extracts of roots of *Asphodelus aestivus* and *Cichorium intybus*, herbs of *Equisetum palustre* and *Viscum album ssp.* album and fruits of *Laurus*[48].

Clinical studies have also confirmed the gastric protection conferred by herbs. In a clinical study of 98 outpatients with chronic gastritis, who were randomly divided into a group treated with herbal pairs and a control group treated with *Banxia Xiexin Tang*, effectiveness was significantly higher in the treated group. The treatment has improved therapeutic effects, and minimized the adverse effects of gastritis[49]. In another clinical study, 103 patients with duodenal ulcer received phytotherapy in the form of infusions and concoctions of medicinal plants. This resulted in ulcer scarring and a decrease in relapse[50]. Furthermore, in a study of 170 patients with duodenal ulcer and gastroduodenitis treated with herbal combinations alone or with addition of antacids, pain and dyspeptic symptoms disappeared in > 85% of both treatment groups, with a similar rate of endoscopic healing[51]. Hence, agents that possess antioxidative activity are expected to play a major role in the treatment of peptic ulcer disease.

EXPERIMENTAL INDUCTION OF ULCERS

Various noxious chemical agents are used to induce acute experimental gastric ulceration. Indomethacin and necrotizing agents including 80% ethanol, 0.2 mol/L NaOH, 25% NaCl are commonly used. Pyloric ligation is applied in antisecretory studies[52-56]. Other universally accepted experimental ulcer models include stress induced by swimming[55], aspirin[56], ethanol/HCl, acetylsalicylic acid, cold-restraint[57] and hypothermic restraint[54]. In addition, gastric ulcers have also been induced by serosal application of acetic acid[58].

FACTORS INVOLVED IN ULCER HEALING

Acid and other noxious agents such as bile acids, non-steroidal anti-inflammatory drugs (NSAIDs) and ethanol enhance the presence of mucosal barrier disruption, H^+ back diffusion and ulcer susceptibility. Adequate mucosal flow and secretion of bicarbonate with formation of an alkaline buffer layer at the epithelial surface, is considered as a first line of mucosal defense. Prostaglandins (PGs) are involved in the ulcer healing process. Growth factors, some gut hormones (e.g. gastrin and cholecystokinin) and melatonin promote ulcer healing through generation of cyclooxygenase-2 (COX-2) and release of PGE2 in the ulcer margin[59,60]. Similar action is achieved by application of antisecretory doses of exogenous PG[61]. In addition to PGs, many other factors including growth factors, nitric oxide or calcitonin gene-related peptide, as well as some gut hormones such as gastrin and cholecystokinin, leptin,

Table 1 Antioxidant constituents of herbs

Antioxidant constituents	Herb	Ref.
Pimentol, biflorin	Clove, allspice	[38]
Phenolic constituents: phenolic acids, phenolic diterpenes, flavonoids, and volatile oils, phenolic volatile oils	Many herbs including clove, cinnamon and oregano	[39]
Piperine	Black pepper	[40]
Curcumin, methoxy phenols, dehydrogingerdione, bakuchiol	Turmeric, from Indian spices, ginger, *Psoralea corylifolia*	[41]
Phenolic compounds: flavonoids, phenolic acids and their derivatives, tannins, stilbenes, and anthraquinones	Polygonum species, spring onion, broccoli, orange, carrot and ginger	[42]
Phenolic diterpenes	*Rosmarinus officinalis* and *Salvia officinalis*	[43]
Phenolic, flavonoid, chlorogenic acid and neochlorogenic acid	Andean spice Sanicula graveolens (Apiaceae)	[44]
Phenylpropanoids (phenolic compounds)	Human diet, spices, aromas, essential oils, propolis and traditional medicine	[45]
Polyphenolic	*Piper umbellatum, Piper nigrum, Piper guineense*	[46]

ghrelin and gastrin-releasing peptide, are involved in gastroprotection. The protective action of gut hormones has been attributed to the release of PG or activation of sensory nerves[62].

