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Research Paper

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 (H_2S). 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 (Malfertheiner *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 therapeutic 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 (Naito *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 mucus 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 ligature. 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

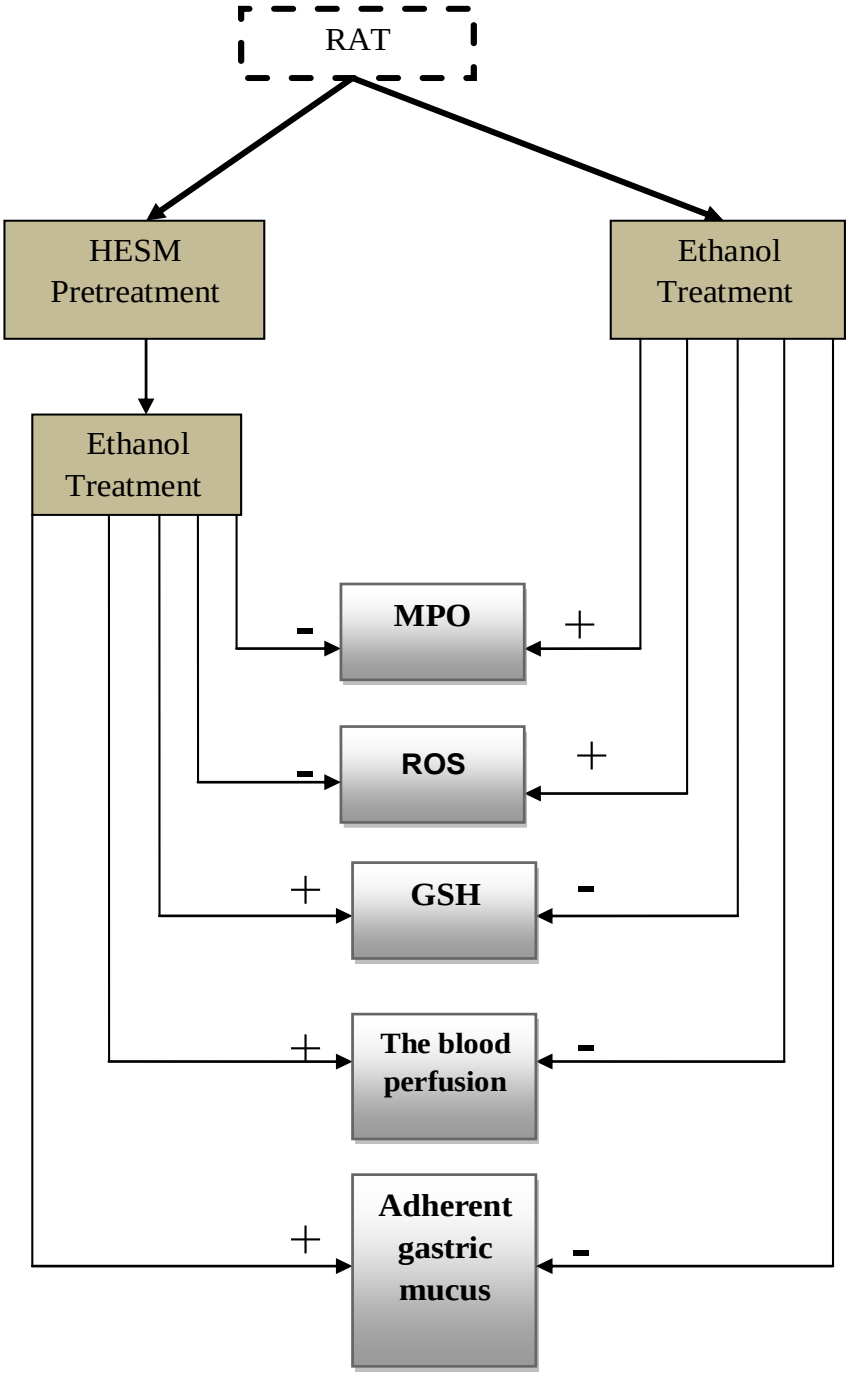

Figure 1. Mechanism of action of HESM.

