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Reviews of herbal and their secondary metabolites in the treatment of ulcerative colitis and peptic ulcer

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ABSTRACT

Peptic ulcer is a disease of the Gastro-intestinal tract (GIT), which includes both gastric and duodenal ulcers. The occurrence of peptic ulcer disease has been attributed to the imbalance between aggressive factors like acid, pepsin, and Helicobacter infection on one hand and the local mucosa defenses like bicarbonate and mucus secretion and prostaglandins synthesis on the other hand. The most serious complications of peptic ulcer disease include hemorrhage, perforation, penetration, and gastric outlet obstruction. Ulcerative colitis is a form of inflammatory bowel disease (IBD). It is a form of colitis, a disease of the colon that includes characteristic ulcers, or open sores. IBD is often confused with irritable bowel syndrome. Ulcerative colitis is associated with a general inflammatory process that affects many parts of the body. Sometimes these associated extra-intestinal symptoms are the initial signs of the disease, such as painful arthritic knees in a teenager and may be seen in adults also. Several classes of pharmacological agents have proved to be effective in the management of the acid peptic disorders viz., antacids, acid suppressive agents, anticholinergic, cytoprotective agents, etc. A widespread search has been launched to identify new anti-ulcer therapies from natural sources to replace currently used drugs of doubtful efficacy and safety. Herbs, medicinal plants, spices, vegetables and crude drug substances are considered to be a potential source to control various diseases including gastric ulcer and ulcerative colitis. In the scientific literature, a large number of medicinal plants and their secondary metabolites with anti-ulcer potential have been reported. As the gastro protective effect can be linked to different mechanisms, once demonstrated the activity, the extracts and more appropriately the active compounds should be assessed for action mechanisms to elucidate their mode of action. Besides, new action mechanisms may be discovered.

INTRODUCTION

Ulcers are deep lesions penetrating through the entire thickness of the gastro intestinal tract (GIT) mucosa and muscularis mucosa (Kaur *et al*., 2012). Peptic ulcers are a broad term which includes ulcers of digestive tract in the stomach or the duodenum. Recent research has shown that this ulcer developed due to aggressive factors. Infection caused by bacteria Helicobacter pylori or reaction to certain medicines as non-steroidal anti-inflammatory drugs (NSAIDs) is the causative agent of the disease (Bandyopadhyay*et al*., 2001). Symptoms of peptic ulcer include abdominal pain and discomfort, loss of weight, poor appetite, bloating, nausea and vomiting and in some cases blood can be present in stool and black stool that indicate gastrointestinal bleeding (Leslie, 1972). Esophageal Ulcer are lesions that occur in esophagus, commonly formed at the end and can be felt as a pain right below the breastbone. This ulcer is associated with acid reflux, prolonged use of NSAIDs and smoking (Mohammad *et al*., 2003). Another type of ulcer is aphthous or mouth in which sores develop in the inner lining of the mouth. Mouth ulcer is common and is usually due to trauma such as from ill fitting dentures, fractured teeth, or fillings. Anemia, measles, viral infection, oral candidiasis, chronic infection, throat cancer, mouth cancer and vitamin B deficiency are some of the common causes of ulcer in the mouth (Crispian and Rosemary, 2000).

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Peptic Ulcer

Peptic ulcer is a disease of the GIT, which includes both gastric and duodenal ulcers. It develops when there is an imbalance between the "aggressive" and "protective" factors at the luminal surface of the epithelial cells. Aggressive factors include *Helicobacter pylori*, Hydrochloric acid,HCl, pepsins, NSAIDs, bile acids, ischemia, hypoxia, smoking and alcohol. While defensive factors include bicarbonate, mucus layer, mucosal blood flow, PGs and growth factors and it affects considerable number of people worldwide(Harold *et al*., 2007). Peptic ulcer formation in either the stomach or duodenum is due to an imbalance between erosive factors such as hydrochloric acid and pepsin and the protectiv emechanisms of the mucosa. Unlike duodenal ulcers, in which the importance of acid secretion is indisputable, gastric (stomach) ulcers can develop despite only minimal amounts of acid. Indeed, past studies have shown that the basal and maximal acid outputs in patients with gastric ulcers are no different than those in normal controls. The gastric mucosa has evolved to tolerate the high acidity of the stomach lumen via an intricate equilibrium of protective mechanisms. The gastric protective mechanisms (preepithelial, epithelial, and subepithelial factors) act in concert (Aric *et al*.,2004). The most serious complications of peptic ulcer disease include haemorrhage, perforation, penetration, and gastric outlet obstruction. Perforation occurs in approximately 2–10 percent of peptic ulcers. It usually involves the anterior wall of the duodenum (60 percent), although it may also occur in antral (20 percent) and lesser- curve (20 percent) gastric ulcers (Ramakrishnan *et al*.,2007).

