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Review Article

Clinical Biomarkers and Use of Herbal Products in Gastric Injury

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Abstract

An ulcer in the stomach is a common digestive system ailment. Gastric ulcers are more likely to develop if one drinks alcohol regularly. Despite the extensive availability of treatment options, there are just a few preventative regimes. In animal trials, herbal remedies have been found to prevent the formation of ethanol-induced stomach ulcers. Histamine receptor 2 antagonists have a similar or higher ability to inhibit the formation of ethanol-induced stomach ulcers to herbal treatments. There are less adverse effects associated with herbal remedies. PubMed, Google Scholar, and Web of Science databases were searched using keywords such as "gastric ulcer," "herbal medicines," and "ethanol-induced gastric injury." The search was performed up to May 15, 2021. Only articles published in English were used in this review. For those who are more susceptible to develop stomach ulcers, certain herbal combinations may be an effective option to prevent the development of gastric ulcers, based on their methods of action and the pathogenesis of gastric ulcers. Dates, pomegranate seeds, and bitter melon are all examples of herbal compounds that are safe and can be ingested. Those who regularly use alcohol may want to consider using these substances as an alternative method of preventing stomach ulcers. Anti- *Helicobactor pylori* herbal components such as *Mitrella kentia*, citrus lemon, and *Cratoxylum arborescens* (Vahl) Blume can be used by *Helicobacter pylori* positive individuals to avoid the creation of ethanol-induced stomach ulcers.

Keywords: Gastric ulcer, Herbal medicine, Clinical biomarkers, Alcohol consumption

المؤشرات الحيوية السريرية واستخدام المنتجات العشبية في علاج امراض المعدة

الخلاصة

قرحة المعدة من امراض الجهاز الهضمي المشتركة والأكثر حدوثا لمن يتناول الكحول بانتظام. على الرغم من توافر خيارات العلاج على نطاق واسع، لا يوجد سوى عدد قليل من الأنظمة الوقائية. في التجارب على الحيوانات ، تم العثور على بعض العلاجات العشبية لمنع تكوين قرحة المعدة الناجمة عن الإيثانول. مثبطات مستقبلات الهستامين 2 لديها قدرة مماثلة للعلاجات العشبية على منع حدوث قرحة المعدة الناجمة عن الإيثانول. هناك آثار سلبية أقل للعلاجات العشبية. تم البحث في قواعد بيانات PubMed وGoogle Scholar وWeb of Science باستخدام كلمات رئيسية مثل "قرحة المعدة" و"الأدوية العشبية" و"إصابة المعدة الناجمةعن الإيثانول". تم إجراء البحث حتى 15 مايو 2021. استخدمت في هذا الاستعراض المقالات المنشورة باللغة الإنجليزية فقط. بالنسبة لأولئك الذين هم أكثر عرضة للأصابة بقرحة المعدة، قد تكون بعض التركيبات العشبية خيارا فعالا لمنع الأصابة، استنادا إلى أساليب عملهم ومسببات الأمراض من قرحة المعدة. التمر وبذور الرمان والبطيخ المر كلها أمثلة على المركبات العشبية الآمنة ويمكن تناولها. أولئك الذين يستخدمون الكحول بانتظام قد يكون لديهم اهتمام باستخدام هذه المواد كوسيلة بديلة للوقاية من قرحة المعدة. يمكن استخدام مكونات عشبية مادة لبكتيريا هيليكوباكتوربيلوري مثل ميتريلا كينتيا والليمون والحمضيات و الفاهل بلوم من قبل الأفراد المصابين بالهيليكوباكتور بيلوري لتجنب الأصابة بقرحة المعدة الناجمة عن الإيثانول.

