Anti-ulcer Activity of Some Selected Medicinal Plants: A review

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Abstract. A peptic ulcer is an ulcer of one of those areas of the gastrointestinal tract that are usually acidic. Peptic ulcer formation occurred due to the acid of excess, peptic activity in gastric juice as well as a breakdown in mucosal defenses. Some of anti-ulcer medicines such as proton pump inhibitors and H2 receptor antagonists are used for peptic ulcer treatment. However, these drugs have shown disease relapse, side effects, and even drug interactions. Many medicinal plants exhibit anti-ulcer activity and found useful in the treatment of peptic ulcer. The purpose of this review is to know more about the anti-ulcer properties of the medicinal plants. Serjania marginata (HESM) leaves, thymol obtained from Thymus, Origanum and Cuphea aequipetala infusion (CAI) In this review there is information about some kinds of plants which are very useful in treating peptic ulcer disease such as hydroalcoholic extract obtained from S. marginata (HESM) leaves, thymol obtained from Thymus, Origanum and CAI. These plants were studied by their mechanisms underlying to the gastroprotective effect of thymol and HESM. Furthermore, the study reported the potential effect of involvement of some factors of the protective effect of medical extract, such as prostaglandins (PG), nitric oxide (NO), and a hydrogen sulfide (H2S). Side the effect of these factors in gastro protective, and finally the paper clarified some local mechanisms of actions of some compounds that were involved in mucosal defense or injury.

Keywords: HESM, thymol, CAI, anti-ulcer, medicinal plant.

INTRODUCTION

Peptic ulcer disease includes both gastric and duodenal ulcers which has been a main reason of morbidity and mortality for over a century (Mallertheiner et al., 2009). According to many researchers, peptic ulcers have some of the main pathologies in human that found in almost 10% of the world population (Grob, 2004; Zapata et al., 2006). Affected by stress with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and Helicobacter pylori, peptic ulcer is described as an unbalance between offensive effects of hydrochloric acid and pepsin, and defensive effects of mucus and bicarbonate (Hoogerwerf et al., 2006; Hoogerwerf et al., 2001). Peptic ulcer appears by eating spicy food and getting stressed. These two factors have been found merely to be intensive factors. However, the real causes found to be a bacterial infection from H. pylori bacteria or a reaction from various types of medicines, mostly by NSAIDs (Marshall et al., 1984). Generally, all the factors of H. pylori bacteria, NSAIDs, emotional stress, alcohol abuse, and smoking are the major etiological factors to peptic ulcer
(Malfertheiner et al., 2009). Many medicines and drugs are used to treat gastric ulcers such as antagonists of the histamine H2 receptor (ranitidine) and the inhibitors of irreversible proton pump (omeprazole) which they are considered as an anti-secretory agent (Jain et al., 2007). Though, the long-period use of such drugs could cause series of adverse effects, such as nephrotoxicity, gynecomastia, thrombocytopenia, hepatotoxicity, and impotence (Chan et al., 2002; Sheen and Triadafilopoulos, 2011). Because of the occurrence of several side effects by using synthetic drugs for many diseases, medicinal plants described as an important source of modern medications. Herbal medicines are identified as nontoxic for treating the ulcers with less adverse effects, therefore, extensive researches are preformed to find out the powerful anti-ulcer agents of plant origin (Srivastava et al., 2011; Vinay et al., 2005; AlMatar et al., 2017; Albarri et al., 2017). Thus, medicinal species were using worldwide as traditional drug to treat ulcer (Borelli and Izzo, 2000; Zakaria et al., 2014). In this communication, we attempted to shed the light on the medicinal application of some compounds derived from some medicinal plants towards using them for anti-ulcer treatment through appraisal of recent literature in the field.