MECHANISMS OF PROTECTION RENDERED BY SPICES AND HERBS

The mechanism of herb-induced gastroprotection varies according to the nature and chemical constituents of the herbs. Three main functions including antisecretory, cytoprotective and antioxidant activities, isolated or in combination, are responsible for gastric mucosal protection.

Antisecretory activity

Several herbs and plants extracts have shown an anti-ulcer effect mainly due to their potent antisecretory action, which could be related to their flavonoid content. In experimental animals, *Cissus quadrangularis* extract and *Maytenus ilicifolia* have been shown to inhibit gastric secretions and ulcer index[63,64]. Similarly, phytosphingosine hydrochloride has been shown to have antisecretory and anti-ulcer effects in animals with pyloric ligation[65]. Methanolic extract of *Momordica charantia* prevents development of peptic ulcer and promotes healing of ulcers induced by acetic acid. Antisecretory studies in pylorus-ligated rats have demonstrated a significant reduction in acidity, pepsin content and ulcer index. On the other hand, the extract also amplifies the gastric mucosal content[66]. A variety of herbs and plant extracts including standardized aqueous extract of *Cecropia glaziovii Sneth* (Cecropiaceae)[67], alkaloid extract and 2-phenylquinoline obtained from the bark of *Galipea longiflora* (*Rutaceae*)[68] and *Landolphia owariensis* extracts[69] have exhibited an anti-ulcer effect.

The inhibition of gastric acid and pepsin output in rats with intact or deactivated sensory nerves treated parenterally with capsaicin could contribute to the capsaicin-induced gastroprotection against acid-dependent mucosal lesions[70].

Cytoprotective activity

In pylorus-ligated rats, methanolic extract of *M. charantia L.* fruit protects against peptic ulcer and promotes ulcer healing *via* enhancing the gastric mucosal content and antisecretory activity in stress-, ethanol-, indomethacin- and cysteamine-induced ulcers[66]. In both ethanol- and indomethacin-induced experimental ulcers, pretreatment with isopulegol, a monoterpene present in essential oils of several aromatic plants, has resulted in significant gastroprotective action, which is apparently mediated through its endogenous PGs and antioxidative properties[71]. Moreover, Weikang (WK) decoction significantly protects against ethanol-induced gastric mucosal injury. This activity is mediated by enhancement of epidermal growth factor (EGF) content in gastric juice, nitric oxide (NO) in gastric tissue, PGE2 and superoxide dismutase (SOD) in plasma, inhibition of malondialdehyde (MDA) and endothelin in plasma, and an increase in mucosal thickness[72]. In swim- and ethanol-stress-induced ulcers, extract of ginger rhizome (*Zingiber officinale*) normalizes antioxidant enzymes and protects against oxidative and gastric mucin damage[55]. The gastroprotective effect of *Vanillosmopsis arborea* bark essential oil is likely mediated by α2-receptor activation[73], whereas the anti-ulcerogenic effect of *Solanum torvum Swartz* (Solanaceae) aqueous and methanol extracts is probably due to cytoprotective mechanisms[74]. Cytoprotective action of total carotenoid and astaxanthin esters depends on their mucin-related protective action as well as enhancing antioxidants enzymes level and H^+, K^+-ATPase inhibitory activity[75]. Synthesis of cytoprotective PGs, increased resistance of gastric mucosa, and inhibition of leukotriene synthesis are possibly responsible for gastroprotection induced by boswellic acids (from *Boswellia*)[57].

In various ulcer models in mice, the gastroprotective activity of *G. longiflora* (Rutaceae) is related to an increase in gastric mucus content and antisecretory activity. Additionally, NO is involved in mucosal protection, which could be attributed to their alkaloids, particularly 2-phenylquinoline[68]. Pretreatment of albino rats with aqueous extract orally once daily for 2 wk significantly inhibited HCl/ethanol-induced ulcers and enhanced gastric mucus production. Additionally, it displayed antisecretory activity in pylorus-ligated rats. The results indicate that the leaf extracts of *Landolphia* possess anti-ulcer properties[69].

