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Spices as Alternative Agents for Gastric Ulcer Prevention and Treatment

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1. Introduction

1.1 Important aspects on ulcer pathogenesis

World-wide, peptic Ulcer disease (PUD) is considered as a common gastrointestinal disorder. It develops as a result of altered balance between offensive and defensive factors. Offensive (aggressive) factors disrupt normal mucosal integrity and allow H+ back diffusion with a subsequent cellular injury. Helicobacter pylori (H. pylori) and nonsteroidal anti-inflammatory drugs (NSAID) represent the major aggressive factors associated with PUD. Experimentally induced gastric ulcer has expanded our knowledge on ulcer pathogenesis. Indomethacine, 80% ethanol and pyloric ligation are the methods commonly applied in experimental ulcer models. Other universally accepted experimental ulcer models include 0.2 mol/L NaOH, 25% NaCl, stress induced by swimming (1), acetylsalicylic acid (2), cold-restraint (3) and hypothermic restraint (4).

A major event in the pathogenesis of NSAID induced gastric ulcer is represented by inhibition of prostaglandin (PG) synthesis, enhancement of gastric acid secretion, suppression of bicarbonate secretion, glutathione (GSH) levels, mucosal circulation, cell proliferation and growth as well as alteration of gastric mucosal barrier integrity. Inhibition of PG biosynthesis enhances generation of leukotrienes and other products of the 5-lipoxygenase pathway (5). These products disrupt the mucosal barrier with subsequent enhancement of gastric mucosal permeability for H + ions and Na+ ions and reduction of transmucosal potential difference (6, 7). Furthermore, NSAID uncouple mitochondrial oxidative phosphorylation, affect mitochondrial morphology, reduce the intracellular ATP levels and alter the normal regulatory cellular function (8). These processes promote erosions and ulcer formation. In addition, generation of reactive oxygen species (ROS) is also considered as a major factor contributing to ulcer pathogenesis. Another, prostaglandin-independent pathway of gastric ulcer pathogenesis is induced by enhanced endothelial adhesion, activation of polymorphonuclear cells (PMN) with subsequent release of oxidative byproducts (9, 10). PMN activation induces depletion of GSH and sulfhydryl compounds (SH) in tissue with enhanced mucosal myeloperoxidase (MPO) and malondialdehyde (MDA) concentration (11). Myeloperoxidase is considered as a marker of oxidative process induced by PMN tissue infiltration.

Similarly, in ethanol-induced gastric mucosal injury there is enough evidence to suggest the role of oxidative burst. Ethanol-induced oxidative damage is commonly associated with

generation of ROS, leading to oxidative stress. Acute ethanol treatment induced oxidative damage is associated with a decreased GSH content in gastric tissue along with an increased MDA and xanthine oxidase activity (12). The oxygen free radicals-induced lipid peroxidation affects mitochondrial energy metabolism and plays a critical role in the pathogenesis of acute ethanol-induced gastric mucosal injuries (13). On the mitochondrial level, ethanol-induced intracellular oxidative stress causes also mitochondrial permeability transition with mitochondrial depolarization that precedes gastric mucosal cells necrosis. This process can be prevented by intracellular antioxidants, such as GSH (14). Acute ethanol administration is also associated with inhibition of catalase and, glutathione peroxidase (GPx) activities with significant increase of MDA contents, MPO activity, and cellular apoptosis (15). Furthermore, ethanol induces inhibition of SH with enhancement of superoxide dismutase (SOD) and glutathione reductase (GR) activities (16). The extent of oxidative damage in stomach as indicated by the ulcer index, gastric mucosal MDA content and alteration of mitochondrial ultrastructure is correlated with ethanol exposure and concentration (13).

2. Introduction in spices

Spices are used in several parts in the world as food additives and carminatives. Since ancient times they are also applied in the traditional management of a variety of disorders. Currently their therapeutic value has gained a considerable interest and several investigators have reported their effects in laboratory animals and in man. It has been experimentally demonstrated that spices, herbs, and their extracts possess antibacterial (17) antifungal (18,19), vermicidal, nematocidal, molluscicidal properties (20-22), anti-inflammatory and antirheumatic activity (23-25), hepatoprotective (26,27), nephro-protective (28), antimutagenic, anticancer potentials (28-30) and antihypercholesterimc potentials (31-34).

A tremendous number of studies have evaluated the antiulcer effect of spices. Although some investigators have reported deleterious effect of certain spices such as red and black pepper, the majority have demonstrated rather a cytoprotective activity in animal (35-37) as well as in human (38).