**Some potential compounds extracted from medicinal plants used in the ulcer treatment**

HESM is hydro-alcoholic extract obtained from *Serjania marginata* leaves. The HESM phytochemical study show the presence of saponins, proanthocyanidins and unusual C, O-flavonoid glycosides (Heredia et al., 2015). Flavonoids are considering as compounds that demonstrate anti-ulcer (La Casa et al., 2000) as well as antioxidant activities (Tapas et al., 2007; Ferreira et al., 2010). It has been revealed that saponins appear to protect ulcerations by activating many protective elements in the mucous membrane. Saponins enhance the number of mucus producing cells (Adão et al., 2011; Choud et al., 2013). Périco et al. (2015) showed the therapeutical potential and the mechanism of action of HESM against ethanol induced gastric injury. Périco et al. (2015) found that the HESM led to a significant inhibition of the gastric lesions by 60% compared to the vehicle-treated control group (p < 0.05) at dose 250 mg/kg using the model of gastric ulcer induced by absolute ethanol (Tarnawski et al., 2012). Absolute ethanol induces a gastric mucosal damage associated with microcirculatory disturbances and increased vascular permeability (Tarnawski et al., 2012). There was too significant decrease in the ulcerative lesions with gastric protection of 58% at dose 250 compared with the vehicle-treated control group (p < 0.05) in the model of I/R (ischemia–reperfusion)-induced gastric ulcer. Ischemia also has harmful effects on gastric mucosa and it is one of the stress-induced gastric mucosal injuries (Laine et al., 2008).

HESM has a role to diminish the impact of myeloperoxidase (MPO) and malondi aldehyde (MDA) levels. MPO is often increased in ulcerogenic lesions that stimulated by ethanol or I/R. MPO defines as a marker of the infiltration/aggregation of neutrophils (Naïto et al., 1998). The reduction in MPO activity is very critical to break the vicious cycle that appears between the infiltration of the inflammatory cells and formation of ROS (reactive oxygen species) through the gastric lesions formation (Santos et al., 2012). The formation of MDA has been considered as a significant index of oxidative tissue damage (Ueda et al., 1989). There is a remarkable change in the glutathione (GSH) levels in the gastric tissue in rats which treated with HESM particularly when high dose (500 mg/kg) of HESM has been applied. GSH is an endogenous antioxidant and its antioxidant properties are related to the presence of a thiol group within its structure (Szabo et al., 1992). Infiltration/aggregation lead to reduction of neutrophils (that determined by MPO activity), which followed by the treatment of HESM. This could be occurred due to the proanthocyanidins and flavonoids that detected in the extract (Sandhar et al., 2011). Flavonoid glycosides can play a role in activating mucosal defenses which lead to stimulate mucus secretion (Sandhar et al., 2011). In addition, these glycosides can chelate ROS and and free radicals produced by ethanol (Abdelwahab, 2013). Nevertheless, proanthocyanidins has been detected in HESM which exhibits a stronger activity of antioxidant than the flavonoid glycosides in the DPPH test (Heredia et al., 2015). Pretreatment with 250 mg/kg of HESM of rats lead to a significant increase in the blood perfusion of stomach by 64% when compared to the vehicle treated control group (P < 0.01). According to Sørbye and Svanes (1994), the blood flow plays an important role in protection of the normal gastric mucosa and healing the damaged mucosa against aggressive drugs, such as ethanol. HESM enhances the secretion of gastric mucous and supports the mucosal barrier without reducing the acidity of the gastric. Sørbye and Svanes observed that an oral treatment with HESM caused an increase (1.2 times) in the amount of adherent gastric mucus compared with the vehicle treated group (p < 0.05). They also found that this extract has not affected the basal levels of prostaglandin E2 (PGE2) in the gastric mucosa, which remains similar to what was observed by sham and vehicle-treated groups after pyloric ligation. It has been reported that the concentration of HESM (75 mg/mL) has shown ability to control *H. pylori* growth in vitro. The results showed that HESM controls *H. pylori* which grow in vitro, with concentration of minimal inhibitory of 75 mg/ml that was highly significant for the extract (Figure 1).