Signs and symptoms

Symptoms of a peptic ulcer include

- abdominal pain, classically epigastric strongly correlated to mealtimes. In case of duodenal ulcers the pain appears about three hours after taking a meal;
- bloating and abdominal fullness;
- waterbrash (rush of saliva after an episode of regurgitation to dilute the acid in esophagus - although this is more associated with gastroesophageal reflux disease);
- nausea, and copious vomiting;
- loss of appetite and weight loss;
- hematemesis (vomiting of blood); this can occur due to bleeding directly from a gastric ulcer, or from damage to the esophagus from severe/continuing vomiting.
- melena (tarry, foul-smelling feces due to presence of oxidized iron from hemoglobin);
- rarely, an ulcer can lead to a gastric or duodenal perforation, which leads to acute peritonitis, extreme and stabbing pain (Bhat and Sriram ,2013)

Diagnosis

The following tests could be done to diagnose peptic ulcer:

- Esophagogastroduodenoscopy (EGD): in which a thin tube with a camera on the end is inserted through the mouth into the GI tract to see the stomach and small intestine. During an EGD, a biopsy may be taken from the wall of the stomach to test for H. pylori.
- X-ray for the upper gastrointestinal tract (GIT) which taken after drink a thick substance called barium.
- Hemoglobin blood test to check if there is anemia.
- Stool guaiac to test if there is blood in the stool (Amani *et al*.,2013)

Ulcerative Colitis

Ulcerative colitis (***Colitis ulcerosa***, **UC**) is a form of inflammatory bowel disease (IBD). It is a form of colitis, a disease of the colon (the largest portion of the large intestine), that includes characteristic ulcers, or open sores. IBD is often confused with irritable bowel syndrome (IBS). Ulcerative colitis has an incidence of 1 to 20 cases per 100,000 individuals per year, and a prevalence of 8 to 246 per 100,000 individuals (Danese and Fiocci,2011).

Symptoms of Ulcerative Colitis

Gastrointestinal

The clinical presentation of ulcerative colitis depends on the extent of the disease process. Patients usually present with diarrhea mixed with blood and mucus, of gradual onset that persists for an extended period (weeks). They may also have weight loss and blood on rectal examination. The inflammation caused by the disease along with chronic loss of blood from the GI tract leads to increased rates of anaemia. The disease may be accompanied with different degrees of abdominal pain, from mild discomfort to painful bowel movements or painful abdominal cramping with bowel movements.

Ulcerative colitis is associated with a general inflammatory process that affects many parts of the body. Sometimes these associated extra-intestinal symptoms are the initial signs of the disease, such as painful arthritic knees in a teenager and may be seen in adults also. The presence of the disease may not be confirmed immediately, however, until the onset of intestinal manifestations(Hanauer,1996)

Severity of the disease

In addition to the extent of involvement, people may also be characterized by the severity of their disease.

- *Mild disease* correlates with fewer than four stools daily, with or without blood, no systemic signs of toxicity, and a normal erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). There may be mild abdominal pain or cramping. Patients may believe they are constipated when in fact they are experiencing tenesmus, which is a constant feeling of the need to empty the bowel accompanied by involuntary straining efforts, pain, and cramping with little or no fecal output. Rectal pain is uncommon.
- *Moderate disease* correlates with more than four stools daily, but with minimal signs of toxicity. Patients may display anemia (not requiring transfusions), moderate abdominal pain, and low grade fever, 38 to 39 °C (100 to 102 °F).

- *Severe disease*, correlates with more than six bloody stools a day or observable massive and significant bloody bowel movement, and evidence of toxicity as demonstrated by fever, tachycardia, anemia or an elevated ESR or CRP.
- *Fulminant disease* correlates with more than ten bowel movements daily, continuous bleeding, toxicity, abdominal tenderness and distension, blood transfusion requirement and colonic dilation (expansion). Patients in this category may have inflammation extending beyond just the mucosal layer, causing impaired colonic motility and leading to toxic megacolon. If the serous membrane is involved, colonic perforation may ensue. Unless treated, fulminant disease will soon lead to death (Kornbluth and Sachar,2004).

Diagnosis

The initial diagnostic workup for ulcerative colitis includes the following:

- A complete blood count is done to check for anemia; thrombocytosis, a high platelet count, is occasionally seen
- Electrolyte studies and renal function tests are done, as chronic diarrhea may be associated with hypokalemia, hypomagnesemia and pre-renal failure.
- Liver function tests are performed to screen for bile duct involvement: primary sclerosing cholangitis.
- X-ray
- Urinalysis
- Stool culture, to rule out parasites and infectious causes.
- Erythrocyte sedimentation rate can be measured, with an elevated sedimentation rate indicating that an inflammatory process is present.
- C-reactive protein can be measured, with an elevated level being another indication of inflammation (Kornbluth and Sachar,2004)

Currently, there is no an effective therapy to cure the disease but the mainstream treatment depends on reduction of the abnormal inflammation in the colon lining and thereby relieves the symptoms of diarrhea, rectal bleeding, and abdominal pain. The treatment depends on the severity of the disease; therefore treatment is adjusted for each individual (Botoman *et al*., 1998). Most people with mild or moderate ulcerative colitis are treated with corticosteroids (dexamethasone) to reduce inflammation and relieve symptoms (Hanauer *et al*., 2004). Nearly 25% of patients with UC requiring steroids therapy become steroid-dependent after one year, and virtually all develop steroid-related adverse events (Faubion *et al*., 2001). Other drugs as immunomodulators (azathioprine and 6-mercapto-purine) that reduce inflammation by affecting the immune system (Bresci *et al*., 1997) and aminosalicylates (Rachmilewitz, 1989) are available.