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INTRODUCTION

Gastric ulcer is the most common upper digestive system ailment. The prevalence of stomach ulcers in Western cultures is 2.0 percent [1], with annual occurrence rates ranging from 0.10-0.19 percent [2]. Gastric ulcers are found in 4.7 percent of Taiwanese people and 6.1 percent of mainland Chinese people [3]. Gastric ulcers were found in about 22% of dyspeptic patients [4]. Stomach ulcers were treated in 0.337 percent of the general population in the United States from 1998 to 2005 [5], and the fatality rate from gastric ulcers was 0.19 percent in 1988 [6]. Not only are stomach ulcers connected to gastric cancer [7], but they also have a negative impact on patients' quality of life, productivity, and medical stress [8]. More than 98 percent of patients with gastric ulcers in Russia, for example, complained of stomach pain [9]. In the United States, annual losses from recent ulcers were $5.65 billion [8]. People who smoke, take nonsteroidal anti-inflammatory drugs (NSAIDs), or drink alcohol are more

likely to develop gastric ulcers [10]. Although there are few preventive medicines available, numerous supervisory medications, such as proton-pump inhibitors, antimicrobial drugs, and antagonists of histamine 2 receptors, have been shown to be effective in the treatment of stomach ulcers [11]. According to some studies, *Helicobacter pylori* (*H. pylori*) infection causes over 90% of peptic ulcers [3], and eradication of H. pylori can treat and prevent stomach ulcers [12]. According to the most recent studies, 10% of H. pylori patients develop stomach ulcers [13]. In addition, a clinical evaluation indicated that H. Pylori eradication had no effect on the prevalence of stomach injuries in patients on long-term NSAID medication [14]. Furthermore, eradication of H. pylori is insufficient to avoid NSAID-associated ulcers as proton pump inhibitors, according to a meta-analysis [15]. Despite the fact that proton pump inhibitors (PPIs), H2 blockers, and prostaglandin E1 analogs give some protection against stomach ulcers [16], the adverse effect rate of these drugs could prohibit them from being used in clinical practice [17]. Experiments in several animal models have demonstrated that herbal medications can effectively prevent the formation of gastric ulcers while having fewer adverse effects, suggesting that herbal medicines could be used to prevent gastric and/or duodenal ulcers [3]. We focused on the anti-ulcerogenic effects and mechanisms of herbal remedies in the animal model of gastric ulcer produced by ethanol because ethanol is one of the main risk factors for stomach ulcers and a big fraction of the population (approximately 0.5 billion) consumes alcohol. The review was conducted to investigate the effectiveness of natural products in the treatment of gastric injuries, biomarkers and mechanisms involved in the progression of the disease.

METHODS

Searches in PubMed, Google Scholar, and Web of Science databases have been conducted up to May 15, 2021, for studies evaluating the risk of adverse clinical outcomes among gastric ulcer patients with alcohol use compared to nonuse of alcohol, with the following keywords and their MeSH terms: ‘gastric ulcer," "herbal medicines," and "ethanol-induced gastric injury." The inclusion criteria were studies that investigated the use of herbal products on patients with ethanol-induced gastric ulcers. The features and impact measurements of the analysis were then extracted, and each article used was analyzed separately.