Thymol (2-isopropyl-5-methylphenol) is a monoterpene phenol derivative of cymene found in abundance in the...
essential oils of *Origanum*, *Thymus* (Lamiaceae), and *Lippia* (Verbenaceae) species (Hazzit *et al.*, 2006; Mendes *et al.*, 2010). Thymol has various biological activities such as anti-inflammatory (Braga *et al.*, 2006; Zhou *et al.*, 2014), antioxidant (Yanishlieve *et al.*, 1999), healing (Riella *et al.*, 2012), anti-hyperglycemic, anti-hyperlipidemic (Saravanan and Pari, 2015), anti-nociceptive, local anesthetic (Haeseler *et al.*, 2002), antimicrobial (Saravanan and Pari, 2008), acaricidal (Araújo *et al.*, 2015), anti-convulsant, and anti-epileptogenic (Sancheti *et al.*, 2014). In 2015, Chauhan and Kang reported that the therapeutic potential and mechanism of thymol action against ethanol induced gastric mucosal injury in rat model. The study demonstrated that 10 mg/kg of thymol protects mucosal damage that induced by ethanol. Furthermore, the levels of antioxidant enzymes such as superoxide dismutase (SOD), glutathione (GSH), and lipid peroxidation (LPO) in the
extracted tissue has been determined. Treatment using thymol improved the production of the previous enzymes. The thymol increased SOD levels compared to the ethanol group (P < 0.05). GSH levels were also improved in the thymol group. The results were similar with what was already reported by AlBatran et al. (2013), who also obtained the same outcome using Parkia speciosa ethanolic leaf extract results. Thymol significantly reduced the lipid peroxide level as compared to the ethanol group (P < 0.05). Lipid peroxidation is another essential marker of oxidative stress that causes loss of fluidity of membranes, impairment of ion membrane integrity and transport and ultimately loss of cellular function (AlBatran et al., 2013). Significantly, pretreatment with thymol decreases the MMP-2 expression. Beside, MMP-9 dose not expressed in any group, except the group of ethanol that play a role in gastric ulceration for MMP-9. It has been suggested that the alcohol consumption induces oxidative stress in the gastric gland (La Casa et al., 2000; Pan et al., 2008), which leads to condense the secretion of MMP-9 that is responsible for the damage of the gastric mucosal (Ganguly et al., 2012). Several studies reported that thymol has the ability to decrease the oxidative stress in an ex vivo model (Chauhan et al., 2014). Epithelial barriers in the stomach protect against toxic agents such as alcohol, pepsins, and hydrochloric acid. Any failure or disturbance in these barriers may cause damage in the stomach epithelial integrity that the ultimately leads to the gastric ulceration (Dimaline and Varro, 2007). Moreover, thymol pretreatment can play an important role contribute to strengthening of the mucosal barrier and maintenance of mucosal integrity in the stomach, thus protecting against the severe effects of ethanol. Ribeiro et al. (2016) also mentioned the gastro-protective effects of thymol on chronic and acute ulcers in rats (Repetto and Llesuy, 2002). Drugs that have antioxidant actions can protect the gastric mucosa from destruction that induced by ulcerogenic agents (Repetto and Llesuy, 2002). Oral administration of thymol, a monoterpenone with recognized antioxidant activity (Yanishlieva et al., 1999), prevented significantly the gastric injuries by ethanol. Treatment with thymol (10, 30 and 100 mg/kg) produced dose dependent inhibition on the total lesion area, compared with the vehicle group (P < 0.05). The treatment with thymol (30 and 100 mg/kg) highly decreased the ulcer index, compared with the vehicle group (P < 0.05) in the indomethacin-induced ulcer. The treatment with thymol (30 and 100 mg/kg) for 7 days presented an important decrease in the total lesion area (P < 0.001) when compared to the vehicle group in the acetic acid-induced chronic ulcer model (Figure 2).

Juan et al. (2014) found that gastro-protective and anti-inflammatory activities of Cuphea aequipetala. The study reported that the pretreatment with the aqueous extract protects gastric mucosa against ethanol challenge. Cuphea aequipetala infusion (CAI) of 10, 30, 100, and 300 mg/kg produces a dose dependent gastroprotective effect (6.4, 33.6, 73.7 and 88.3%, respectively). Some other medical plants have anti-ulcerogenic activity are listed in Table 1.

