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An Evidence-based Review on Medicinal Plants used for the Treatment of Peptic Ulcer in Traditional Iranian Medicine

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Abstract: Many medicinal plants have been identified in Traditional Iranian Medicine (TIM) for the treatment of Peptic Ulcer (PU) but they are still unknown to scientific community. In the present study anti PU activity of these remedies were systematically reviewed and identified. For this purpose, medicinal plants proposed for the management of PU in TIM were collected from TIM sources and they were searched in modern medical databases like PubMed, Scirus, Sciencedirect and Google Scholar to find studies confirmed their efficacy. Findings from modern investigations support the claims of TIM about the efficacy of many of these plants in PU. For example, the oleogum resin of *Boswellia carterii* and *B. serrata* as a beneficial remedy for PU in TIM were demonstrated to have wound healing, cytoprotective, antisecretory, antacid, prostaglandin production and inflammatory modulating properties. Fruit and leaves of *Myrtus communis* was found to be antioxidant, anti *H. pylori*, wound healing, antisecretory, antacid and cytoprotective. The aerial part from *Melissa officinalis* exerts its beneficial effects in PU by antioxidant, anti *H. pylori*, prostaglandin elevating, cytoprotective, antisecretory, antacid and leukotriene reducing properties. Furthermore, *Polygonum* species demonstrated its function on PU with prostaglandin enhancement, inflammatory modulation, wound healing, cytoprotection, antacid, antioxidant and anti-*H. pylori* activity. In contrast, for some of herbal remedies used in TIM such as *Dolichos lablab* flower, *Symphytum* species, *Zizyphus spina-christi* fruit, *Alisma plantago-aquatica*, *Cupressus sempervirens* fruit, *Acacia Arabica* gum, *Cyperus* species root, *Althaea officinalis* flower and *Nymphaea alba* flower there is no enough evidence in modern medicine to prove their effectiveness in the management of PU. Pharmacological and clinical studies for evaluation of efficacy of these herbs in PU and their possible mechanisms of action are recommended.

Key words: Evidence-based medicine, gastrointestinal pharmacology, medicinal plants, peptic ulcer, traditional iranian medicine

INTRODUCTION

Peptic Ulcer disease (PU) is a complex and multicausal disease which encompass gastric and duodenal ulcer, occurs when biological balance between defense and aggressive factors in gastrointestinal tract is disturbed (Sunbul *et al*., 2011). Among aggressive factors, gastric acid and pepsin secretion (Borrelli and Izzo, 2000), active free radicals and oxidants (Repetto and Llesuy, 2002), leukotrienes (Wallace *et al*., 1990), endothelins (Borrelli and Izzo, 2000) and exogenous factors such as ethanol (Soll and Graham, 2009) or NSAIDs (Takeuchi, 2012) can be listed. In contrast, gastric mucus, bicarbonate (Allen and Garner, 1980), normal blood flow (Borrelli and Izzo, 2000), prostaglandins (Cryer, 2001), nitric oxide (NO) (Martin *et al*., 2001) and antioxidant enzymes such as catalase or Glutathione (GSH) (Repetto and Llesuy, 2002) work defensive. Most of the gastric lesions originate in a chronic infection of gastric mucosa with *Helicobacter pylori* (*H. pylori*). *H. pylori* is a common human pathogen with asymptomatic stomach colonization in nearly 70% of the population and approximately in 10 B 20% are susceptible for PU (Vitor and Vale, 2011). Medicinal plants identified in traditional medicine have a long history of consumption in nutrition and medicine in different nations. Thus, traditional medicines is a virgin resource for investigation on their efficacy and phytochemical constituents (Rahimi *et al*., 2012; Rahimi and Ardekani, 2013; Ardekani *et al*., 2011; Rahimi *et al*., 2013; Khanavi *et al*.,

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2012). There are many natural remedies in Traditional Iranian Medicine (TIM) that have been used for management of PU. Various mechanisms have been explained in TIM sources for their effectiveness including astringent, wound healing, antiseptic and anti-inflammatory activities (Aghili, 2009; Avicenna, 1983; Arzani, 2005). Present study conducted to review medicinal plants considered as gastroprotective and healing agents on PU in TIM resources and beside that to gather evidence for their effectiveness and biological mechanisms in modern investigation.