Treatment with Synthetic Drugs

Several classes of pharmacological agents have proved to be effective in the management of the acid peptic disorders. These groups include: antacids (aluminum hydroxide, magnesium trisilicate), acid suppressive agents (Antisecretory drugs) which include proton pump H+/K+ ATPase inhibitors (omeprazole, lanzoprazole), histamine H2 receptor antagonist (cimetidine, ranitidine) and anticholinergic (M1) (pirenzepine), cytoprotective agents (sucralfate and prostaglandin analogs (misoprostol), antimicrobials for eradication of H. pylori (amoxicillin, clarithromycin) and Triple therapy (one week triple therapy consisting of a proton pump inhibitor such as Omeprazole and the antibiotics Clarithromycin and Amoxicillin) (Waller *et al*., 2005; Katzung, 2004).

A widespread search has been launched to identify new anti-ulcer therapies from natural sources to replace currently used drugs of doubtful efficacy and safety. Herbs, medicinal plants, spices, vegetables and crude drug substances are considered to be a potential source to control various diseases including gastric ulcer and ulcerative colitis. In the scientific literature, a large number of medicinal plants and their secondary metabolites with anti-ulcer potential have been reported.

METHODOLOGY

MEDLINE search

To collect the data which support this idea we performed a systematic review using PubMed, Google and MEDLINE databases. All English-language articles published between 1987 and 2011 were searched using the terms ‘antiulcerogenic’, ‘anti-ulcer’, ‘gastroprotective’, ‘gastric antiulcerogenic’, ‘cytoprotective, ‘antisecretory’, ‘peptic ulcer’, ‘ulcerative colitis’, ‘antiulcerative colitis’, ‘natural products’, ‘Helicobacter pylori’, ‘plant extracts’ or ‘protective’. Plants names, families and authorities were confirmed using http://www.tropicos.org/ and http://www.theplantlist.org / sites.

Capturing study design and effects details regarding the study design

Population, duration and phytochemical group and effects on UC and PUD were captured in a database. Assessing the scientific support for an extract. Evidence for the support of an extract was assessed from multiple studies (i.e., >1 article). The spelling of all extracts and family names was checked at http://www.ipni.org. Botanical descriptions were checked using MEDLINE and by referring to http://www.wikipedia.org and http://www.nybg.org.

RESULTS AND DISCUSSION

Herbal Treatment of Ulcerative Colitis

Aloe vera(Xanthorrhoeaceae)

Aloe vera is a perennial, drought-resistant, succulent plant with a whorl of elongated, pointed leaves. The nomenclature of Aloe sap and Aloe gel are often ambiguous. Unlike Aloe vera sap, Aloe vera gel is colorless and contains no anthraquinones and this gel is responsible for many of medicinal properties of Aloe vera reported in folk medicine(Rao *et al*.,2007). *Aloe vera* juice has anti-inflammatory activity and been used by some doctors for patients with UC. It was the single most widely used

herbal therapy(Langmead *et al*.,2002). A double-blind, randomized trial was undertaken by Langmead *et al* (2004) to examine the effectiveness and safety of *aloe vera* gel for the treatment of mild-to-moderate active UC. Thirty patients took 100 mL of oral *aloe vera* gel and 14 patients had 100 mL of a placebo twice daily for 4 weeks. Clinical remission, improvement, and response occurred in 9 (30%), 11 (37%), and 14 (47%), respectively, in aloe vera-treated patients compared with 1 (7%), 1 (7%), and 2 (14%), respectively, in controls. Although the numbers are small in this study, the number of patients who responded to *aloe vera* is more than those who took placebo. However, the numbers are similar to placebo responses in other trials and the placebo response rate is very low. The exact mechanisms of action of *aloe vera* are unclear. The same author had carried out *in vitro* studies on human colonic mucosa and revealed that *aloe vera* gel could inhibit prostaglandin E2 and IL-8 secretion, indicating its role in antimicrobial and anti-inflammatory responses.

Boswellia serrata(Burseraceae)

Boswellia or Indian frankincense is an ayurvedic herb that is derived from the resin of the plant, and has also been used traditionally to treat UC. Boswellic acid, the major constituent of *Boswellia*, is thought to contribute to most of the herbal pharmacologic activities.

In vitro studies and animal models have shown that boswellic acid could inhibit 5-lipoxygenase selectively with anti-inflammatory and antiarthritic effects(Dahmen *et al.*,2001). Since the inflammatory process in IBD is associated with increased function of leukotrienes, the benefits of *Boswellia* in the treatment of UC have proven a positive result. Moreover, it has also been found to directly inhibit intestinal motility with a mechanism involving L-type Ca^{2+} channels. *Boswellia* has been found to reduce chemically induced edema and inflammation in the intestine in rodents. Other studies suggest that it has cytotoxic properties (Frank *et al*.,2009).