**Potential involvement of some factors in the protective effect of medicinal extract**

The potential contribution of sulfhydryl (SH) compounds, prostaglandins (PG) and nitric oxide (NO) in the gastro-protective effect of the HESM, CAI and Thymol were studied previously. The studies used a model of gastric lesions induced by ethanol in vivo (rats, mice). They found that the gastroprotective action of the HESM does not depend on SH, NO and PG while their results of thymol was different which showed that NO and H₂S did not affect in the protective activity of thymol (30 mg/kg) against ethanol-induced gastric damage, while PGs affect in the protective activity of thymol they can see that the gastroprotective effect of thymol (30 mg/kg) was reversed by pretreatment of animals with indomethacin (AlBatran et al., 2013). PGE2 stimulates K<sub>ATP</sub> channels that mediate at least in part the activity of this endogenous agent in gastro-protection (Peskar et al., 2002; Lira et al., 2009). Besides, the involvement of NO, H₂S, and PGE2 in the protective effect of CAI on ethanol-induced ulcer have been investigated. Thus, NO has no effect on the CAI protective activity against ethanol-induced gastric damage, while H₂S and PGs affect the CAI protective activity (Palacios et al., 2014). It was noticed that the gastro-protective effect of thymol has been influenced by PGs. Therefore, the prostaglandin mechanism in gastrointestinal protection is critical to be mentioned here (Figure 3).

**Prostaglandin in the mechanism of gastrointestinal protection**

PG inhibits gastric acid activity, produces an excess in gastric blood flow, stimulates the secretion of mucus and bicarbonate (HCO<sub>3</sub>⁻) and enhances the content of mucosal sulfhydryl, thus prevent damaging of the gastric mucosa induced by various irritants and necrotizing substances (Wallace, 1997; Tarnawski and Caves, 2004; Tarnawski et al., 2004). Two isoforms of Cyclooxygenase (COX), named as constitutive isoform COX-1 and an inducible isoform COX-2, have proposed. It has been stated that COX-1-derived PGs contribute to the gastric integrity maintenance and gastro-protection, while the expression and activity an increase of COX-2 lead to produce high levels of PG which causes deleterious local and systemic effects such as fever associated with inflammation and the increase in vascular constriction and pain (Vane et al., 1998; Park et al., 2013). The studies that has done previously reported that the handling
of nonselective COX inhibitors (e.g., especially acetylsalicylic acid), except the therapeutic effect resulting from the pro-inflammatory COX-2 activity inhibition, might also induce an opposing effect such as bleedings of gastrointestinal (GI) and damages of epithelial due to the inhibition of COX-1 (Gluszko and Bielinska, 2009; Brzozowski, 2010). On the other hand, COX-2 might also have beneficial effects for the physiological function of the gastric mucosal barrier because COX-2 inhibition by selective COX-2 inhibitors enhanced the susceptibility of gastric mucosa to damage, similarly as conventional NSAIDs and selective COX-1 inhibitors (Brzozowski et al., 2001; Brzozowski et al., 1999). Furthermore, the inhibitors selection of COX-1 (SC-560) and COX-2 (rofecoxib, celecoxib) not only cause gastric lesions spontaneously but also significantly