Literature search

A prominent animal model for the study of stomach ulcers is the ethanol-induced rat ulcer. Many herbal components have been proven in studies to protect against the development of stomach ulcers produced by ethanol in the mouse model (Table 1). Many studies have demonstrated that pre-fed rats with ginseng extract at doses ranging from 250 to 1250 mg/kg body weight had a 28-day dose-dependent anti-ulcerogenic effect [18,19]. Furthermore, in pre-fed rats with aqueous sukari date extract, the occurrence and severity of stomach ulcers caused by ethanol decreased significantly for 14 days [20]. In an ethanol-induced ulcer paradigm, rats administered *Morus alba* extract for four days had a significantly lower ulcer index, with defensive efficiency comparable to lansoprazole [21]. Not only for the long-term administration processes of herbal constituents, but also for the short-term application of herbal extracts has anti-ulcerogenic advantages. Another study found that pre-feeding rats with *Boesenbergia rotunda* methanol extractor one hour before gastric ulcer development resulted in a dose-dependent decrease in ulcer rate, as well as an increase in gastric pH and mucus content [22]. The 20 percent water extract of *Laurus nobilis* virtually completely covered stomach damage induced by absolute ethanol (0.5 ml/100g body weight) when given 2 hours before ulcer induction [23]. Through the co-administration of herbal substances and ethanol, we must also avoid the development of ethanol-induced stomach ulcers. At a dose of 600 mg/kg bodyweight for 7 days, coadministration of ethanol with *Achyranthes aspera*, for example, leads in a 36 percent reduction of ulcerogenesis [24]. In addition to oral treatment, herbal extracts are frequently injected intraperitoneally (IP) or subcutaneously (SC) to provide anti-ulcerative benefits [25]. The antiulcerogenic activity of the herbal component is on par with or better than that of traditional treatments. *Boesenbergia rotunda*, for example, was more effective at 400 mg/kg than omeprazole (20 mg/kg), a proton pump inhibitor used to treat stomach ulcers [23]. The pomegranate methanol extract inhibited the ethanol-mediated ulcer model in the same way that the H2 histamine antagonist ranitidine did [26]. Similarly, administration of rats with *Corchorus olitorius* leaf extract (400 mg/kg body weight) stabilized stomach pH and prevented ulcer formation 100% of the time, but omeprazole only prevented ethanol-induced gastric ulcers 80% of the time [27]. The inhibitory effects of a 25mg/kg dose of beeswax extract were stronger than the same dose of cimetidine for ethanol-induced stomach ulcers [28]. This study demonstrates that using herbal substances on a regular or occasional basis can help avoid stomach ulcers induced by ethanol. Furthermore, the antiulcerogenicity of herbal substances is dose dependent, i.e., the larger the dose, the better the efficiency. Certain herbal compounds, on the other hand, are lower with a larger dose of protection than at a lower level of protection. For example, at 50 mg/kg, guarana extract inhibited stomach ulcers by 56%, and at 100 mg/kg, it inhibited gastric ulcers by 37 percent [29]. The induction of ulcer formation was 66 percent prevented at 50 mg/kg of St. Hil's modest anacardium extract, but only 9 at 200 mg/kg [30]. This could be due to an unfavorable reaction to a more herbal product. The methods of herbal preparation can impact the efficacy of a variety of herbal medications. For example, aqueous extract of dates reduced 40% of the ulcer index when administered orally, whereas ethanol extract inhibited 55% of the ethanol-induced gastric ulcer [31]. In addition, the generated stomach ulcer model is inhibited by 125 mg of ethanol or chloroform *Cuneata euphorbia* extract, which is similar to the effect of the same amount of ethyl acetate extract [32]. Melanchauski *et al*. confirmed that 100 mg/kg of *Ailanthus excels* bark inhibits ethanol-induced ulcerogenesis by 56%, while the same amount of conventional carbenoxolone inhibits ulcerogenesis by 83% [33].

Table 1: Herbal ingredients that inhibit the progress of ethanol-induced gastric injury

Herbal Ingredients	Animal Species	Pretreatment time	References
Boesenbergia rotunda (L.) Mansf.	Rat	1 hr	Abdelwahab *et al*., 2011 [22]
Morus alba L.	Rat	4 days	Ahmad *et al*. 2013 [66]
Achyranthes aspera Linn.	Rat	7 days	Das *et al*. 2013 [24]
Corchorus olitorius leaves	Rat	1 hr	Al Batran *et al*. 2013 [27]
Parkia speciose leaves	Rat	1 hr	Al Batran *et al*. 2013 [52]
Opuntia ficus indica F. flowers	Rat	1 hr	Alimi *et al*. 2013 [67]
Bark of *Rhus tripartitum* root	Rat	1 hr	Alimi *et al*. 2013 [67]
Gymnema sylvestre	Rat	1 hr	Al-Rejaie *et al*. 2012 [68]
Strawberry	Rat	10 days	Alvarez-Suarez *et al*. 2011 [69]
Samanea saman (Jacq) Merr bark	Rat	1 hr	Arumugam *et al*. 2011 [70]
Euphorbia cuneata Vahl	Rat	1 day	Awaad *et al*. 2013 [32]
M. pruriens leaves	Rat	1 hr	Golbabapour *et al*., 2013 [19]
Ginseng leaves & root	Rat	1 hr or 28 days	Huang *et al*., 2013 [18]
Ailanthus excels bark	Rat	1 hr	Melanchauski *et al*., 2010 [33]
Moringa oleifera (Lam) leaves	Mouse	5 days	Kashiwada *et al*., 2012 [71]
Moringa oleifera root	Rat	1 hr	Gholap *et al*., 2012 [72]
Bauhinia purpurea L. leaves	Rat	30 min	Negi *et al*., 2012 [73]
Gynura procumbens leaves	Rat	1 hr	Hassan *et al*., 2010 [74]
Chelerythrine	Mouse	4 days	Li WF, *et al*., 2014 [54]
Terminalia belerica Roxb.	Mouse	1 hr	Jawanjal *et al*., 2012 [75]
Pithecellobium dulce	Rat	30 days	Megala and Geetha, 2012 [63]
Momordica dioica roxb.	Rat	5 days	Bakare *et al*., 2010 [76]
Momordica charantia L.	Rat	15 min or 1 hr	Horax *et al*., 2010 [77]
Moringa oleifera (Lam) leaves	Mouse	5 days	Kashiwada *et al*., 2012 [71]