Gupta *et al., (2001)* studied the treatment of 30 patients with chronic UC, and gave 20 patients a *Boswellia* gum preparation (900 mg daily divided into 3 doses for 6 weeks), and 10 patients sulfasalazine (3 gm daily divided into 3 doses for 6 weeks).

They concluded that *Boswellia* was an effective treatment with few side effects, because 14 out of the 20 patients treated went into remission, and furthermore, 18 out of the 20 patients found an improvement in one or more parameters. In comparison, in the group taking sulfasalazine, 4 out of 10 went into remission, and 6 out of 10 showed improvement in one or more of the above parameters. In animal models of inflammation, it has been shown to be effective against Crohn's disease, UC, and ileitis (Krieglstein *et al*.,2001)

Tormentil(Rosaceae) extracts

Tormentil extracts have antioxidative properties and are used as a complementary therapy for chronic IBD. In individual patients with UC positive effects have been observed by Huber *et al*.,(2007). In their studies, sixteen patients with active UC (clinical activity index $\geq$ 5) received *tormentil* extracts in escalating doses of 1200, 1800, 2400, and 3000 mg/day for 3 weeks each. Each treatment phase was followed by a 4-week washout phase.

The outcome parameters were side effects, clinical activity index, C-reactive protein, and tannin levels in patient sera. Mild upper abdominal discomfort was experienced by 6 patients (38%), but did not require discontinuation of the medication. During therapy with 2400 mg of *tormentil* extracts per day, median clinical activity index, and C-reactive protein improved from 8 (6 to 10.75) and 8 (3 to 17.75) mg/L at baseline to 4.5 (1.75 to 6) and 3 (3 to 6) mg/L, respectively.

During therapy, the clinical activity index decreased in all patients, whereas it increased during the washout phase. Neither undegraded nor metabolized tannins could be detected by liquid-mass spectrometry in sera. *Tormentil* extracts appeared safe up to 3000 mg/day.

Wheat grass (Triticum aestivum)

The wheat grass juice has been used for the treatment of various GI conditions. A double-blind study by Ben-Arye *et al.*,(2002) has demonstrated that supplementation with wheat grass juice for 1 month results in clinical improvement in 78% of people with UC, compared with 30% of those receiving a placebo. The amount of wheat grass used is 20 mL per day initially, and this is increased by 20 mL/day to a maximum of 100 mL per day (approximately 3.5 ounces).

No serious side effects are noticed. Wheat grass juice appears to be effective and safe as a single or adjuvant treatment of active distal UC(Fei Ke *et al*.,2012).

Psyllium (Plantaginaceae)

Psyllium comes from a shrub-like herb called Plantago ovata and is classified as a mucilaginous fiber due to its gel-forming properties in water. It has a long history of use as a laxative as it absorbs water and expands as it travels through the digestive tract.

The *psyllium* husk contains a largely insoluble fiber (hemicellulose), which helps to retain water within the bowel and effectively increases stool moisture content and weight. Soluble fibers (including *psyllium*) are noted for their effect on the stomach and small intestine, whereas insoluble fibers are noted for their effect on the large intestine, although some carbohydrates (such as *psyllium*) have an effect on both (Shale and Riley, 2003).

*Psyllium*also has hypocholesterolemic effects, although the exact mechanism by which *psyllium* husk brings about a reduction of cholesterol is not totally clear. In a double-blind trial carried out by Fernández-Bañares *et al*.,(1999), patient with UC had a reduction in symptoms such as bleeding and remained in remission longer than those who took 20 g of ground *psyllium* seeds twice daily with water compared with those who were on the medication mesalazine alone.

Germinated barley(Hordeum vulgare) foodstuff

Two open-label Japanese trials have shown the efficacy of Germinated barley foodstuff (GBF) in the treatment of UC, consisting mainly of dietary fiber and glutamine-rich protein that function as a probiotic (Araki *et al.*,2001; . Bamba *et al.*2002; Fukuda *et al.*,2002; Kanauchi *et al.*,2002). In the first report, 11 patients given *GBF* for 4 weeks as an adjunctive treatment showed a greater decrease in clinical disease activity than 9 patients given conventional therapy alone.

In a follow-up study, 24 weeks of treatment of 21 patients with *GBF* together with continuing 5-aminosalicylic acid and steroid therapy reduced rectal bleeding and nocturnal diarrhea. Adjunctive *GBF* also produced a lower relapse rate over 12 months when given to 22 patients with UC in remission than did conventional therapy in 37 patients (. Hanai *et al.*,2004). The potency of GBF on modulating microflora, as well as the high water-holding capacity, may play an important role in the treatment and prolongation of remission in UC (Bamba *et al.*,2002).