3. Factors involved in ulcer healing

In the presence of mucosal barrier disruption, several factors including acid, bile acids, NSAID and ethanol promote H+ back diffusion and enhance the susceptibility to develop ulcer. On the other hand, optimal mucosal microcirculation and bicarbonate secretion with formation of an alkaline buffer layer at the epithelial surface is considered as a first line of mucosal defense and gastroprotection. Other factors including prostaglandins (PG), growth factors (GF), nitric oxide (NO) or calcitonin gene-related peptide (CGRP), as well as some gut hormones such as gastrin, cholecystokinin (CCK), leptin, ghrelin, gastrin-releasing peptide (GRP) and melatonin are involved in mucosal defense system and the ulcer healing process. The protective action of gut hormones is attributed to the release of cyclooxygenase-2 (COX-2) and PGE2 at the ulcer margins (39, 40) or activation of sensory nerves (41). In addition, Tumor necrosis factor – α (TNF-α), released during gastric mucosal injury, activates PG pathway and promotes epithelial cell repair and healing (42). EGF and other growth factors are also pivotal for the process of mucosal healing. Furthermore, in response to gastric injury and inflammation, gastrin and parietal cells contribute to the regulation of mucosal proliferation (43).

4. Why spices, herbs and plant extracts are considered as an alternative ulcer therapy?

Ulcer healing and prevention of recurrence represent the central goals of treatment. The treatment is targeted at either counteracting aggressive factors like acid, pepsin, active oxidants, platelet aggravating factor (PAF), leukotrienes, endothelins, bile or exogenous factors including (NSAID) or enhancing mucosal defense such as mucus, bicarbonate, blood flow, PG and NO (44). Antiscretory drugs including H_2-receptor antagonists (H_2-RA) and proton pump inhibitors (PPI) alone or combined with antibiotics in the presence of H. pylori infection are currently considered as the most acceptable drugs for ulcer treatment. The main action of antisecretory drugs is acid suppression. These agents lack effect on other factors involved in ulcer pathogenesis and therefore, do not meet all treatment goals. In addition, acid suppressors are expensive and associated with adverse effects and ulcer recurrence. Hence, efforts are on to search for suitable alternative treatment from medicinal plants resources. Already a large percentage of world population relies on medicinal plants to treat a variety of disorders including PUD. In addition to their ability to act on various pathogenetic factors, they are cheap and easily accessible. Furthermore, a large number of spices and plant extracts evaluated by various researchers for their anti-ulcer effects have a favorable outcome. (29, 45-48)

The antiulcer effect of spices/herbs is based on the activities of their chemical constituents, which attenuate the gastric secretion, enhance mucosal integrity, interfere with oxidative burst, NO, SH compounds and inhibit H. pylori growth. Due to their variable phytochemical constituens they may exhibit antisecretory, cytoprotective, antoxidant or combined activities.

5. Herbs and gastric secretion

A variety of spices and their extracts possess a potent antiscretory activity. Pylorus-ligation in rats represents the model of antisecretory studies. A number of spices, herbs and plants methanolic or aqueous extracts possess an antisecrertoy activity. For instance, Cissus quadrangularis , Maytenus ilicifolia, phytosphingosine, Cecropia glaziovii Sneth (Cecropiaceae), alkaloid extract and 2-phenylquinoline obtained from the bark of Galipea longiflora (Rutaceae) and Landolphia owariensis induce significant inhibition of acidity, pepsin content and ulcer index (49-54), respectively. This potent antisecretory action of spices and plant extracts is likely related to their flavonoid content. Maytenus ilcifolia is considered among flavenoid-rich plant extracts (55).

In rats with pylorus ligation, antisecretory effect of methanolic extract of Momordica charantia L. is demonstrated by decrease in acidity, pepsin content and ulcer index with an increase in gastric mucosal content (56).

Likewise, the protective effect of Cissus quadrangularis extract is mediated by inhibition of gastric secretion with decrease in ulcer index as well as enhancement of mucosal defense (49).

6. Herbs and cytoprotection

Several spices and plants extracts promotes ulcer healing via enhancing gastric mucosal content beside their antisecretory activity in pylorus-ligated rats. Ginger rhizome extract-induced cytoprotective activity is based on its antioxidative and gastric mucosal protective

activities (1). Total carotenoid and astaxanthin esters protect mucin, enhance antioxidants enzymes level and H+, K+-ATPase inhibitory activity (57). Furthermore, boswellic acid-induced gastroprotection depends on generation of cytoprotective PG, enhanced gastric mucosal resistance, and inhibition of leukotriene synthesis (3). Similarly, Galipea longiflora (Rutaceae) protect gastric mucosa by enhancement of mucus content and antisecretory activity (53). In addition to its antioxidant activity, Cissus sicyoides , induce increase of NO and SH compounds and enhances defense mechanism (58). In pylorus-ligated rats, beside its antiscretory action, Momordica charantia L. extract also significantly increases gastric mucosal content (56). Increase in Glycoprotein level, gastric mucin content and SH concentration are essential for the gastroprotection. Their levels are raised by treatment with Cissus quadrangularis extract (49)

7. Herbs and antioxidants

Recently, oxidants are found to play a critical role in PUD pathogenesis. Experimental NSAID and ethanol induced microvascular and gastric mucosal injuries are at least partially caused by ORS release (59). Therefore, implementations of agents with antioxidative properties are useful for the prevention of injuries and promotion of gastric ulcer healing. Many spices have phytochemicals with antioxidative activities. For instance, Coriander contains many antioxidant constituents including d-linalool, borneol, geraniol, geranyl acetate, camphor, carvone, which are responsible for its antioxidative property (60). Black cumin (Nigella sativa), peperine and thymoquinone, the active constituents of pepper and Nigella sativa, respectively have also the ability to inhibit ROS in experimentally induced gastric lesions in rats (29, 60, 61).