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), anti-microbial (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 monoterpene 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 H_2S 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_{ATP} channels which 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, H_2S, 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 H_2S 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_3^-) 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

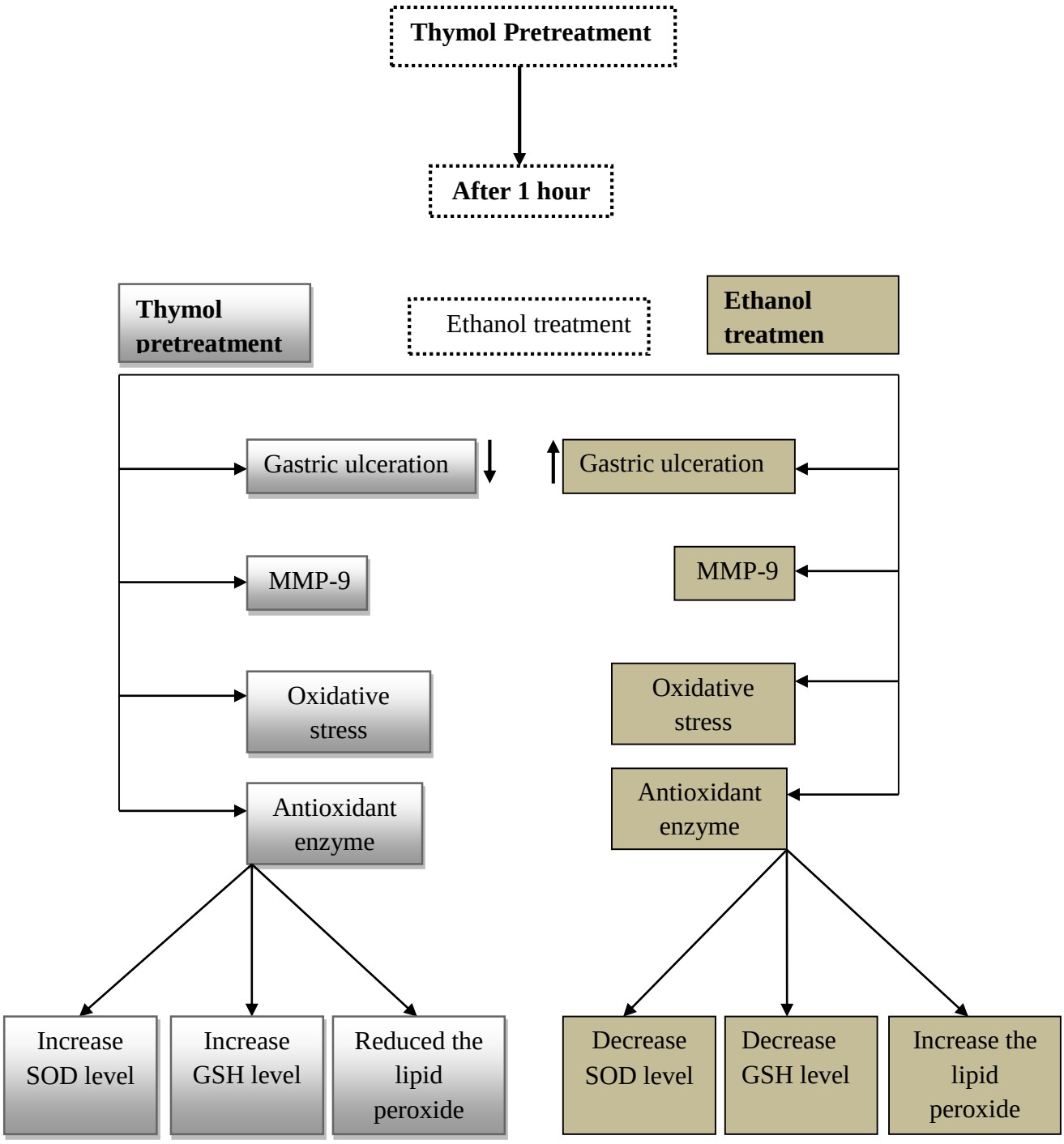

Figure 2. Mechanism of thymol action against ethanol induced gastric mucosal injury in rat model.

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

Table 1. Anti-ulcer activity of many selected medicinal plants.

Name of plant	Extract	Animal model	Result(s)	Mechanism of action	Reference(s)
Cupheaa equipetala	*Cupheaa eqipetala* infusion (CAI)	Ethanol in mice	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)	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	Palacios *et al*. (2014)
Calotropis procera bark	Methanolic (MET) aqueous (AQ)	Ethanol in mice	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) ($p<=0.05$)	It has been suggested that both MET and AQ extracts could act by increasing the production of prostaglandins	Escobedo *et al*. (2012)
Mouririelliptica	Methanolic extract (ME), Ethyl acetate fraction (EAF)	Ethanol in mice	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.	Maintaining the level of PGE_2 to activate expression of COX-2 and stimulate proliferative factors that re-established the gastric mucosa integrity.	Moleiro *et al*. (2009)
		NSAIDs	ME showed gastro-protection ($P < 0.05$) at125 or 500 mg/kg doses, while EAF exhibited gastro-protection only at the dose of 100 mg/kg ($P < 0.05$).		
		In pyloric ligation	Animals pretreated orally or intraduodenally with ME presented significantly decreases in ulcerative lesion (37 and 58%, respectively).		