Figure 2. Mechanism of thymol action against ethanol induced gastric mucosal injury in rat model.
<table>
<thead>
<tr>
<th>Name of plant</th>
<th>Extract</th>
<th>Animal model</th>
<th>Result(s)</th>
<th>Mechanism of action</th>
<th>Reference(s)</th>
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<tbody>
<tr>
<td><em>Cuphea equipetala</em></td>
<td><em>Cuphea equipetala</em> infusion (CAI)</td>
<td>Ethanol in mice</td>
<td>It was found that the administration of 10, 30, 100 and 300 mg/kg CAI did produce a dose-dependent gastro-protective effect (6.4, 33.6, 73.7 and 88.3 respectively)</td>
<td>CAI increases the prostaglandin content then stimulates gastric mucous production and bicarbonate secretion leading to protect the mucosa from damage which induced by noxious agents. CAI may decrease active oxidant species production and may decrease active oxidant species production, involving sulfhydryl-containing compounds of the mucosa</td>
<td>Palacios et al. (2014)</td>
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<td><em>Calotropis procera</em> bark</td>
<td>Methanolic (MET) aqueous (AQ)</td>
<td>Ethanol in mice</td>
<td>Both MET and AQ have statistically significant gastro-protective effects in terms of the length and number of gastric ulcers, compared with the vehicle (negative control) (p&lt;0.05)</td>
<td>It has been suggested that both MET and AQ extracts could act by increasing the production of prostaglandins</td>
<td>Escobedo et al. (2012)</td>
</tr>
<tr>
<td><em>Mouririelliptica</em></td>
<td>Methanolic extract (ME), Ethyl acetate fraction (EAF)</td>
<td>Ethanol in mice</td>
<td>ME doses spends 58% and 71% gastro-protective action at a dose of 250 and 500 mg/kg, respectively, EAF also exerts 68% and 54% gastro-protective action at a 50 and 100 mg/kg dose respectively.</td>
<td>Maintaining the level of PGE$_2$ to activate expression of COX-2 and stimulate proliferative factors that re-established the gastric mucosa integrity.</td>
<td>Moleiro et al. (2009)</td>
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<td>NSAIDs</td>
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<td>ME showed gastro-protection (P &lt; 0.05) at 125 or 500 mg/kg doses, while EAF exhibited gastro-protection only at the dose of 100 mg/kg (P &lt; 0.05).</td>
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<tr>
<td>In pyloric ligation</td>
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<td></td>
<td>Animals pretreated orally or intraduodenally with ME presented significantly decreases in ulcerative lesion (37 and 58%, respectively).</td>
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<tr>
<td>Plant Species</td>
<td>Extract Type</td>
<td>Additional Component</td>
<td>Method</td>
<td>Protective Action</td>
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<tr>
<td>Lithraea molleoides</td>
<td>Methanolic extract infusion</td>
<td>acetylsalicylic acid (ASA)</td>
<td>Infusion</td>
<td><strong>Lithraea molleoides</strong> (LmE) extract and Lithraea molleoides infusions (Lml) significantly prevent the gastric injury that caused by ASA at all tested doses. This result suggests that the gastro-protective action may be referred to the increase of prostaglandin synthesis. This effect may be referred to the anti-inflammatory activity. <strong>Garro et al. (2015)</strong></td>
<td></td>
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<tr>
<td>Herba Pogostemonis</td>
<td>Patchouli alcohol</td>
<td>Ethanol</td>
<td>Pretreatment</td>
<td>According to the PA-pretended groups (10, 20 and 40 mg/kg dose), the ulcer area was significantly decreased (P &lt; 0.01) in a dose-dependent manner. <strong>Zheng et al. (2014)</strong></td>
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<tr>
<td>Margaritaria discoidea</td>
<td>Ethanolic extract</td>
<td>Ethanol</td>
<td>Pretreatment</td>
<td>Pretreatment with PA at dose of 10 mg/kg resulted in a significant reduction in ulcer area (0.58 ± 0.12 mm²), with inhibition rate of 81.94% (P &lt; 0.05). <strong>Solidiya et al. (2015)</strong></td>
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<tr>
<td>Ethanol</td>
<td>LmE 250, LmE 500, Lml 10 and Lml 20 are able to protect the mucosa of gastric from damage that caused by ethanol, HCl and NaOH.</td>
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</table>

**Note:** The table continues with more entries related to various plant species and their protective effects on gastric injury.
Table 1. Contd.

| Cymbopogon citrates | Cymbopogon citratus extract | Ethanol in rats | They treated orally with *C. citrates* extract prior to ethanol, a significant decrease was observed in both severity and number of gastric lesions. The U.I. (Ulcer Index) significantly reduced in all prevention groups (P < 0.01) when compared to the positive group. Likewise, when administrated after ethanol administration (treatment groups), *C. citratus* extract also produced a significant reduction in the U.I. (P < 0.01). | Sagadas *et al.* (2015) |

| Cenostigma macrophyllum | The hydroalcoholic fraction from leaves of *C. macrophyllum* (Cm-FHA) | Absolute ethanol induced ulcer in mice | Oral administration of the hydroalcoholic fraction of leaves of *Cenostigma macrophyllum* Tul. var. acuminata Teles Freire (Cm-FHA) reduced the area of gastric lesions induced by absolute ethanol compared with the control group (Cm-FHA 100 or 200 mg/kg: 32.8±4.0 or 33.2 ± 6.3 mm², respectively. | Viana *et al.* (2013) |