Zingiber Officinale Roscoe (Zingiberaceae)

The potential role of Zingiber Officinale Roscoe (Zingiberaceae) extract was evaluated by El-Abhar *et al*., (2008) in modulating the extent and severity of ulcerative colitis. Results showed a valuable effect of ginger extract against acetic acid-induced ulcerative colitis possibly by its antioxidant and anti-inflammatory properties.

The protective effects of Angelica sinensis (Oliv.) Diels (Apiaceae) polysaccharides could be explained partially by that oxidative stress and GSH (glutathione) depletion which are highly associated with the pathological mechanism of UC, and the protective effects of AS polysaccharides are closely related to the prevention of oxidative stress, which may occur during neutrophil infiltration in the pathological process of UC (Wong *et al*., 2008).

Rheum tanguticum Maxim. ex Balf. (Polygonaceae)

The effect of Rheum tanguticum Maxim. ex Balf. (Polygonaceae) polysaccharide (RTP) on hydrogen peroxide-induced human intestinal epithelial cell injury and they found that, Pretreatment of the cells with RTP could significantly elevate cell survival, SOD activity and decrease the level of MDA, LDH activity and cell apoptosis.

RTP may have cytoprotective and anti-oxidant effects against H_2O_2-induced intestinal epithelial cell injury by inhibiting cell apoptosis and necrosis. This might be one of the possible mechanisms of RTP for the treatment
of ulcerative colitis in rats (Liu *et al*., 2005).

Green tea (Camellia sinensis (L.) Kuntze, Theaceae)

Green tea (Camellia sinensis (L.) Kuntze, Theaceae) was found to be effective in the treatment of ulcerative colitis. Both diarrhea and loss of body weight can be significantly attenuated by the treatment with green tea extract. The mechanism of action was associated to remarkable amelioration of the disruption of the colonic architecture, significant reduction of colonic myeloperoxidase (MPO) and tumor necrosis factoralpha (TNF-alpha) production. Green tea extract also reduced the appearance of nitrotyrosine immunoreactivity in the colon and reduced the up-regulation of intercellular adhesion molecule 1 (ICAM-1) (Mazzon *et al*., 2005).

Some Secondary Metabolites Used To Treat Ulcerative Colitis:

Butyrate

Butyrate is an important energy source for intestinal epithelial cells and plays a role in the maintenance of colonic homeostasis. Butyrate enemas have been studied for use in treating UC. Some studies have shown that the topical use of butyrate may help decrease the inflammation in the colon. Nancey *et al.*, (2005) proposed a possible explanation for the decreased oxidation in UC patients who showed that butyrate oxidation could be reduced by TNF-α at concentrations found in inflamed human mucosa. This anti-inflammatory effect of butyrate via NF-κB inhibition, contributing, for example, to decreased concentrations of myloperoxidase, cyclo-oxygenase-2, adhesion molecules, and different cytokine levels, has been confirmed in several *in vitro* and *in vivo* studies (Segain *et al*.,2000; Song and Xia,2006). A diminished capacity of the intestinal mucosa to oxidize butyrate has been reported by Kato *et al*.,(2007) in patients with active UC. However, in patients with inactive UC a normal butyrate oxidation has been found *in vivo*, suggesting that in UC patients, abnormal butyrate oxidation is not a primary defect in colon mucosa (Simpson *et al*.,2006).

Administration of enteric-coated tablets (4 g of butyrate daily) in combination with mesalazine vs mesalazine alone significantly improved the disease activity score in patients with mild-to-moderate UC (Vernia *et al*.,2000).

Licorice

Licorice, which is derived from the root of the plant, is used extensively in TCM for a variety of conditions and ailments. Licorice has also got immune modulatory and adaptogenic property, which is required for the pathogenesis of UC. A number of active chemicals, including glycyrrhizin are thought to account for its biologic activity. Diammonium glycyrrhizinate is a substance that is extracted and purified from licorice, and may be useful in the treatment of UC (Kudo *et al*.,2011). Yuan et al.,(2006) has also reported that diammonium glycyrrhizinate could improve intestinal mucosal inflammation in rats and, importantly, reduce expression of NF-κB, TNF-α, and ICAM-1 in inflamed mucosa.

Clinical studies on licorice have also been performed in combination with other herbs and demonstrated to be effective in the management of UC(Madisch *et al*.,2004). The antiestrogenic action documented for glycyrrhizin at high concentration has been associated with glycyrrhizin-binding estrogen receptors. However, estrogenic activity has also been reported for licorice and is attributed to its isoflavone constituents (Somjen *et al*.,2004). It has

been suggested that glycyrrhizin may exert its mineralocorticoid effect via an inhibition of 11b-hydroxysteroid dehydrogenase. Evidences have proven that glycyrrhizin could also suppress both plasma renin activity and aldosterone secretion. In addition, licorice has been shown to have chemopreventive effects through influencing Bcl-2/Bax and inhibiting carcinogenesis (Somjen *et al*.,2004; Jo *et al*.,2004; Takahashi *et al*.,2004).