Many other spices/herbs and plant extracts protect against experimentally-induced gastric mucosal injuries through their potential antioxidative effect. These include ginger rhizome, carotenoid and astaxanthin esters, Cissus sicyoides extract, isopulegol and the herb collection Korniozil (1, 57, 58, 62, 63), respectively. Through the interaction with endogenous PG and antioxidative properties, isopulegol, monoterpene a constituent of essential oils of several aromatic plants, induce significant gastroprotection. Total carotenoid and astaxanthin esters increase the levels of the antioxidant enzymes catalase, SOD, and GPx in gastric homogenate and protect gastric mucin (57). Korniozil also protects against experimentally induced stress ulcers, with restoration of lipid peroxidation and antioxidative system function along with enhancement of gastric mucous coat regeneration (63). Ginger rhizome extract gastroprotective activity is also based on restoration of antioxidant enzymes and gastric mucin generation in addition to inhibitory effect on H. pylori growth (1). Due to its antioxidative properties, Cissus sicyoides oral extract increase also NO and SH and induces also protection (58]

The alkaloid indigo, obtained from the leaves of Indigofera truxillensis Kunth (Fabaceae), prevents ethanol induced depletion of SH and GPx activity, inhibits GR and MPO activities and partially inhibits gastric mucosa DNA damage caused by ethanol (64).

8. Herbs combined activities

Due the presence of several active constituents, some spices/herbs and plant extracts protect the gastric mucosa via different mechanisms. For instance, Weikang decoction acts as antisecretory, cytoprotective and antioxidative agent. It enhances mucosal thickness, NO in

gastric tissue, PGE2 in plasma, (EGF) content in gastric juice and SOD in plasma. In addition it inhibits also MDA and endothelin in plasma (65). Many other spices like Rocket Eruca sativa, black cumin, black pepper, clove, cardamom, caraway , peppermint, saffron, coriander and anise possess also antisecretory, cytoprotctive and antioxidative activities (4, 29, 66-73). They also replenish gastric wall mucus concentration and SH levels and significantly reduce MDA level.

Besides its H. pylori bactericidal effect, Davilla elliptica also enhances NO, H_2O_2, TNF - α production and GSH bioavailability. These activities are related to its phytochemical constituents acylglycoflavonoids, phenolic acid derivatives and tannins (74). Also Brazilian medicinal plant methanolic extracts have an anti-H. pylori effect and protect the gastric mucosa by increasing PGE2, antisecretory and gastroprotective properties (75) The gastroprotection of Vochysia tucanorum Mart. methanolic extract and buthanolic fraction provided by the antioxidant activity and maintenance of gastric mucosa NO levels is interrelated to its phytochemical constituent Triterpenoid (76)

9. Herbs- PG interaction

Gastric protection is maintained in a state of equilibrium between aggressive and protective factors. In experimental ulcer model, indomethacin increases acid secretion, activates oxidative stress and inhibits the release of cyclooxygenase-1 (COX-1), PGE2, bicarbonate, and mucus (77). Similar to conventional NSAID, COX-2 inhibitors also delay the healing of chronic gastric ulcer and suppress the epithelial cell proliferation, angiogenesis and maturation of the granulation tissue in experimental animals. COX-2 is important for gastric mucosal defense (78). Indomethacin- induced gastric damage is associated with an increase of acid and oxidative parameters and inhibition of protective factors such as COX- 1, PGE2, bicarbonate, and mucus release (77).

Generally, PG are products of arachidonic acid and their biosynthesis is influenced by local, hormonal and neural factors. They stimulate gastric and duodenal bicarbonate secretion and the production of mucus glycoproteins. PG are also able to protect the gastric mucosa against experimentally induced gastric injuries in an acid independent manner known as “cytoprotection" (79). PG play a pivotal role in the gastric mucosal defensive system and contribute to the overall protective process against gastric mucosal injuries. They exhibit a variety of defensive mechanisms including mucus-alkaline secretion, mucosal hydrophobicity, mucosal microcirculation, tissue lysosomes stabilization, SH preservation, rapid proliferation and mucosal cells renewal. Mucosal integrity protection can also be accomplished even by small quantities of PG. Gastroprotection is attained by stimulation of mucosal protective PG biosynthesis or by the inhibition of preulcerogenic arachidonic acid metabolites (80). In addition, PG antiulcer activity is determined mainly by their antioxidant property with inhibition of lipid peroxidation as well as SOD and catalase activities (81).