A new flavonoid derivative, DA-6034, also prevents ulcers induced by ethanol, aspirin, indomethacin, stress, and acetic acid, and enhances endogenous PGE2 syn-

thesis and mucus content in the gel layer of the gastric mucosa. Promotion of the gastric defensive systems is the likely cause of its gastroprotective activities[56].

Antioxidative activity

Oxidants are implicated in the pathophysiology of various diseases, including peptic ulcer disease, and antioxidants may therefore contribute to their prevention and treatment. NSAIDs account for some of the most commonly used drugs worldwide and may activate the oxidative process. For instance, treatment with indomethacin induces neutrophil activation with release of ROS and microvascular injuries, which is considered as the prime event in gastric mucosal damage[76]. Therefore, investigators have continued to search for agents with antioxidative properties, which prevent or at least reduce ROS-induced mucosal damage. Such agents include isopulegol, which has shown significant gastroprotective effects in ethanol- and indomethacin-induced ulcer models. Gastroprotective action is probably mediated by its antioxidative properties, synthesis of endogenous PGs and K^+ (ATP) channel opening[71]. Other herbs with antioxidative actions include carotenoid and astaxanthin esters, the herb collection Korniozil, and ginger rhizome. For instance, total carotenoid and astaxanthin esters have experimentally protected gastric mucin and increased levels of the antioxidant enzymes catalase, SOD, and glutathione peroxidase in gastric homogenate[75]. In addition, Korniozil also protects against experimentally induced stress ulcers, with enhancement of gastric mucous coat regeneration, along with restoration of lipid peroxidation and antioxidative system function[77]. Ginger rhizome extract has shown gastroprotective activity in animals with swim- and ethanol-stress-induced ulcers. This activity is based on gastric mucin generation, restoration of antioxidant enzymes and inhibition of *Helicobacter pylori* (*H. pylori*) growth[55].

The gastroprotective effect of *Cissus sicyoides* extract administered orally in rodents treated with various ulcerogenic agents is also due to its antioxidative properties, increase of NO and SH groups, with enhancement of mucosal defense mechanisms and microcirculatory response. Therefore, the authors have supported its use for gastric ulcer treatment[78].

Studies on piperine have demonstrated an antioxidative effect *in vitro*, lipid peroxide inhibition *in vivo*, and enhancement of the bioavailability of phytochemicals. The protective activity of piperine is linked to its antioxidative action and ability to inhibit ROS[40]. Thymoquinone, the active constituent of *Nigella sativa*, has been shown to protect against gastric mucosal damage induced by ethanol. These effects can be ascribed to improvement in the antioxidant status, increased serum levels of serum glutathione, SOD, inhibition of radical oxygen species, and increased mucin content of the gastric mucosa[29,79].

Other activities: PG-herb interaction

PG synthesis is important for gastric mucosal protection. PG has been used as an antisecretory drug to treat peptic ulcer disease. However, the use of a sufficient therapeutic dose is associated with adverse effects, which limits its use, especially after the introduction of antisecretory drugs such as H2-receptor antagonists and proton pump inhibitors. Several studies on herbs and plant extracts that activate PG synthesis have emphasized their role in gastroprotection and healing of gastric mucosal injuries. Silva *et al*[71] have reported a significant dose-related protective effect of isopulegol, a monoterpene that is obtained from essential oils of several aromatic plants, against indomethacin- and ethanol-induced ulcers. This protective action is probably mediated by endogenous PGs, K^+ (ATP) channel opening, and antioxidant properties. Similarly, Alqasoumi *et al*[54] have reported a PG and/or antisecretory, as well as antioxidant-mediated gastroprotective activity of Rocket extract. Boswellic acid, a triterpenoid used clinically to treat arthritis, has exhibited a mucosal protective action through PG synthesis stimulation and leukotriene synthesis inhibition[57]. Endogenous PGs and PG EP1 receptors have an important role in the adaptive protection and functional responses in mice treated with sodium taurocholate[80]. The active ingredient of chilli, capsaicin, which is believed to be ulcerogenic, on the contrary, prevents ulcer formation through its antisecretory action, as well as stimulation of mucus, alkali secretions and mucosal microcirculation. In addition, capsaicin stimulates afferent neurons in the stomach and transmits signals to the central nervous system, which trigger an anti-inflammatory response and gastroprotection[81]. Treatment with small doses of topical capsaicin protects the gastric mucosa from damage by strong irritants[69].