Slippery elm (Ulmus fulva)

Slippery elm is a supplement that is made from the powdered bark of the slippery elm tree. It has long been used by Native Americans to treat cough, diarrhea, and other GI complaints. Recently, slippery elm has been studied for use as a supplement for IBD(Langmead *et al*.,2002). A study has confirmed the antioxidant effects of slippery elm when used in patients with IBD. The research so far has been promising, but there is not enough to warrant the widespread use of slippery elm in the treatment of IBD (Langmead *et al*.,2006).

Proanthocyanidins

The therapeutic effect and mechanism of proanthocyanidins isolated from grape seed (GSPE) were investigated for their activity in the treatment of recurrent ulcerative colitis (UC) in rats. GSPE treatment facilitated recovery of pathologic changes in the colon after induction of recurrent colitis, as demonstrated by reduced colonic weight/length ratio and macroscopic and microscopic damage scores (Wang *et al*., 2010). Li *et al*., (2008) confirmed this fact as, GSPE exerts a beneficial anti-inflammatory effect in the acute phase of TNBS-induced colitis in rats by down regulating some of the mediators involved in the intestinal inflammatory response, inhibiting inflammatory cell infiltration and antioxidation damage, promoting damaged tissue repair to improve colonic oxidative stress, decreasing production of proinflammatory cytokines interleukin IL-1beta, and increasing production of anti-inflammatory cytokines IL-2 and IL-4.

Bromelain

Bromelain is an anti-inflammatory and has been used as a digestive aid and a blood thinner, as well as to treat sports injuries, sinusitis, arthritis, and swelling. *Bromelain* has been studied for use as a supplement for IBD, especially UC. Emerging research on pineapple suggests that pineapple's "active" component, *bromelain*, may help relieve the inflammation associated with UC. The mechanisms that are primarily responsible for its anti-inflammatory effects are still unclear. However, proteolytic activity is required for the anti-inflammatory effect of*bromelain* on T-cell activation and cytokine secretion *in vitro* and in murine models of IBD *in vivo* (Mynott *et al*.,2002; Hale *et al*.,2002).

The major mechanism of action of *bromelain* appears to be proteolytic in nature, although evidence also suggests an immunomodulatory and hormone-like activity acting via intracellular signaling pathways. *Bromelain* has been shown to reduce cell surface receptors, such as hyaluronan receptor CD44, which is associated with leukocyte migration and induction of pro-inflammatory mediators (Manhart *et al*.,2002; Hale *et al*.,2005). Additionally, *bromelain* is also reported to significantly reduce $CD4^+$ T-cell infiltrations, which are primary effectors in animal models of inflammation in the gut. *Bromelain*has been found to be effective in improvement of clinical and histologic severity of colonic inflammation in a murine colitis model of IL-10-deficient mice (Kane and Goldberg, 2000).

Previous work also reported by Blackwood *et al*., (2000) on the clinical trial with *bromelain* in the treatment of mild UC. Although those 2 patients were unable to achieve remission on standard therapy, clinical and endoscopic evidence of improvement was documented.

Curcumin

Curcumin is a compound in turmeric (Curcuma longa) that has been reported to have anti-inflammatory activity. It has been found to induce the flow of bile, which helps break down fats. Additionally, it could reduce the secretion of acid from the stomach and protect against injuries such as inflammation along the stomach (gastritis) or intestinal walls and ulcers from certain medications, stress, or alcohol.

In a preliminary trial, 5 of 5 people with chronic ulcerative proctitis had an improvement in their disease after supplementing with *curcumin. Curcumin* inhibits the activation of NF-κB. NF-κB promotes the synthesis of many antioxidant enzymes. *Curcumin* directly binds to thioredoxin reductase and irreversibly changes its activity from an antioxidant to a strong pro-oxidant. The amount of *curcumin* used was 550 mg twice a day for 1 month, followed by 550 mg 3 times a day for 1 month (Holt *et al*.,2005). Hanai and colleagues (2006) published the results of the first randomized, multicenter, double-blind, placebo-controlled trial from Japan to study *curcumin*'s effect on UC maintenance.

All 97 patients who enrolled and 89 patients who completed the study took a standard dose of mesalamine or sulfasalazine and either 1 g of curcumin or placebo twice daily for 6 months and then were followed for another 6 months off study medications. The relapse rate at 6 months on therapy was greater for the placebo group than for those who took *curcumin* (P = 0.049). Thus, *curcumin* may confer some additional therapeutic advantages when used in combination with conventional anti-inflammatory medications in UC (Fei Ke *et al*.,2012).

Antiulcer Activity Of Some Secondary Metabolites:

Many secondary metabolites have been found to have antiulcer properties, these include a group of flavonoids (Anthocyanins, ctechin etc) (table 1), alkaloids (Canthin-6-one, Taspine etc) (table 2), terpenoids (Nerolidol, Cynaropicrin etc) (table 3), saponins (Araloside, Aescin etc) (table 4), phenolics (Gallic acid, Thymoquinon etc) (table 5) and some mscelaneous plants (Acer tegmentosum Maxim, Alhagi maurorum Boiss etc)(table 6).

Table. 1: Flavonoids with anti-ulcer activity.