Table 1. Contd.

Lithraea molleoides	Methanolic extract infusion	acetylsalicylic acid (ASA)	*Lithraea molleoides (*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.	Garro *et al*. (2015)
		Ethanol	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.		
Herba Pogostemonis	Patchouli alcohol	Ethanol	According to the PA-pretended groups (10, 20 and 40 mg/kg dose), the ulcer area was significantly decreased ($P < 0.01$) in a dose-dependent manner.	It could involve the induction of COX-mediated PGE2, enhancement of antioxidant and anti-inflammatory status, protection of GBF and (non-protein sulfhydryl group) NP-SH, as well as boost of gastric mucus production.	Zheng *et al*. (2014)
		Indomethacine in rats	Pretreatment with PA at dose of 10 mg/kg resulted in a significant reduction in ulcer area (0.58 ± 0.12 mm^2), with inhibition rate of 81.94% ($P < 0.05$).		
Margaritaria discoidea	Ethanolic extract	Ethanol	Pre-treatment with the extract at doses of 50, 100 and 150 mg/kg indicated 46.94, 68.51 and 76.68% of protection respectively if compared with the control group.	The extract increased the level of SOD, CAT and GSH activities. It also decreased the level of lipid peroxidation. These results showed that the extract could exert its gastro-protective effect by an antioxidant mechanism.	Sofidiya *et al*. (2015)

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. ($P < 0.01$).	The polyphenolic chemical composition of the extract may contribute, at least in part, to the gastro-protection.	Sagradas *et al*. (2015)
Cenostigma macrophyllum	The hydro-alcoholic fraction from leaves of *C. macrophylum* (Cm-FHA)	Absolute ethanol induced ulcer in mice	Oral administration of the hydroalcoholic fraction of leaves of *Cenostig mamacrophyllum* 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 mm^2, respectively.	This effect is mediated possibly, in part, by release of nitric oxide, channel opening of ATP-sensitive potassium channels (K_{ATP}) and antioxidant mechanisms due to the increase in catalase activity.	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 mm^2) 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 mm^2, respectively.		

Table 1. Contd.

Daucus carota	Effect of 50% ethanol extract from *D. carota* roots	Absolute ethanol-induced ulcer	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. Pre-treated in animals at doses of 100 mg/kg and 200 mg/kg with EDC showed a significant inhibition of Pyloric ligation induced ulcer.	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.	Chandra *et al*. (2015)
Solanum cernuum Vell.	The total hydroethanolic crude extract of *Solanum cernuum* (ESC)	HCl/Ethanol-induced ulcer NSAIDs-induced ulcers in mice Acetic acid-induced chronic ulcer in mice	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 ($p < 0.05$). Treatment with ESC extract (100, 250 and 500 mg/kg) decreases the percentage of lesion area, when compared with the control group ($P< 0.001$) in the indomethacin induced ulcer model. 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.	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.	Abreu *et al*. (2015)

Table 1. Contd.

Celtis iguanaea (Jacq.)	Hexane extract (HE)	HCl/ethanol	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 mechanism of gastro-protective effect of *C. iguanaea* HE suggests the participation of mucous as well as the involvement of adrenergic, NO and prostaglandins.	Martins *et al*. (2014)
		The hypothermic restraint stress	HE treatment significantly decreased the lesions index (LI) when compared to the control group by 49.2% and 43.8%, respectively.		
		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.		