PGs have been found to reduce enhanced duodenal mucosal permeability induced by hydrochloric acid[82]. In acute injury, small bowel mucosa function recovers with the restitution of epithelium, which is believed to be pivotal for epithelial repair, and occurs only in the presence of PG-mediated paracellular space closure[83]. Hatazawa *et al*[84] have studied the role of PGs/COX in the healing of indomethacin-induced small-intestinal ulcers in rats. They have reported ulcer healing by endogenous PGs, which is mediated by PG EP4 receptors, and involvement of COX-2 in the early stage and COX-1 in the late stage of healing. Bacterial lipopolysaccharide is involved in gastric mucosal protection in rats, *via* activation of COX and endogenous PG genes[85]. In rats, *Teucrium polium* has demonstrated protection against indomethacin-induced gastric ulcer through PG synthesis, EGF receptor (EGFR) expression and modulation of mucin secretion, besides its antioxidative activity, and it lack of toxicity[86].

EGF and effect of herbs

Ulcer preventive activity of herbs in experimentally induced gastric injury is thought to be mediated through their antisecretory and antioxidative properties, as well as PG generation. Various factors are involved in mucosal defense and repair, including gastrin, parietal cells and tumor necrosis factor (TNF)-α. Gastrin and parietal cells play an important role in the regulation of mucosal proliferation in response to gastric injury and inflammation[87]. Similarly, TNF-α, which is released during gastric mucosal

injury, also contributes to epithelial cell repair in the gastric mucosa *via* its receptor and activation of the PG pathway[88]. EGF and other growth factors are also pivotal for the process of mucosal healing. EGF and transforming growth factor (TGF)-α have a common receptor (EGFR). They promote ulcer healing through enhancement of cell proliferation, overexpression of growth factors, inhibition of gastric secretion and enhancement of blood flow at the ulcer margin[89]. Treatment with EGF significantly induces extracellular signal-regulated kinase (ERK) activity, COX-2 and PGE2 generation, and cell proliferation. The EGF-induced proliferation of gastric epithelial cells is probably mediated by the ERK/COX-2 pathway[90]. Gastric mucosa regeneration, with cell proliferation, migration, tissue injury repair and ulcer healing are controlled by activation of EGFR. Although TGF-α acts under normal circumstances and following acute injury, EGF acts mainly during the healing process of chronic ulcers. Both TGF-α and EGF, and other growth factors including basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), promote restoration of connective tissue and angiogenesis in injured gastric mucosa. Further growth factors involved in regeneration include keratinocyte growth factor, hepatocyte growth factor and trefoil peptides[91]. Regeneration of injured human gastric epithelial monolayers has been promoted by EGFR-dependent phosphoinositide 3-kinase activation[92].

Besides its role in gastric inflammation and injury, EGF plays an important role in the regulation of cancer growth. Phosphorylation of EGFR and inhibition of heparin-binding EGF-like growth factor (HB-EGF) carboxyl-terminal fragment (CTF), and HB-EGF-CTF nuclear translocation are considered crucial in inhibitory regulation of cancer cell growth[93]. Overexpression of EGF has often been found in gastric cancer. Growth factors alter the localization of tight-junction-associated proteins such as ZO-1 and occludin[94]. Baek *et al*[95] have also reported EGF overexpression and urokinase plasminogen activator receptor in human gastric cancers. In epithelial and mesenchymal cells, EGF binds to tyrosine kinase receptor and promotes malignant formation as well as tissue repair[96].