| Ischemia-reperfusion-induced gastric ulcers | The gastric lesion’s total area induced by ischemia-reperfusion reduced (46.6 ± 6.9 and 12.8 ± 2.0 mm²) after treatment orally with Cm-FHA (100 and 200 mg/kg, respectively). |

| Cold restraint stress-induced gastric ulcers | The administration of oral doses at 100 and 200 mg/kg and 200 mg/kg of Cm-FHA were able to decrease the gastric lesions to 3.5 ± 1.0 and 2.5 ± 1.4 mm², respectively. | This effect is mediated possibly, in part, by release of nitric oxide, channel opening of ATP-sensitive potassium channels (K<sub>ATP</sub>) and antioxidant mechanisms due to the increase in catalase activity. |
### Table 1. Contd.

<table>
<thead>
<tr>
<th><strong>Daucus carota</strong></th>
<th>Effect of 50% ethanol extract from <em>D. carota</em> roots</th>
<th>Absolute ethanol-induced ulcer</th>
<th>Pre-treated in animals with Daucus carota root (EDC) at the doses of 100 mg/kg and 200 mg/kg, a significant inhibition of ethanol mucosal injury was detected, showing an ulcer index of 6.83 ± 0.61 and 5.17 ± 0.70, respectively.</th>
<th>EDC exhibits the activity of anti-ulcerogenic by significantly decreasing pH, volume and total acidity, and without altering the gastric wall mucous much if compared with the control group.</th>
<th>Chandra <em>et al.</em> (2015)</th>
</tr>
</thead>
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<tr>
<td><strong>Solanum cernuum Vell.</strong></td>
<td>The total hydroethanolic crude extract of <em>Solanum cernuum</em> (ESC) HCl/Ethanol-induced ulcer</td>
<td>The pre-treatment orally with ESC extract decreased the total area and percentage of lesions in the ethanol induced ulcer model when compared with the negative control group (p &lt; 0.05).</td>
<td>Treatment with ESC extract (100, 250 and 500 mg/kg) decreases the percentage of lesion area, when compared with the control group (P&lt; 0.001) in the indomethacin induced ulcer model.</td>
<td>The high content of flavonoids and ferulic acid, which have high antioxidant activity and consequently strong ability to induce cell survival mechanisms via the Nrf2/ARE signaling pathway, are the main components that are responsible for these desirable gastro-protective effects of the leaf extract.</td>
<td>Abreu <em>et al.</em> (2015)</td>
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<td></td>
<td>NSAIDs-induced ulcers in mice</td>
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<td>Treatment with the extract of ESC (250 mg/kg) during a week significantly decreased the injury size that produced by acetic acid if it is compared with the control group. The curative ratios were 81.83% for ESC extract.</td>
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<td></td>
<td>Acetic acid-induced chronic ulcer in mice</td>
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</table>
### Table 1. Contd.

<table>
<thead>
<tr>
<th>Species</th>
<th>Extract</th>
<th>Solvent</th>
<th>Treatment and Results</th>
</tr>
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<tbody>
<tr>
<td><em>Celtis iguanaea</em> (Jacq.)</td>
<td>Hexane (HE)</td>
<td>HCl/ethanol</td>
<td>Mice treatment with hexane extract (HE) at the doses of 100 or 200 mg/kg, decreased the gastric lesions by 34.3% and 43.2% respectively. The hypothermic restraint stress significantly decreased the lesions index (LI) when compared to the control group by 49.2% and 43.8%, respectively.</td>
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</table>

*Acetic acid-induced gastric ulcer* HE treatment decreased the ulcerated area significantly if compared to the control group. The reduction in the formation of LI was by 68.4% and 57.8%, respectively. The mechanism of gastro-protective effect of *C. iguanaea* HE suggests the participation of mucous as well as the involvement of adrenergic, NO and prostaglandins.

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**Figure 3.** The mode of action of NO, SH and PGs.
Table 2. Some compounds involved in the defense or injury of ulcer with their mechanisms.