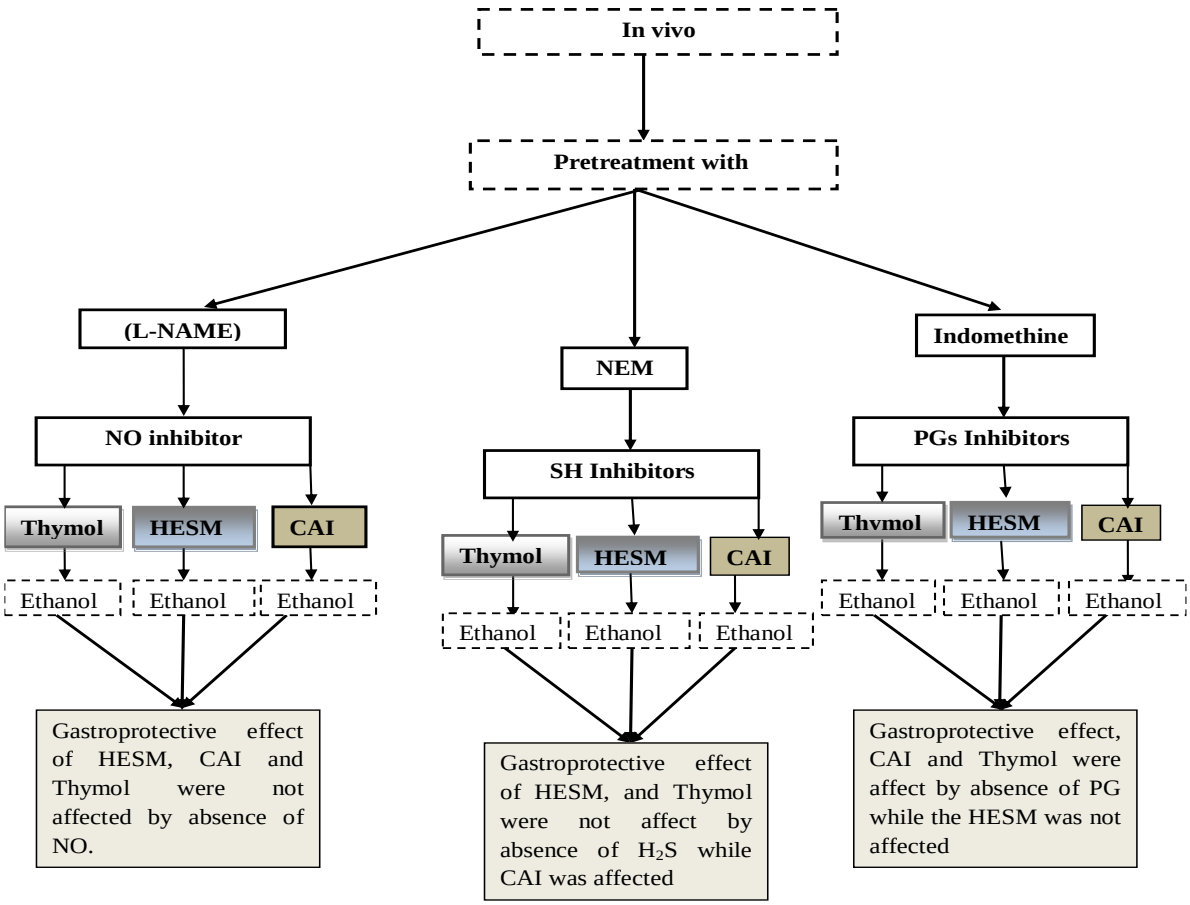

Figure 3. The mode of action of No, SH and PGs.

Table 2. Some compounds involved in the defense or injury of ulcer with their mechanisms.

Compound/receptor	Mechanism of action	Reference(s)
Bicarbonate, mucous, phospholipids	- Form an unstirred 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	Szabo *et al*. (1992); Ali *et al*. (1995)
Hydrogen sulfide (H_2S)	- Increases mucosal blood flow - Stimulates bicarbonate secretion - Reduces proinflammatory cytokine production and - Leukocyte-endothelial adherence - Increases prostaglandin synthesis - Decreases reactive oxygen metabolite production - Enhances tissue repair	Wallace *et al*. (2010); Wallace (2012)
Hemeoxygenase-1 (HO-1)	- 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)
Matrix metalloproteinase (MMPs)	- 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)
Trefoil factor family (TFF) proteins (TFF1-3)	- Enhancing the functions of the mucosal barriers by mucous gel stabilizing and epithelial restitution promoting.	Hoffmann *et al*. (2005); Hoffmann *et al*. (2004)
TRRV-1 receptors	- The of both activation on 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)

Table 2. Contd.

Toll-like receptors (TLRs)	- It has an important role in hosting the microbial interaction by sensing conserved the microbial structures. - Induce the responses inflammatory and might delay healing from ulcer.	Miyake *et al*. (2007); Kumar *et al*. (2011); Smith *et al.* (2003); Nadatani *et al*. (2013); Lagunes *et al*. (2013)
Proteinase-activated receptors (PARs)	- Increases mucous secretion and enhances mucosal blood flow - Inhibit the secretion of the gastric acid	Nishikawa *et al*. (2002); Kawabata et al. (2004); Kawabata *et al*. (2001)
Adenosine A2A receptors	- When activated, it reduces the elevated pro-inflammatory cytokine level in gastric mucosa following NSAID-induced lesions	Odashima *et al*. (2005); Odashima *et al.* (2006); Koizumi *et al.* (2009)

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 H_2S, 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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