Herb-induced growth factor enhancement may support treatment strategies for gastric ulcer and cancer. Capsaicin-sensitive nerves contribute to healing of acetic-acid-induced chronic gastric ulcer through stimulation of EGF expression in salivary glands, serum and gastric mucosa[97]. Weitongning herb increases EGF and NO content in ulcer scars, which improves ulcer healing and reduces recurrence[98]. Also, in ethanol-induced gastric mucosal injury, WK decoction has shown a significant gastroprotective effect that is mediated by increased levels of NO in gastric tissue, PGI2 and SOD in plasma, and EGF in gastric juice[72]. Mexican tea herb and pilular adina herb have also demonstrated protection of gastric mucosa through stimulation of NO and EGF secretion and enhancement of EGFR expression[99]. Wang *et al*[100] have also reported increased expression of EGF and EGFR mRNA in experimental gastric ulcer in rats treated with Kuiyangping, with possible promotion of ulcer healing and decreased ulcer recurrence. *Angelica* and *Chuanxiong* spices given to rats with myocardial infarction may affect VEGF expression and promote endothelial cell proliferation[101]. This angiogenic effect may also be applied to the formation of new vessels in granulation tissue and restitution of injured gastric mucosa.

Through their effect on EGF, herbs may prove beneficial in the management of cancer. Constituents of ginger have inhibited EGF-induced cell transformation[102]. Inhibition of EGFR tyrosine kinase proliferation and invasion of gastric cancer cells has also been achieved by curcumin[103]. Molecular therapies that target growth factors EGF and VEGF and their receptors have shown promise against hepatocellular carcinoma in the absence of beneficial effects of chemotherapy[104]. Recent data combining EGFR and VEGF inhibitors have suggested the superiority of targeting multiple pathways rather than a single pathway[105]. The anticancer potential of curcumin has been demonstrated by inhibition of EGF-induced upregulation of aquaporin and ovarian cancer cell migration[106].

Role of NO mediation by herbs

Tsai *et al*[107] have evaluated the effect of some spices on NO overproduction generated by inducible NO synthase (iNOS), which is implicated in disease development. Rosemary, tarragon, oregano, basil, marjoram, allspice, and thyme have demonstrated poor to moderate activity. In contrast, cinnamon has excellent ability to scavenge NO. NO-scavenging activity of herbs is probably related to their high content of phenolic compounds, which scavenge NO or suppress iNOS. In another study, pretreatment with NOS inhibitor attenuated the gastroprotective effect induced by polyalthic acid[108]. Moreover, plant-extract-induced gastroprotection is probably related to the enhancing effect on NOS inhibitor expression, gastric microcirculation and release of NO[109]. Participation of NO, PGs and SH compounds may explain the anti-ulcerogenic action of diterpenoid from *Croton reflexifolius*[108].

Non-protein-SH compounds and herbal involvement

Non-protein (NP)-SH compounds contribute to gastric mucosal defense. Depletion of NP-SH alters mucosal integrity. *Commiphora opobalsamum* (L.) Engl. (Balessan) protects against various models of experimental gastric ulcers in rats. It has been shown to protect in a dose-dependent manner against mucus and NP-SH depletion with a large margin of safety[52]. Methanolic *C. sicyoides* extract given orally to rodents has been shown to inhibit experimental gastric injuries induced by necrotizing agents, *via* participation of NP-SH compounds and NO, and enhancement of the defense system[78]. Maintaining adequate gastric mucus concentration and NP-SH levels is essential for gastric mucosa integrity and function. Other herbs and plant extracts also have the ability to preserve the defense system of the gastric mucosa. For instance, pretreatment with *Ginkgo biloba* extract has been shown to inhibit, in a dose-dependent manner, ethanol-induced NP-SH compound production, depletion of gastric wall mucus con-

centration, and lipid peroxidation, and preserve mucosal function[110]. Similarly, anise aqueous suspension, and rocket and anise have significantly replenished ethanol-induced gastric wall mucus concentration and NP-SH depletion in experimental studies[54,111].