An orally administered olive oil extract of *Momordica charantia* L. at a dose of 330 mg/kg lowered the ulcer index by 95% fifteen minutes before the production of a gastric ulcer, while an ethanol extract at a dose of 310 mg/kg only reduced the ulcer index by 56% [34]. The methanolic extract at 100 mg/kg, on the other hand, resulted in a 61% reduction in ulcer index [35]. Hexane extracts of *Combretum duarteanum* Cambess leaf and *Dodonaea viscosa* also performed better than the ethanolic or water extracts [36]. As a result, to maximize the efficacy of each herbal product, proper extraction processes should be applied. Herbal medications and extracts, in general, are beneficial. Animals administered the *Cardiospermum halicacabum* Linnextract (4 and 6 g/kg) orally for two weeks showed no severe clinical or macroscopic toxic symptoms in the acute toxicity studies. In short-term toxicity experiments, herbal extract therapy (400 and 800 mg/kg (p.o.) for 14 days) had no effect on rat mortality [37]. There was no mortality or significant toxicity in mice administered *Parkia speciosa* leaf extract at dosages of 1, 3, or 5 g/kg for 14 days, according to clinical and histological data [27]. The *Laurus nobilis* extract could effectively inhibit the generation of ethanol-induced stomach ulcers at 200 mg/kg bodyweight, while the LD50 for *Laurus nobilis* seed extract in male albino mice was 13.66 g/kg body weight [23]. Similarly, a single oral dose of *Mouriri pusa* ethanolic extract at a dose of 500 mg/kg revealed strong antifungal activity in an ethanol-induced ulcer model. However, when rats were given a single oral dose of the *Mouriri pusa* methanol extract up to a dose of 5000 mg/kg, no signs or symptoms of acute toxicity were seen. No animals perished throughout the 14-day period after receiving the methanolic extract, and no changes in daily body weight or organ weight were observed by the end of the trial. During autopsy, no substantial changes or lesions in either animal's inner organs were discovered [38]. Dates, strawberries, cashews, and bitter melon, for example, are edible herbal elements that have an anti-ulcerogenic action. As a result, herbal compounds are safe to use in medicine.

DISCUSSION

Biomarkers of ethanol-induced gastric injury

When 50-100% ethanol is added to the mucosa, it causes a multitude of microcirculatory disturbances. There was substantial engorgement of stomach mucosal microvessels, platelet thrombi, and capillary endothelial damage, according to morphologic examinations. During the development of a stomach deformity, recent *in vivo* microscopic investigations have revealed a key series of microcirculatory disturbances. Within one minute of ethanol exposure to the gastric mucosa, submucosal venular constriction occurs [39]. After a few minutes, the blood flow to the superficial mucosal microvessels ends, but the microvessels remain packed with red blood cells. Only until mucosal blood circulation slows and stops mucosal microvascular permeability improve dramatically. Within 10 minutes of the commencement of microcirculatory standstill, serious histologic damage ensues. Stomach submucosal venular constriction is a common early reaction in the chain of events leading to gastric mucosal lesion formation after ethanol exposure. It may be responsible for the mucosal blood circulation stasis, which creates an outflow obstruction, making the mucosa more prone to ethanol injury. Because ethanol causes gastric mucosal secretion of leukotriene-C4 (LTC4), a potent venular constrictor in the rat gastrointestinal submucosa, and this ethanol-induced venous constriction is blocked by intragastric application of BW755C, a lipoxygenase inhibitor, leukotrienes are potential mediators of this response [40]. An imbalance of key aggressive and protective factors is the primary etiology of stomach ulcers. The stomach mucosa is constantly threatened by endogenous violent stimuli such as prolonged hydrochloric acid and pepsin production, refluxed bile, leukotrienes, stress, and reactive oxygen species (ROS). In ethanol-damaged gastric tissue, overrunning neutrophils are a major source of reactive oxygen species (ROS). Increased secretion of oxygen-