Methods: In order to achieving this aim, electronic databases including Scirus, Sciencedirect, PubMed, Scopus, Web of Science and Google Scholar were explored for each of the medicinal plants proposed in TIM for PU and all retrieved articles were evaluated to achieve any *in vitro*, *in vivo*, or clinical evidence for their efficacy and possible mechanisms. The retrieved studies either demonstrate obviously effectiveness of these herbs or indirectly their efficacy on the involved mechanisms in the treatment of PU.

FINDINGS AND DISCUSSION

Medicinal plants used for the treatment of PU in TIM

***Acacia arabica*:** *A. senegal* gum protected against cold restraint stress-induced gastric ulcer in rat (Omayma *et al*., 2011). Aqueous extract of *A. arabica* gum showed protection against meloxicam-induced intestinal damage and attenuated intestinal enzymes (lipase, amylase, alkaline phosphatase and lactate dehydrogenase) activity (Abd El-Mawla and Eldien, 2011).

***Acorus calamus* L.:** The rhizome showed antioxidant activity *in vitro* and *in vivo* in ethanol-induced oxidative stress in rat (Ilaiyaraja and Khanum, 2011). The rhizome protected against gastric ulcer induced by pyloric ligation, indomethacin, reserpine and duodenal ulcer induced by cysteamine. It also protected against cytodestructive agents and reduced acidity of gastric juice (Rafatullah *et al*., 1994). The rhizome did not show inhibitory activity against H. pylori *in vitro* (Babarikina *et al*., 2011). *A. calamus* leaves demonstrated wound healing activity in rat (Jain *et al*., 2010).

***Alisma plantago-aquatica*:** It showed antioxidant activity *in vitro* (Kim *et al*., 2007). Its rhizome inhibited iNOS expression *in vitro* (Kim *et al*., 1999). The rhizome as a constituent in a polyherbal formulation demonstrated protective activity against ethanol-induced ulcer in rat via its antioxidant activity (Jeon *et al*., 2012).

***Althaea officinalis* L.:** It exhibited protective effect on ethanol-induced gastric ulcer in rats (Hage-Sleiman *et al*., 2011) and inhibited urease enzyme (a vital enzyme for *H. pylori* growth in stomach) *in vitro* (Nabati *et al*., 2012). Its hydroalcoholic extract demonstrated antioxidant activity (Jahed Khaniki *et al*., 2012).

***Bambusa arundinacea*:** *B. vulgaris* secretions inhibited urease enzyme *in vitro* (Nabati *et al*., 2012). *B. arundinacea* leaves demonstrated antioxidant activity and protected against aspirin and pylorus ligation-induced gastric ulcer in rats with no significant effect on gastric juice secretion and acidity (Muniappan and Sundararaj, 2003; Naz *et al*., 2012).

***Boswellia carterii* and *B. serrata*:** Boswellic acids isolated from the oleo gum resin of *B. serrata* protected gastric mucosa against acute and chronic ethanol/HCl-, cold restraint stress-, asprin-, indomethacin-and pyloric ligation-induced ulcer in rat. The mechanism of gastroprotective function is attributed to production of prostaglandins, increasing pH and reducing volume of gastric juice, inhibition of leukotriene synthesis and improvement of gastric cytoprotection (Singh *et al*., 2008). Oleo gum resin from *B. carterii* and *B. serrata* healed acetic acid-induced chronic gastric ulcer in rat via., enhancing regeneration of mucosal ulcers (Mei and Zeng, 2012). A topical formulation from *B. serrata* oleo gum resin showed *in vivo* wound healing activity (Mallik *et al*., 2010).

***Cupressus sempervirens*:** Essential oil isolated from fruits in al topical formulation did not exhibit remarkable wound healing activity in rats (Tumen *et al*., 2012). The essential oil inhibited the growth of *H. pylori in vitro* (Ohno *et al*., 2003).