Other mediators involved in gastric mucosal protection besides PG include growth factors, NO, CGRP and some gut hormones such as gastrin and CCK. In addition, leptin, ghrelin and gastrin-releasing peptide (GRP) have also the ability to protect gastric mucosa against corrosive agents-induced mucosal damage. Gut hormones protective activity is attributed to PG release (41). Ulcer healing is controlled by contribution of growth factors and gut hormones, increase of COX-2 induction and local PGE release in the ulcer area. Endogenous PG generated at ulcer margin play a key role in ulcer cure (82)

In acute injury, in the presence of PG-mediated paracellular space closure, mucosal permeability, PG helps the mucosal permeability to recover with epithelial restitution (83,

84). The ulcer healing by endogenous PG is mediated by PGEP4 receptors, as well as involvement of COX-2 in the early stage and COX-1 in the late stage of healing. Bacterial lipopolysaccharide contributes also through COX and endogenous PG genes activation to gastric mucosal protection in rats (85).

Mainly through their effect on PG, several plant extracts promote ulcer healing. For instance, Hyptis spicigera essential oil major constituents, monoterpenes, enhances PGE2-induced gastric mucus and reduces ulcer size in addition to increasing COX-2 and EGF expression in gastric mucosa and acceleration of ulcer healing (86).

Other spices and plant extracts involved in activation of PG synthesis and healing of gastric mucosal injuries include Boswellic acid, isopulegol, Teucrium polium (3, 62, 87). Endogenous PG and PGEP1 receptors play a key role in the adaptive protection (88). Chilli is believed to be detrimental to the gastric mucosa, however, its active ingredient capsaicin, decreases acid secretion and activates the defensive system by enhancing mucus, alkali secretions as well as mucosal microcirculation and hence, it prevents ulcer formation. Furthermore, capsaicin stimulates afferent neurons in the stomach and transmits signals to the central nervous system, which trigger an anti-inflammatory response and gastroprotection (89). Furthermore, Citrus lemon, Alchornea triplinervia and Myristica malabarica have demonstrated gastroprotective effect. Citrus lemon belongs to Rutaceae family and contains two main components, limonene and β-pinene. In ethanol and indomethacin gastric ulcer models, while Citrus lemon and limonene induce complete gastroprotection, β-pinene is not effective. Citrus lemon and limonene protective effect is linked with PGE2 and mediated by enhancing mucus secretion, HSP-70 and VIP (90). The antiulcer effect of ethyl acetate fraction of Alchornea triplinervia, a medicinal plant used in Brazil to treat gastrointestinal ulcers, is mainly related to its flavonoids content and mediated by increasing gastric mucosal prostaglandin PGE2 levels (75).

While PGE2, and vascular endothelial Growth Factor (VEGF) levels decrease, EGF and endostatin levels increase in indomethacin- induced ulceration in mice. Through modulation of PG synthesis and angiogenesis, Myristica malabarica plant extract restores these parameters. In comparison omeprazole, which offered similar healing, did not alter these parameters (91).

Coenzymes Q10, an essential cofactor in the mitochondrial electron transport pathway possess a potent antioxidant action. Pretreatment of indomethacin induced gastropathy with CoQ10 prevents ROS generation, mitochondrial dysfunction, vascular permeability erosions, ulcers and helps to restore PGE_2, NO and GSH levels (92).

10. Herbs and EGF

Growth factors and their receptors are also important for maintaining physiological function of gastric mucosa. They maintain and enhance defensive and inhibit aggressive factors. Following acute mucosal injury and during the initial stages of experimental gastric ulcer healing, R-associated tyrosine kinase is essential for regulation of cell proliferation, EGFR gene activation, EGFR phosphorylation, and increased mitogen-activated protein (MAP) kinase activity. H. pylori is a major cause of PUD and contributes also to inhibition of healing. In experimental gastric ulcer model, H. pylori vacuolating cytotoxin interfers with ulcer healing and inhibits cell proliferation, binding of EGF to its receptor, EGF-induced EGFR phosphorylation, and MAP and extracellular signal-related kinase (ERK-2) activation (93,94).. Growth factors and their receptors are pivotal for the process of gastroprotection

and ulcer healing. EGF and transforming growth factor (TGF)-α and their common receptor (EGFR) inhibit gastric secretion, boost overexpression of growth factors, blood flow at ulcer margin and promote cell proliferation with ulcer healing (95). The process of gastric mucosal tissue repair and healing is controlled by EGFR activation (96). EGF-induced gastric epithelial cells proliferation is likely intervened by ERK /COX-2 pathway (97). Various GF exhibit different functions of the mucosal repair. They are implicated in the process of tissue healing with cell migration, proliferation, differentiation, secretion, and degradation of extracellular matrix. While EGF , TGF- α , and trefoil factors (TFFs), usually present in the gastric juice or mucosa, as well as hepatocyte growth factor (HGF) are responsible for epithelial structure reconstitution, basic fibroblast growth factor (bFGF), (VEGF), transforming growth factor-β (TGF-β) and platelet derived growth factor (PDGF), are essential for connective tissue reconstitution(98,99).