derived free radicals and proteolytic enzymes, as well as neutrophil binding to the vascular endothelium, have been proposed as key events in the pathophysiology of various types of digestive ulceration, including gastric damage caused by intragastric ethanol delivery [41]. To protect the intestinal epithelium from a variety of violent stimuli, a complex protection mechanism has evolved, involving the production of surface mucus and bicarbonate, surface active phospholipids, control of gastric mucosal blood flow, non-enzymatic and enzymatic antioxidants, epithelial regeneration acceleration, and epithelial homeostasis maintenance. Prostaglandin, particularly prostaglandin E2 (PGE2), is regarded to be an important gastric mucosal defense element since it increases these protective actions. Heat shock proteins [41] were identified to be another essential protective component. They aid in the control of inflammation as well as the maintenance of mucosal integrity. Their altered expression could indicate mucosal inflammation, which could result in tissue damage. The most stress-inducible heat shock protein is thought to be heat shock protein 70 (HSP70). As a result, it has been labeled a stress biomarker. By protecting mitochondria and engaging with the stress-induced apoptotic mechanism, it is hypothesized to have cytoprotective characteristics. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) play essential roles in the pathogenesis of gastric inflammation and the prevention of gastric ulcers [42]. Ethanol, like other stomach irritants like hydrogen peroxide and acids, promotes necrosis and apoptosis in gastric mucosal cells, causing damage to the gastrointestinal mucosa. Through a similar mechanism that includes mitochondrial damage, these gastric stresses elicit apoptotic DNA fragmentation, chromatin condensation, and caspase activation in gastric mucosal cells [43]. For many years, it was considered that prolonged stomach acid secretion aggravated gastric mucosa ulcers. As a result, limiting gastric acid secretion is at the heart of ulcer treatment, which includes everything from vagotomy to anti-cholinergics, histamine H2 receptor antagonists, antacids, and most recently, proton pump inhibitors (PPIs). Since many ulcer patients secreted hydrochloric acid at regular rates, it was clear that increased acid secretion was insufficient to cause ulcers on its own [44]. Alcohol concentrations of more than 5% have minimal influence on stomach acid secretion. As a result, the vast majority of commercially available drugs are ineffective against gastric ulcer problems, and their long-term usage is linked to serious side effects. As a result, more dependable and secure anti-ulcer treatments are urgently required [45]. A mismatch between detrimental influences in the lumen and defense processes in the stomach mucosa is thought to be the origin of gastric ulcers. While ethanol, stress, and NSAIDs are all thought to cause severe stomach discomfort, the exact mechanism is unknown. Non-NSAID laboratory models of gastric ulcer induction include those that focus on ethanol and tension. Ethanol is thought to harm the stomach by altering protective elements like mucus production and blood supply to the mucosa. Furthermore, ethanol can harm the stomach by producing free radicals, inhibiting cell proliferation, and aggravating the inflammatory response [46]. By accelerating cytoplasmic components and interfering with the activity of mucosal cell membranes, high amounts of ethanol cause rapid necrosis of superficial mucosal cells. During the first few seconds, ethanol causes vasoactive mediators such as LTC4 and histamine to be released into the mucosa, disrupting superficial mucosal cells, particularly mucosal mast cells. In conjunction with histamine, LTC4 generates a series of severe constrictions that move from small mucosal venules to bigger submucosal venules and eventually to larger veins [46]. Venostasis can also be caused by constriction of the stomach muscle around venular or venous infiltration sites. Shortly after, arteriole swelling begins, perhaps triggered primarily by histamine, but other locally related autacoid and ethanol metabolites are also likely to be involved. Extreme arteriolar and artery dilatation and constriction caused mucosal capillary enlargement, hyperemia, and a considerable increase in mucosal capillary pressure, which, when paired with the permeability-enhancing effects of LTC4, histamine, and ethanol, resulted in intense mucosal fluid retention. The stomach epithelium begins to rise and burst as the intracellular tension and volume increase. As the concentration of ethanol rises within the superficial layers of this hyperemic tissue site, it causes hemolysis of stationary red blood cells and deposition of blood and tissue products inside and all around the dilated mucosal capillaries, worsening the local vascular stasis. Mucosal bleeding is thought to occur when intra-capillary pressure rips open superficial capillary connections. When submucosal venous spasm is as forceful as breaking the very delicate submucosal veins, submucosal bleeding is thought to occur [48]. Even though the precise mechanisms for preventing the formation of gastric ulcers remain unknown, evidence suggests that the antiulcer benefit of herbal extracts may be due to divergent pathways including anti-oxidation, PGE2 stimulation for the acid section, histamine release inhibition, and anti-microbial effects [49].