***Cyperus* species:** *C. rotundus* rhizome showed significant wound healing activity in rat (Puratchikody *et al*., 2006). It protected against ischemia and reperfusion gastric damage induced by celiac artery clamping in rat via., its antioxidant activity (Guldur *et al*., 2010).

***Dolichos lablab*:** *D. lablab* in a polyherbal formulation showed antacid activity *in vitro* (Wu *et al*., 2010). Seed extract of *D. lablab* had antioxidant properties *in vitro* (Marathe *et al*., 2011). It did not show significant antibacterial properties against *H. pylori* (Lee *et al*., 2003). The leaves of *D. lablab* demonstrated gastroprotective activity against aspirin and ethanol-induced ulcer (Tarin and Chichioco-Hernandez, 2011).

***Hyssopus officinalis*:** The aerial parts also exhibited wound healing properties via enhancement of collagen and antioxidant activity on cell culture (Alexandru *et al*., 2011).

***Laurus nobilis*:** Gastroprotective activity of aqueous and oily fraction of seeds on ethanol-induced gastric ulcer in rats has been proven (Afifi *et al*., 1997). The fruits demonstrated strong gastroprotective function against ethanol-induced ulcer in rat (Gurbuz *et al*., 2002). *L. nobilis* leaves demonstrated wound healing (Nayak *et al*., 2006), anti *H. pylori* (Mahady *et al*., 2005) and antioxidant activities (Speroni *et al*., 2011).

***Melissa officinalis* L.:** The aerial parts showed antioxidant properties *in vitro* (Canadanovic-Brunet *et al*., 2008). The essential oil and the main component citral inhibited contraction of isolated rat ileum in response to KCl, acetylcholine and serotonin in a concentration-dependent manner (Sadraei *et al*., 2003). The leaves and essential oil revealed antimicrobial activity against *H. pylori in vitro* (Mahady *et al*., 2005; Weseler *et al*., 2005). The leaf extract protected gastric mucosa from indomethacin and pylorus ligation-induced gastric ulcer through suppressing gastric acidity, acid secretion and leukotriene in gastric juice and increasing defense factors including mucin, pepsin and prostaglandin E_2 in gastric juice (Khayyal *et al*., 2006).

***Myrtus communis* L.:** A topical formulation of *M. communis* in low doses demonstrated wound healing activity in rat excision wounds (Rezaie *et al*., 2012). *M. communis* fruits protected against gastric ulcer caused by ethanol, indomethacin and pyloric ligation in rat via suppressing gastric secretion and acidity and enhancing its mucosal barrier (Sumbul *et al*., 2010). *M. communis* essential oil demonstrated strong antimicrobial activity against *H. pylori in vitro* (Deriu *et al*., 2007). *M. communis* leaf, stem and flower essential oil and methanolic extract showed antioxidant properties *in vitro* (Wannes *et al*., 2010).

***Nymphaea alba*:** Its extract strongly inhibited urease enzyme *in vitro* (Nabati *et al*., 2012). *N. alba* rhizome showed antidiarrheal action via fluid infiltration and reduction in gastrointestinal tract transit in the rat (Bose *et al*., 2012a). It also revealed antioxidant activity *in vitro* (Bose *et al*., 2012b). *N. lotus* in a polyherbal formulation exhibited wound healing activity in rats (Dwivedi *et al*., 2010).

***Oxalis* species:** *O. corniculata* whole plant demonstrated wound healing activity in rats (Taranalli *et al*., 2004). It also protected against gastric ulcer induced by pylorus ligation and indomethacin via reducing gastric secretion and free and total acidity (Sakat *et al*., 2012). Furthermore, *O. corniculata* leaves exhibited gastroprotective function on pyloric ligation-and ethanol-induced ulcer in rat through antioxidant activity and reducing gastric secretion and acidity (Patil *et al*., 2011).