In gastric mucosal injury, EGF released from salivary glands and TGF-α from gastric mucosa are of particular value in mucosal integrity maintenance and repair. EGF and TGF-α have similar spectra of biological activity in the repair mechanism. Accumulation of EGF and EGFR overexpression in the ulcer area contributes together to repair process. During the ulcer healing process they activate cells migration from the ulcer margin and cell proliferation along with formation of granulation tissue and microvessels, angiogenesis (100). During initial stage of experimental ulcer healing, EGFR-associated tyrosine kinase plays an essential role in the regulation of cell proliferation by activation of the EGFR gene, EGFR phosphorylation, and enhancement of MAP kinase activitay. The presence of H. pylori vacuolating cytotoxin counteracts this process (93).

Numerous growth factors accelerate gastric epithelial and mesenchymal injury healing in vitro with acceleration of cell migration and proliferation. Gastric epithelial healing is mainly accelerated by a group of growth factors including EGF, TGF-α and HGF, while mesenchymal healing is predominantly accelerated by TGF-β and bFGF. Both, gastric epithelial and mesenchymal injury healing are significantly accelerated by PDGF, factor-betabeta and insulin-like growth factor-1 (IGF-1). During the healing process, IGF-1 regulates the gastric epithelial-mesenchymal interaction (96,101).

In injured gastric mucosa, growth factors TGF-α, HGF and IGF accelerate epithelial restitution and variably regulate the regeneration of human gastric epithelial cells through modulation of cell shape adaptation, migration and proliferation (102). Growth factors endorse EGFR-dependent PI3K activation, which promotes cell migration and restitution in injured human gastric epithelial monolayers (103).

Smoking is known as a risk factor for PUD. The detrimental effect of smoking is exhibited by inhibition of cell proliferation, mucus secretion and angiogenesis due to deficiency in EGF biosynthesis and its mRNA expression. The shortage of these factors is responsible for the delay in ulcer healing (104).

Several spices and plant extracts such as Mexican tea herb and pilular adina herb, Chuanxiong spices, Capsaicin, Kuiyangping, Weitongning and Angelica sinensis interact with EGF synthesis and hence contribute to the gastroprotection. For instance, Mexican tea herb and pilular adina herb stimulate NO, EGF secretion and EGFR expression and herewith protect the gastric mucosa integrity (105). Capsaicin-sensitive nerves induced ulcer healing is mediated by stimulation of EGF expression in salivary glands, serum and gastric mucosa (106). Also Kuiyangping, promotes ulcer healing in rats and decreases recurrence via increased expression of EGF and EGFR mRNA (107). Furthermore, Weitongning herb increases EGF and NO content in ulcer scars, and hence improves ulcer healing and reduces recurrence (108). In experimental myocardial infarction, Angelica and Chuanxiong spices

promote endothelial cell proliferation and VEGF expression(109) and likewise may also promote angiogenesis and tissue repair in experimental ulcer. In indomethacin-induced gastric mucosal injury, crude extract from Angelica sinensis promotes EGF-mediated gastric mucosal healing via DNA synthesis, stimulation and augmentation of EGF mRNA expression (110). Picrorhiza kurroa (Scrofulariaceae) rhizomes possess an antioxidative property indicated by reduction of thiobarbituric acid reactive substances (TBARS) and protein carbonyl in addition to enhancing expression of EGF, VEGF, COX-1 and 2 enzymes associated with an increase of mucin and mucosal PGE2, which explain its ability to heal indomethacin-induced acute gastric injury in mice (111). Similarly, Myristica malabarica spice constituting two major antioxidants, malabaricone B and malabaricone C suppressed thiobarbituric acid reactive substances and protein carbonyls levels. Malabaricone C is more potent in modulating expression of EGF receptor and COX isoforms, mucin secretion, PGE2 synthesis and in controlling all these factors (112). Furthermore, ulcer cure by malabaricone B and malabaricone C is related to their ability to modulate angionetic factors. They significantly increase the mucosal EGF level serum VEGF level and microvessels formation. In contrary, the healing effect of misopristol and omeprazole is not correlated with angiogenesis enhancement (113).

11. Herbs and nitric oxide

In combination with other factors, NO significantly add to mucosal protection. The inflammatory process is mediated by inducible nitric oxide synthase (iNOS) and interleukin-8 (IL-8). Nitric oxide donors (SIN-1 and NOC-18) augment IL-8 and nitrite in mRNA, expression of IL-8. Production of large amounts of NO by iNOS may activate NF-kappaB and AP-1 and the expression of IL-8 in gastric epithelial cells (114). While iNOS is found in inflammatory cells in ulcer bed, NOS is located at the vascular endothelium and mucosal cells in normal and ulcerated gastric tissues. Endothelial NOS and NO significantly contribute to ulcer healing (106,115). Maintenance of NO synthesis is essential for an adequate mucosal defense. Conversely, Inhibition of NO synthesis in mucosal injury models is associated with an increase in ulcer index and asymmetric dimethylarginine (ADMA) levels along with a significantly decreased dimethylarginine dimethylaminohydrolase (DDAH) activity. ADMA Administration is associated with an inflammatory process with inhibition of NO synthesis and elevation of TNF-α levels and indicates the importance of ADMA in precipitating gastric mucosal injury (116). Such a process can be prevented by the use of extracts obtained from herbs and plants rich in phenolic compounds. Methanolic extract and buthanolic fraction of Vochysia tucanorum Mart., possess an antioxidant activity and protect NO levels in gastric mucosa. This protective effect is probably mediated by its phenolic compounds containing various active phytochemical constituents, triterpenoids (76). Triterpenoids are also active constituents of Croton reflexifolius and may explain its gastroprotective effect. Pretreatment with NOS inhibitor attenuates the gastroprotective effect induced by polyalthic acid (117). Furthermore, plant-extract-induced gastroprotective activity is likely related to the enhancing effect on release of NO in addition to NOS inhibitor expression and gastric microcirculation (118).