Antioxidant activity

The occurrence of gastric ulcers is linked to oxidative stress. In the mucosal tissue of stomach ulcers, lipid peroxidation has enhanced and catalase has decreased. Glutathione levels were consistently lower in the oxidative tissue of gastric ulcers, whereas malondialdehyde (MDA) levels were constantly greater. Antioxidant properties are present in all herbal anti-ulcerogens. *Morus alba* extract, for example, considerably increases the enzyme levels of superoxide dismutase (SOD), glutathione reductase (GR) in ethanol-induced stomach ulcers [50]. In stomach ulcers produced by ethanol, extracts of *Jasmin sambac* halted the decrease in SOD activity and reduced MDA levels. SOD activity and MDA levels in rats prefed with *Jasminum sambac* extracts were compared to those previously fed with omeprazole [51]. In an ethanol-mediated gastric ulcer model, *Corchorus olitorius* leaf extract was more helpful for sodium activity and MDA than omeprazole at a dose of 400 mg/kg body weight. Antioxidation may potentially be a mechanism through which herbal substances reduce the growth of stomach ulcers [52]. (Table 2).

Table 2: Mechanisms utilized by herbal extracts to prevent gastric ulcer

Herbal Ingredient	Anti-oxidative properties	Acid secretion	H^+/K^+ ATPase	Others
Boesenbergia rotunda (L.) Mansf.	Yes	↓	N/D	↑Mucus, ↓inflammaiton
Morus alba L	Yes	↓	N/D	↑Mucus, ↓Pepsin content
Cardiospermum halicacabum Linn.	Yes	N/D	N/D	↓Inflammation
Corchorus olitorius leaves	Yes	N/D	N/D	↑HSP70
Parkia speciose leaves	Yes	N/D	N/D	↑Glycoprotein & HSP70, ↓BAX protein
Opuntia ficus indica F. flowers	Yes	N/D	N/D	
Rhus tripartitum bark & root	Yes	↓	N/D	
Gymnema sylvestre	Yes	N/D	N/D	↑Non-protein sulfhydryles
Strawberry	Yes	N/D	N/D	
Samanea saman (Jacq) Merr bark	N/D	↓	N/D	
Ginkgo biloba	Yes	↓	N/D	↑Mucus, ↑Non-protein sulfhydryles, ↓c-Jun kinase activity
Nigella sativa oil	Yes	↓	N/D	↑Mucus, ↓Histamine
M. pruriens leaves	Yes	N/D	N/D	↑Mucus, ↑Glycoprotein & HSP70, ↓BAX protein, ↑PGE2,
Ginseng leaves and roots	N/D	N/D	N/D	↑HSP70, ↓apoptosis
Sesame oil	Yes	N/D	N/D	↑Gastric mucosal NO levels
Garlic oil	Yes	N/D	N/D	
Foeniculum vulgare	Yes	N/D	N/D	↑Nitrite & nitrate
Moringa oleifera (Lam) leaves	Yes	N/D	N/D	
Bauhinia purpurea L. leaves	N/D	↓	N/D	↑Glycoprotein, ↓inflammaiton
Maytenus ilicifolia Mart. ex. Reiss	(-)	↓	↓	↓Nitric oxide, Mucus (-)
Naringenin	N/D	↓	N/D	↑Mucus, ↑Glycoprotein & hexosamine, ↓PGE2

PGE2: prostaglandin E2; HSP70: 70 Kilo-Dalton heat shock protein; BAX: Bcl-2-associated X (-): No effect; N/D: No Data Computing; H/P ATPase: Hydrogen/Potassium Adenosine Triphosphatase