Flavonoids	Ulcer model	Molecular formula	Reference
Anthocyanosides	Pylorus-ligated,reserpine, Phenylbutazone	$C_{15}H_{11}ClO_6$	Magistretti *et al.*, 1988
Catechin	Stress	$C_{15}H_{14}O_6$	Lorenz *et al.*, 1975
Genistin	Phenylbutazone, serotonin pylorus-ligated,	$C_{21}H_{20}O_{10}$	Rainova *et al.*, 1988
Kaempferol	Ethanol	$C_{15}H_{10}O_6$	Izzo *et al.*, 1994
Leucocyanidin	Aspirin	$C_{15}H_{14}O_7$	Lewis *et al.*, 1999
Luteolin-7- glycoside	Pylorus-ligated, stress		Rainova *et al.*, 1988
5-Methoxyflavone	Indomethacin	$C_{16}H_{12}O_3$	Blank *et al.*, 1997

Table. 2: Alkaloids reported to have anti ulcerogenic activity

Source	Isolated compound	Molecular formula	Reference
Simaba ferruginea A. St.-Hil., Simaroubaceae (rhizome)	Canthin-6-one	$C_{14}H_8N_2O$	Almeida *et al*. (2011)
Croton lechleri Müll. Arg., Euphorbiaceae	Taspine	$C_{20}H_{19}NO_6$	Miller *et al*. (2000)
Capsicum annuum L., Solanaceae	Capsaicin	$C_{18}H_{27}NO_3$	Kang *et al*. (1995)

Table. 3: Terpenoids with anti-ulcer activity.

Source	Isolated compound	Molecular formula	Reference
Baccharis dracunculifolia DC., Asteraceae (essential oil)	Nerolidol	$C_{15}H_{26}O$	Klopell *et al*. (2007)
Centaurea helenioides Boiss., Asteraceae, (flowers)	Cynaropicrin	$C_{19}H_{22}O_6$	Yayli *et al*. (2006)
Many plants	Oleaolinc acid	$C_{30}H_{48}O_3$	Rodr‚guez *et al*. (2003)

Table. 4: Saponins with anti-ulcer activity.

Source	Isolated compound	Molec lar formula	Reference
Aralia elata (Miq.) Seem., Araliaceae (root bark)	Araloside	$C_{46}H_{74}O_{16}$	Lee *et al*. (2005)
Aesculus hippocastanum L., Sapindaceae (seeds)	Aescin	$C_{55}H_{86}O_{24}$	Marhuenda *et al*. (1993, 1994)
Glycyrrhiza glabra L., Glycyrrhiza radix Br. and Glycyrrhiza uralensis Fisch., Fabaceae	Glycyrrhizic acid	$C_{42}H_{62}O_{16}$	Aly *et al*. (2005) and Baker(1994)
Panax ginseng C.A. Mey. (Araliaceae) leaves and roots	Ginsenoside Rb1	$C_{54}H_{92}O_{23}$	Jeong *et al*. (2003) and Sun *et al*. (1992)

Table. 5: Phenolics with anti-ulcer activity.

Source	Isolated compound	Milecular formula	Reference
Terminalia belerica Roxb. (Combretaceae) fruits	Gallic acid	$C_7H_6O_5$	Bhattacharya *et al*. (2007b)
Nigella sativa L. (Ranunculaceae)	Thymoquinon	$C_{10}H_{12}O_2$	Kanter *et al*. (2006), Arslan *et al*. (2005) and El-Abhar *et al*. (2003)
Turmeric Curcuma longa Linnaeu(Zingiberaceae)	Curcumin	$C_{21}H_{20}O_6$	Swarnakar *et al*. (2005)
Piper betle L. (Piperaceae) leaves	Allylpyrocatechol	$C_9H_{10}O_2$	Banerjee et al. (2008) and Bhattacharya *et al*. (2007a)
Rhamnus triquerta Wall. (Rhamnaceae)	Emodin	$C_{15}H_{10}O_5$	Goel and Das Gupta (1991)

Table. 6: Plants of miscellaneous with antiulcer activity.

Name	Family	Part used	Reference
Acer tegmentosum Maxim.	Sapindaceae	Leaves and heartwood	Yoo *et al*. (2009)
Alhagi maurorum Boiss	Leguminosae	Aerial parts	Awaad *et al*. (2006)
Aralia elata (Miq.) Seem	Araliaceae	Root bark	Lee *et al*. (2005)
Apium graveolens L.	Apiaceae	Seeds	Zhou *et al*. (2009)
Aristolochia paucinervis	Aristolochiaceae	Rhizome and leaves	Gadhi *et al*. (2001)
Artemisia douglusiana Schouw	Asteraceae	Aerial parts	Maria *et al*. (1998)
Bidens bipinnata L.	Asteraceae	Ariel parts	Atta *et al*. (2005)
Brassica oleracea L.	Brassicaceae	Ariel parts	Moon *et al*. (2010)
Ceiba pentandra G.	Bombacaceae	Bark	Ibara *et al*. (2007)
Conyza dioscoridis (Linn) Desf	Asteraceae	Ariel parts	Atta *et al*. (2005)