12. Herbs and SH compounds

The pathogenesis of gastric ulcer is complex. Several endogenous substances including SH compounds are important for the cytoprotection. They are involved in motivation of PG

synthesis, protection of gastric mucosal integrity as well as in the antioxidative process. SH mucosal concentration is suppressed, especially in ethanol-induced gastric mucosal injuries. Preservation of mucosal microcirculation for rapid restitution and cell proliferation is considered as a key target of gastroprotection by either PG or SH compounds (119).
Several spices and plant extracts have protective effect against ethanol-induced SH depletion. Among these spices, Black seed, coriander, peppermint, black pepper, clove, anise aqueous suspension, and rocket replenishe ethanol-induced gastric wall mucus and SH depletion in experimental studies (4,66,67,71-73). Similarly, Ginkgo biloba extract preserves mucosal function via inhibition of ethanol-induced SH and gastric wall mucus depletion and lipid peroxidation (120). Methanolic extracts of C. sicyoides and Commiphora opobalsamum (L.) Engl. (Balessan) also enhances the defense system in rodents and inhibits gastric injuries through SH and NO involvement (58).

13. Herbs and cytokines

Altered immune system function significantly contributes to the pathogenesis of ulcer disease, particularly T-helper lymphocytes and released cytokines. The gastroprotection induced by Phyllanthus emblica L. also upregulates anti-inflammatory cytokine IL-10 concentration through its antioxidative activity, modulates anti-inflammatory cytokines and inhibits pro-inflammatory cytokines TNF-α and IL-1β (121).
The process of ulcer formation is considerably induced and regulated by IL-1β, TNF-α, IL-4, -6, -8, -12 cytokines. Cytokines, IL-1β and IL-1RN genes modulate the inflammatory response and therefore play an important role in the course of the disease (122).
In many gastric injuries, TNF-α is involved in the induction of chemokine expression. It increases the number of macrophages and monocyte chemotactic protein-1 (MCP-1) mRNA expression in mucosal scar. Increased MCP-1 may play a key role in regulating leukocyte recruitment and chemokine expression in gastric ulcer. TNF-α increases also macrophage inflammatory protein (MIP)-2 and cytokine-induced neutrophil chemoattractant (CINC-2α) mRNA expression and MPO activity (123). Cytokine gene polymorphisms influence mucosal cytokine expression and the degree of inflammation in H. pylori infection (124).
Furthermore, IL-1β enhances adhesion molecules expression, intercellular adhesion molecule 1 and leucocytic β2 integrins as well as the concentrations of TNF-α in ulcer scar and contributes to the recurrence of gastric ulcers in rats. The presence of gastric acid is important for the recurrence process of IL-1β-induced gastric ulcer. Gastric acid activates the inflammatory process in scarred mucosa during ulcer recurrence (125).
The outcome of H. pylori infection is influenced by the host response, which in susceptible individuals determines the development of ulcer. In H. pylori infected antral mucosa response is associated with an increase of proinflammatory IL-1β , IL-6, TNF α cytokines, and IL-8; the immunoregulatory gamma interferon (IFN-γ); and the anti-inflammatory TGF-β (126). A correlation between genetic polymorphisms and H. pylori-related diseases is well-established. While IFN-γ +874 AA genotype is associated with cagA positive infections, IL-10 −819 TT and TNF-A −857 TT are associated with intestinal metaplasia and duodenal ulcer, respectively (127).
Among various gastropathies gastritis is the only gastric disorder associated with significant oxidative stress marker expression of TNF-α, IL-8 and H. pylori cagA+/vacAs1 genotype. These probably represent the main oxidative markers responsible for ROS level increase with a decrease of the expression of the Manganese superoxide dismutase (MnSOD) and GPx (128).

In Western countries, polymorphism of pro-inflammatory cytokine genes is associated with the development of duodenal ulcer and gastric cancer. Similarly, polymorphisms in TNF-α rather than IL-1β are associated with an increased risk for gastric ulcers and gastric cancer in Japan. Increased risk of gastric ulcer development is associated with carriage of the alleles TNF-α-857 T, TNF-α-863 A and TNF-α-1031 C. Simultaneous carriage of more than one high-producer allele of TNF-α further increase the risks for gastric ulcer and cancer (129). In chronic H. pylori infection Pro-inflammatory cytokines are produced in the gastric mucosa by inflammatory cells. In contrast to Asians, in western population the inflammatory cytokine gene polymorphisms IL-4-590, IL-6-572 and IL-8-251 are more associated with development of PUD. Polymorphisms of these and other cytokines such as IL-1β, IL-1RN and TNF-α, may help to predict those at higher risk to develop peptic ulcer and those , who require H. pylori eradication(130).