<table>
<thead>
<tr>
<th>Compound/receptor</th>
<th>Mechanism of action</th>
<th>Reference(s)</th>
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</table>
| Bicarbonate, mucous, phospholipids | - Form an unstimulated layer on the mucosal surface. The layer plays a role as a physical barrier against luminal pepsin  
- This layer retains secreted bicarbonate to maintain a neutral pH at the epithelial cells | Wallace (2008); Laine et al. (2008); Gyires et al. (2013); Allen et al. (2005); Odashima et al. (2006) |
| Prostaglandins             | - Increase the secretion of mucous and bicarbonate  
- Decrease gastric epithelium and acid back-diffusion permeability  
- Enhance mucosal blood flow  
- Inhibition of acid secretion and motility  
- Inhibition of inflammatory mediator release from mast cells | Wallace and Devchand (2005); Wallace (2006); Takeuchi et al. (2014); Kotani et al. (2006) |
| Calcitonin gene-related peptide (CGRP) and nitric oxide | - Increasing the mucin synthesis  
- Inducing the submucosal vasodilation and enhance mucosal blood flow  
- Acid secretion inhibition  
- Inducing the effects of anti-inflammatory | Li et al. (1992); Holzer et al. (1998); Gyires et al. (2007); Holzer et al. (2007) |
| Somatostatin               | - Decrease the elevated level of substance P, VIP and leukotriens  
- Has antioxidant, anti-inflammatory and anti-apoptotic roles | Karmeli et al. (1994); Nassar et al. (2011) |
| Protein and non-protein sulfhydryls | - Antioxidant or reactive metabolite-eliminating effects  
- Counteract oxidative stress  
- Increases mucosal blood flow  
- Stimulates bicarbonate secretion  
- Reduces proinflammatory cytokine production and leukocyte-endothelial adherence  
- Increases prostaglandin synthesis  
- Decreases reactive oxygen metabolite production  
| Hydrogen sulfide (H₂S)     | - Counteract oxidative stress, catalyzes the oxidative degradation of the pro-oxidant heme to antioxidant and cytoprotective CO and biliverdin  
- Promotes tissue repair | Bindu et al. (2013); Llesuy and Tomaro (1994); Guo et al. (2003) |
| Hemeoxygenase-1 (HO-1)     | - Involved both in the pathogenesis and healing of peptic ulcers | Pradeep et al. (2011); Kim et al. (2011); Ganguly et al. (2009); Li et al. (2013) |
| Matrix metalloproteinase (MMPs) | - Enhancing the functions of the mucosal barriers by mucous gel stabilizing and epithelial restitution promoting. | Hoffmann et al. (2005); Hoffmann et al. (2004) |
| Trefoil factor family (TFF) proteins (TFF1-3) | - The activation of sensory neurons and epithelial cells stimulates the efferent function of afferent nerve endings and releases CGRP/NO, which manifests in protection of gastric mucosal. | Szolcsanyi and Bartho (2001); Holzer et al. (1988); Mozsik et al. (2007) |
delay the healing of acute gastric lesions and extended the healing of chronic gastric ulcers (Wallace, 2008; Laine et al., 2008). Consequently, some studies suggested that COX-2 could play a critical role in the preservation of gastric mucosal integrity, ulcer healing and gastro-protection, questioning as to whether the managing of specific COX-2 inhibitors is clinically safe (Brzozowski et al., 2001; Brzozowski et al., 1999). (Table 2)

**CONCLUSION**

Peptic ulcer is a gastro intestinal disorder occurred due to the imbalance between the aggressive factors such as acid, pepsin and *Helicobacter pylori*, and defensive factors like bicarbonate secretion, prostaglandins, gastric mucus, and innate resistance of the mucosal cell factors. In this review we attempt to summarize the bioactive compounds derived from plants such as HESM, thymol and CAI for the treatment of peptic ulcer. It is proved that plant extracts have significant antiulcer activity in animal models. It was found that the potential effect of involvement of some factors in protective effect property of medical extract, like prostaglandins, NO, and H2S, was varied according to the type of the plant extract.

**Conflict of interest**

The authors confirm that this article content has no conflict of interest.

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