Antioxidant properties of some secondary metabolites having antiulcer property

Anthocyanins

Anthocyanins can attenuate oxidative damage and accelerate antioxidant enzymes in naproxen-induced gastric ulcer. ROS are important factors in the anti-ulcer model through their regulation of antioxidants and various signaling molecules. Taking anthocyanins' antioxidant properties into account, H2DCFDA method and flow cytometry was used (fluorescence-activated cell sorting, FACS) to examine whether the isolated anthocyanins could possibly show suppressive effects on the intracellular ROS production. Naproxen (1 mg/mL for 3 h) significantly increased ROS levels, and post-treatment with anthocyanins isolated from black rice bran at concentrations of 5 lg/mL and 10 lg/mL significantly attenuated naproxen-induced ROS production after only 3 h of the anthocyanins treatment. Generation of oxidative stress during naproxen-induced gastric ulcer can be seen as the major cellular mechanism leading to gastric damage(Sun-Joong *et al*., 2014).

It was found that the level of the lipid peroxidation products TBARS, which was used as a presumptive measure of ROS mediated damage, was also increased in cells treated only with naproxen, but was later reduced in a dose dependent manner in those cells subsequently treated with anthocyanins (Sun-Joong *et al*.,2014).

Phenolic Compuonds

The antioxidant activities in the Cabernet Sauvignon and Merlot wines from four wine grape-growing regions in China were measured by different analytical assays: 2,2-diphenyl-1-picrylhydrazyl (DPPH·), cupric reducing antioxidant capacity (CUPRAC), superoxide radical-scavenging activity (SRSA) and the contents of total phenols, total flavonoids, total flavanols and total anthocyanins were determined. The results showed that the contents of phenolic compounds and the levels of antioxidant activity in the wine samples greatly varied with cultivar and environmental factors of vine growth. The contents of phenolic compounds and antioxidant activities in Cabernet Sauvignon and Merlot wines from the Yuquanying region of Ningxia were significantly higher than other three regions, followed by the wines from Shacheng region of Hebei, and these parameters were the lowest in Cabernet Sauvignon and Merlot wines from the Changli regions of Hebei and Xiangning region of Shanxi. Taken together, a close relationship between phenolic subclasses and antioxidant activity was observed for the wine samples. Moreover, there were significant discrepancies in the individual phenolic composition and content of four regional Cabernet Sauvignon and Merlot wines, among which the individual phenolic compounds (catechin, epicatechin, cinnamic acid, quercetin-3-*O*-glucuronide, quercetin-3-*O*-glucoside,laricitrin-3-*O*-glucoside and isorhamnetin-3-*O*-glucoside revealed a significant correlation ($p < 0.05$) with the antioxidant capacity in present study, especially for catechin and epicatechin (Bao and Zhen, 2012).

Astaxanthin

The 1,1-diphenyl-2-picrylhydrazyl radical scavenging activities of total carotenoid, astaxanthin esters and saponified astaxanthin were compared with the activities of synthetic astaxanthin and butylated hydroxyl anisole (BHA). Saponified astaxanthin showed the maximum free radical scavenging activity (IC50 of 8.1 µg/ml) that is 4.5 fold higher in comparison to standard astaxanthin (IC50 36.5 µg/ml). Saponified astaxanthin was also demonstrated to exhibit maximum reducing power (59,600 U/g) followed by total carotenoid (38,350 U/g) and astaxanthin esters (33,550 U/g). Dose dependent increase in activity suggests that, it is proportionally increased to the concentration of astaxanthin in the sample. (Burde *et al*.,2008)

CONCLUSION

Quite a lot of classes of pharmacological agents have proved to be effectual in the management of the acid peptic disorders. An extensive search has been launched to identify new anti-ulcer therapies from natural sources to replace currently used drugs of doubtful effectiveness and safety. Herbs, medicinal plants, spices, vegetables and crude drug substances are considered to be a potential source to control various diseases including gastric ulcer and ulcerative colitis. In the scientific literature, a large number of medicinal plants and their secondary metabolites with anti-ulcer potential have been reported. As the gastro protective effect can be linked to different mechanisms, once demonstrated the activity, the extracts and more appropriately the active compounds should be assessed for action mechanisms to elucidate their mode of action. Besides, new action mechanisms may be discovered.Several studies on the gastroprotective effect of herbal mixtures and pure secondary metabolites isolated from several plants and their derivatives suggest that most studies can be undertaken with doses in the range 100–300 mg/kg of herbal mixtures, and 50–200 mg/kg for the secondary metabolites and derivatives. Even at those doses, the extract amount administered is a multiple of the traditional doses. If there is no detectable or very low activity in these concentrations, the active compound is either inactive, presents low effect or is inactive in the assay system used. As the gastroprotective effect can be linked to different mechanisms, once demonstrated the activity, the extracts and more appropriately the secondary metabolite should be assessed for action mechanisms to elucidate their mode of action. Furthermore, new action mechanisms may be discovered.

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