Inhibition of inflammation

Gastric ulcers cause mucosal inflammation, which is particularly important for reoccurring gastric ulcers. Many herbal ingredients help to keep the mucosa from becoming inflamed. A methanolic extract of *Boesenbergia rotunda* has been shown to limit leucocyte penetration into the stomach wall in ethanol-induced gastric ulcers [53]. In the past, oral administration of American ginseng extract at daily doses of 250, 500, and 1250 mg/kg for two weeks lowered IL-1 protein levels by 29.3%, 27.5%, and 54.4%, respectively, depending on the amount of vehicle treatment [18]. At a dose of 5 mg/kg once daily for four days, chelerythrine, an active ingredient of an antiulcerogenic drug (Papaveraceae), significantly reduced inflammatory cell infiltration, IL-6, and TNF-α in stomach mucosa and serum [54]. In addition, the use of herbal components for a short period of time lowers mucosal irritation. For example, orally administered ethanolic extracts of *Artemisia asiatica* dramatically reduced mucosal IL-1β and TNF-α while considerably boosting the anti-inflammatory cytokine IL-10 one hour before producing a gastric ulcer with ethanol [55]. Oral extracts of Himalayan cinquefoil or Sukari date also reduced mucosal histamine levels and microvascular permeability considerably. As a result, herbal components' anti-inflammatory qualities may be another way by which they prevent the formation of stomach ulcers [56].

Antimicrobial activity

H. pylori infection is one of the causes of stomach ulcers [57]. Antibiotics can help with stomach ulcer treatment [58]. Antimicrobial activity can be seen in some antiulcerogenic natural compounds. An antiulcerogenic drug, an extract of *Mitrella kentii* bark, inhibited *H. pylori* J99 with a minimum inhibitory concentration (MIC) of 125 g/ml, according to Sidahmed *et al*. [59]. Swallow root extract, a different antiulcerogenic component, exhibits a MIC of 150 g/ml against *H. pylori* isolated from stomach ulcer patients [60]. *Davilla nitida* extract showed anti-*H pylori* efficacy with a MIC of 125 g/ml [61]. The methanolic extract of *Mouriri elliptica* Martius has a higher antibacterial efficacy against *H. pylori* collected from gastric ulcer patients, with a MIC of 0.025 g/ml [38]. With a MIC of 250 g/ml, the acetate fraction of *Byrsonima fagifolia* inhibited not only *H. pylori* but also *Escherichia coli* and *Staphylococcus aureus* [62]. As a result, certain herbal substances may have antimicrobial effects, which could be an additional method for inhibiting the development of stomach ulcers.

Prostaglandin E2 (PGE2) inhibition

Prostaglandin E2 (PGE2) levels in the mucosa are lower in stomach ulcers, and PGE2 treatment speeds up the healing process [63]. *Pithecellobium dulce* extract, given at a dose of 200 mg/kg every day for 30 days, prevented mucosal PGE2 decline and had the same potency as 30 mg/kg omeprazole [64]. One hour before ulcer induction, oral treatment of *Anacardium humile* St. Hil extract resulted in a threefold increase in mucosal PGE2 levels [30]. Furthermore, oral *Tectona grandis* extract elicited a 50% increase in mucosal PGE2 levels in an ethanol-induced stomach ulcer mouse. Some anti-ulcerogenic herbal substances, on the other hand, reduce mucosal PGE2 levels, which may explain why long-term administration of some herbal ingredients may not be effective in the treatment of gastric ulcers [65].

Conclusion

Herbal compounds can successfully prevent the occurrence of stomach ulcers through a variety of mechanisms. Anti-ulcerogenic herbal substances are generally safe, and some, like date, pomegranate, and bitter melon, are even delicious. This substance could be

an alternative to reducing the risk of a stomach ulcer, especially for people who consume alcohol on a regular basis. Anti-*H. pylori* herbal components such as *Mitrella kentia*, citrus lemon, and *Cratoxylum arborescens* (Vahl) Blume, alone or in combination with other herbal ingredients, may be an alternative for *H. pylori* positive persons to avoid the creation of ethanol-induced stomach ulcer. Evidently, a randomized double-blind clinical investigation is required before herbal components can be widely employed in therapeutic diseases.

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Conflict of interests

No conflicting interests

Data sharing statement

N/A

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