Spices and other plant extracts may interfere with cytokines function, regulate the inflammatory process and help in ulcer healing. In gastric ulcer model, both curcumin and bisdemethoxycurcumin, a yellow pigment in rhizomes of Curcuma longa, promote gastric ulcer healing. While curcumin suppress iNOS and TNF-α protein production, bisdemethoxycurcumin lowers the increased iNOS protein expression level without any effect on TNF-α. The gastroprotective property of bisdemethoxycurcumin is related to its capability to decrease gastric acid secretion and suppress iNOS-mediated inflammation (131). Medicinal plants may also modulate lipopolysaccharide-induced proinflammatory cytokine production in murine macrophage cells and in mice treated with the stimulant lipopolysaccaharide. This has been demonstrated by the use of three herbal constituents, apigenin (chamomile), ginsenoside Rb1 (ginseng) and parthenolide (feverfew). All of these herbal constituents have inhibited lipopolysaccaharide-induced IL-6 and/or TNF-α production in culture(132).

14. Herbs and H. pylori

H, pylori represents the main cause for PUD and its eradication is imperative for ulcer healing and reduction of ulcer recurrence rate. The current eradication rate is below 90% and the resistance rate is growing up. Therefore, the search for potent H. pylori bactericidal agents from plants resources is emerging. Several spices and plant extracts possess H. pylori growth inhibitory activities. Curcumin (133), black cumin (134), eugenol, cinemaldeyde (135), turmeric, cumin, ginger, chilli, borage, black caraway, oregano and parsley (136) have an anti-H. pylori activity. Oil extract of Chamomilla recutita affects H. pylori morphological and fermentative properties and inhibits urease production (137). H. pylori adhesion to the gastric mucosa, an important stage of infection is inhibited by extracts of turmeric, borage and parsley (136), curcumin and its methanolic extract restrain the growth of all strains of H. pylori in vitro (133)]. Moreover, eugenol and cinnamaldehyde have 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 (135). Besides, phenolic compounds of Oregano (Origanum vulgare L.), a Mediterranean herb, possess an inhibitory effect on H. pylori growth (138).

Also, aqueous-ethanol extracts of over 25 of Pakistani medicinal plants including Mal. philippines (Lam) Muell. Mallotus philippines (Lam) Muell., Curcuma amada Roxb., Myrisctica fragrans Houtt., and Psoralea corylifolia L have potent anti-H. pylori activity (139). In addition, methanolic extract of 25 0f 50 Taiwanese folk medicinal plants have also

demonstrated compelling anti-H. pylori action (140). Furthermore, of 53 Mexican traditional medicinal plants especially extracts of Artemisia ludoviciana subsp. mexicana, Cuphea aequipetala, Ludwigia repens,and Mentha x piperita and methanolic extracts of Persea americana, Annona cherimola, Guaiacum coulteri, and Moussonia deppeana have verified a persuasive H. pylori inhibitory effect (141).
At last, the anti- H. pylori effect of 70 Greek plant extracts and a variety of commercially available herbs used in traditional medicine such as extracts of Chamomilla recutita, Conyza albida, Origanum vulgare Anthemis melanolepis, Cerastium candidissimum, Dittrichia viscosa, and Stachys alopecuros have inhibited a standard strain and 15 H. pylori clinical isolates (142).

15. Adverse events

Spices, herbs and other plant extracts have been used in traditional medicine for thousands of years. Recently, in several parts of the world there is a growing acceptance for using these agents to treat various conditions including PUD. Most of these extracts have been effective; however their safety and toxicity have not been well-evaluated. The increasing use of herbal medicine is expected to be more frequently associated with adverse reactions. Clinical evaluation of these adverse effects is not easy due lack of standardization, randomization, adequate number of patients and difficulty in using an appropriate placebo. Herbs are believed to be safe and have no adverse effect. However similar to other drugs they may induce intrinsic or extrinsic adverse effects. Some of their multiple constituents, such as anti-cancer plant-derived drugs, digitalis and the pyrrolizidine alkaloids are cytotoxic. Nevertheless, their adverse effects are less frequent than those of synthetic drugs (143).
Hepatotoxicity induced by curcumin and its derivatives (144) as well as by turmeric and its ethanolic extract in vulnerable mice has been reported (145). Also animals treated with Cinnamon zeylanicum, Piper longum and R. chalepensis have developed abnormalities in liver, spleen, lung or reproductive organs, in addition to an increase in count and motility of sperm and decrease in hemoglobin level (146,147). Kava (Piper methysticum), used as anxiolytic herb in Western countries has been potentially found to be hepatotoxic. Its hepatotoxicity is correlated with overdose, prolonged treatment, concurrent medication, and the quality of raw material (148). Suspected herb-induced liver injury (HILI) is evaluated by the causality score using this multidisciplinary approach and Roussel Uclaf Causality Assessment Method (RUCAM) (149).
In addition to hepatic toxicity, alteration of body weight has been described in rodents treated with Foeniculum vulgare ethanolic extracts and Ruta chalepensis (150). Furthermore, in experimental model, piperine has decreased mating performance and fertility and intrauterine injection has caused loss of implants without histological abnormalities (151). Herbal-induced toxicity is influenced by herbs related factors (quality, dose and nature of constituents) and individual risk factors (genetics, age, concomitant drugs, and concomitant diseases) (152). Therefore, simultaneous administration of herbs with conventional medications should generally be discouraged (153).
Herbal medicine-associated adverse reactions are expected to occur more frequently as a result of the fast mounting use of these agents in treatment. Some commonly used herbs like St John's wort (Hypericum perforatum), a popular herbal anti-depressant, lead to a decrease of the activity of immunosuppressive agents i.e.cyclosporine and subsequent tissue rejection in transplanted patients. Like other medicinal plants it also interferes with cytochrome P450 activity and metabolism of other drugs (154).