H. pylori bactericidal activity of herbs

The association between *H. pylori* and peptic ulcer disease is well-established and eradication is pivotal for ulcer healing and minimizing the relapse rate. Although the eradication rate of currently used regimens ranges between 80% and 90%, the problem of developing resistance is emerging. A number of investigators have evaluated the effect of herbs and plant extracts on *H. pylori*. Methylene chloride cinnamon extract has also shown an inhibitory effect on the free urease of *H. pylori*[112]. Also curcumin and its methanolic extract have inhibited the growth of all strains of *H. pylori in vitro*[113]. In addition, gingerol, a polyphenolic constitute of ginger root, has also demonstrated inhibitory activity on CagA+ strains of *H. pylori*[114]. Moreover, eugenol and cinnamaldehyde prevented growth of *H. pylori* obtained from human gastric tissue, and inhibited the growth of all 30 tested *H. pylori* strains, with a lack of resistance[115]. In a declining order, turmeric, cumin, ginger, chilli, borage, black caraway, oregano and liquorice have demonstrated partial bactericidal activity against *H. pylori*. *H. pylori* adhesion to the stomach has been inhibited by extracts of turmeric, borage and parsley[116]. Zaidi *et al*[117] have reported that > 50% of 50 commonly used Pakistani medicinal plants have inhibited the growth of eight *H. pylori* strains. *Curcuma amada* Roxb., *Mallotus philippines* (Lam) Muell., *Myrisctica fragrans* Houtt., and *Psoralea corylifolia* L aqueous-ethanol extracts have demonstrated a potent anti-*H. pylori* activity and *Mal. philippines* (Lam) Muell. has exhibited potent bactericidal activity.

SAFETY AND TOXICITY OF SPICES

The majority of experimental studies have reported a lack or low levels of toxicity for most spices. However, there are many case reports, and *in vivo* and *in vitro* toxicological studies that have demonstrated the toxicity of certain herbs and their constituents[118]. Some investigators have reported hepatotoxicity of curcumin and its derivatives[119], as well as turmeric and its ethanolic extract in vulnerable mice[120]. Longer treatment with high turmeric dose has been associated with a significant decline in body weight gain and alterations in liver weight[121]. In contrast, chronic treatment with *Foeniculum vulgare* ethanolic extracts of fruit and *Ruta chalepensis* aerial parts have resulted in a significant weight gain in male mice[122]. Changes in liver, spleen, lung or reproductive organs, along with a significant increase in sperm count and motility, and decreased hemoglobin have been reported in *Cinnamon zeylanicum*, *Piper longum* and *R. chalepensis*-treated animals[122,123]. In an experimental model, piperine (10 and 20 mg/kg) decreased mating performance and fertility. Five days post-mating, oral treatment induced considerable anti-implantation activity. In addition, intrauterine injection of piperine has caused loss of implants. However, piperine treatment has not produced any histopathological effect in the ovaries and uterus at the cellular level[124]. Although initial reports on the safety of black pepper and its active ingredient piperine were controversial, the current literature has established its safety in animals. Moreover, piperine has shown antimutagenic and antitumor activities. Curcumin administered at higher doses has resulted in nuclear, genome and more extensive mitochondrial damage in human hepatoma G2 cells, mediated by the elevated concentration of ROS and lipid peroxidation. Curcumin also has caused genotoxicity in PC12 cells and has induced suicidal death of normal erythrocytes[125-127]. At elevated concentrations, thymoquinone may be genotoxic and cytotoxic, induce programmed cell death in erythrocytes, and cause glutathione depletion and liver damage[128,129].

CONCLUSION

It continues to be debatable whether spices and herbal xenobiotics are beneficial to gastric mucosal damage, and whether their toxicity outweighs any benefits. It is, however, clear that the consumption of certain common spices in food and the intake of herbal supplements may help the fight against peptic ulcer disease in humans. This review provides insights into the future use of herb- and spice-based drugs as alternative treatments for gastric ulcer. Dietary and nutritional practices in the oriental region and the consumption of spices in moderate quantities may be of benefit for the prevention of gastric ulcer. The review suggests the need for further investigations into the benefit of herbal xenobiotics and spices on the gastric mucosa, with in-depth *in vivo* studies, sustained clinical trials and cohort analyses. There is enough evidence to conclude that spices have a beneficial effect on gastric ulcers, despite various reports of their toxicity.

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