Examples of Drugs known to interact with St John's wort include besides cyclosporine tacrolimus as well as HIV non-nucleoside and protease inhibitors (155). Other drugs interfering with St. John's wort CYP 3A4 induction include , oral contraceptives.and indinavir(156).

Literature review of 128 case reports or case series, and 80 clinical trials have revealed that St John's wort-induced cytochrome P450 and P-glycoprotein induction, decreases plasma levels of a large variety and frequently used medications. Clearance of caffeine and midazolam may be influenced by Echinacea (157).

Herbal agents such as St. John's wort, interact differently with various drugs. It may increase the clearance of some medications via cytochrome P-450 mixed-function oxidase or through P-glycoprotein efflux pump modulation. On the other hand, it may decrease digoxin, theophylline, warfarin, protease inhibitors, cyclosporine, tacrolimus, and tricyclic antidepressants concentration with subsequent reduction of their therapeutic effect. A third category of drugs such as procainamide carbamazepine and mycophenolic acid are not affected by St. John's wort. herb (158).

Therapeutic drug monitoring is usually estimated by immunoassay technique. The potential interference St. John's wort, with commonly by this method monitored drugs has been evaluated. A significant interference with digoxin, quinidine, procainamide, N-acetyl procainamide theophylline, tricyclic antidepressants, phenytoin, carbamazepine, valproic acid and phenobarbital serum levels is lacking (159). Due to unwanted effects, ginseng and ginkgo should not be combined with anticoagulants and valerian with barbiturates (160). Elderly patients are more likely to develop diseases and ingest more medications. They are also prone to develop suppression of cytochrome P450 (CYP) activity. Taking herbal agents make them more vulnerable to herb-drug interactions (161). Herbal toxicity may also affect other central organs like the kidney. Case reports of interstitial fibrosis progressing to chronic renal failure and termed as aristolochic acid nephropathy may complicate treatment with slimming herbs belonging to Aristolochia family (162). Despite all of these reports of adverse events, spices are generally safe when used in standared doses. Popular traditional Chinese medicine has relatively less adverse effects and appears safer than other drugs (163).

The safety of herbal agents during pregnancy has been evaluated in 392 pregnant women 8% have reported taking chamomile, licorice, fennel, aloe, valerian, Echinacea oil 27, propolis and cranberry. Only four out 109 have reported insignificant adverse events in form of constipation after tisane, rash and itching after local application of aloe or almond oil. A higher incidence of threatening miscarriage and preterm labors was observed among regular users of chamomile and licorice (164).

In disparity, many spices and plant extracts, in commonly used dose, up to 500mg/kg body weight have not exhibited adverse effect. These include cardamom (62, 68), black pepper (66), clove (67), caraway (69), saffron (70),coriander(71), peppermint (72), anise (73), davilla elliptica and nitida (74) ,Brazilian medical plants (75) and Alchornea triplinervia (76) and Hyptis spicigera Lam (86). Even in pregnancy, ginger, peppermint, and Cannabis have been used to treat nausea were effective and lack clinical evidence of harm (165). Clinically, spices like turmeric and curcumin have been well-tolerated even with high doses and lack any toxicity (166).

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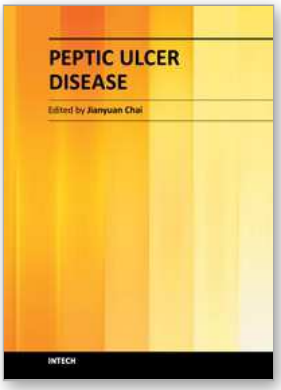

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Peptic ulcer disease is one of the most common chronic infections in human population. Despite centuries of study, it still troubles a lot of people, especially in the third world countries, and it can lead to other more serious complications such as cancers or even to death sometimes. This book is a snapshot of the current view of peptic ulcer disease. It includes 5 sections and 25 chapters contributed by researchers from 15 countries spread out in Africa, Asia, Europe, North America and South America. It covers the causes of the disease, epidemiology, pathophysiology, molecular-cellular mechanisms, clinical care, and alternative medicine. Each chapter provides a unique view. The book is not only for professionals, but also suitable for regular readers at all levels.

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