***Pistacia lentiscus*:** The oleo-gum resin showed antioxidant activity *in vitro* (Mahmoudi *et al*., 2010). Topical administration of *P. lentiscus* virgin fatty oil revealed wound healing properties (Djerrou *et al*., 2010). The oleo-gum resin demonstrated gastroprotective activity on different models of gastric ulcer in rats. It also reduced gastric free acidity in pylorus-ligated rats. It did not demonstrate significant protection in cysteamine-induced duodenal ulcers (Al-Said *et al*., 1986). Al-Habbal *et al*. (1984) showed significant healing activity of the oleo-gum resin in patients with duodenal ulcer and the same was confirmed *in vitro* (Marone *et al*., 2001). The oleo-gum resin and its major constituent, triterepenic acids, reduced growth of *H. pylori* in stomach of the infected mice without significant suppression of chronic gastritis and inflammatory infiltration associated with *H. pylori* (Paraschos *et al*., 2007). In a randomized pilot clinical study, the oleo-gum resin demonstrated antibacterial activity against *H. pylori* and exhibited significant eradication of the bacteria (Dabos *et al*., 2010). In contrast, Loughlin *et al*., (2003) reported that mastic gum could not eradicate *H. pylori* infection in mice and did not show significant reduction in their gastric bacterial load.

***Plantago* species:** *P. ovata* water soluble seed husk polysaccharides promoted proliferation of human epithelial cells through growth factor receptors (Deters *et al*., 2005). *P. ovata* husk stimulated NO synthase in rabbit jejunum *in vitro*. Furthermore, it demonstrated secretion stimulating and muscarinic activity at doses of 100 and 300 mg kg^{-1} and antisecretory and antidiarrheal activity at higher doses (Mehmood *et al*., 2011). Mucopolysaccharides derived from the husk showed wound cleansing and wound healing properties in guinea pigs (Westerhof *et al*., 2001). *P. lanceolata* leaves revealed dose dependent peptic ulcer ameliorating activity in acetic acid-induced chronic gastric ulcer in rat and protective effect in indomethacin-and pylorus ligation-induced gastric ulcer and cysteamine-induced duodenal ulcer by its antisecretory and cytoprotective activity in mice, rats and mice, respectively (Melese *et al*., 2011). *P. major* leaf demonstrated gastroprotective activity and decreased

total acidity in aspirin-and ethanol-induced ulcer in rat (Atta *et al*., 2005; Phipps and Mahmood, 2006; Than *et al*., 1996). It also showed wound healing properties in rats (Mahmood and Phipps, 2006). Aerial parts of *P. major* showed anti *H. pylori* activity *in vitro*. In contrast, its inhibition on urease enzyme was poor (Castillo-Juarez *et al*., 2009; Nabati *et al*., 2012).

***Polygonum* species:** Two compounds isolated from *P. tinctorium*, tryptanthrin and kaempferol, inhibited *H. pylori* growth (Kataoka *et al*., 2001). *P. minus* extract revealed antioxidant activity *in vitro* (Huda-Faujan *et al*., 2007). It also prevented from ethanol-induced gastric ulcer in rat by inhibiting leucocyte infiltration in submucosa and increasing pH of gastric juice (Wasman *et al*., 2010). Qader *et al*. (2012) showed gastroprotective activity of different fractions from *P. minus* leaves in rat ethanol-induced ulcer via promoting antioxidant enzymes activity, increasing pH of gastric juice and mucus content and elevating hexosamine (the main glycoprotein of mucous tissue) and prostaglandin E2 level in gastric mucosa (Qader *et al*., 2012). The wound healing activity of *P. cuspidatum* extract has been proved in rat (Wu *et al*., 2012).

***Portulaca oleracea* L.:** *P. oleracea* showed antioxidant properties and anti H-pylori activity (Dkhil *et al*., 2011; Cho *et al*., 2008). Moreover, it accelerated wound healing in mice (Rashed *et al*., 2003). The leaves protected mice against HCl-and ethanol-induced gastric ulcer via reducing gastric acidity and increasing pH of gastric juice (Karimi *et al*., 2004).

***Quercus* species:** *Q. ilex* L. root bark and its tannic acid showed gastroprotective activity against ethanol-induced gastric ulcer in rats (Gharzouli *et al*., 1999). *Q. suber* and *Q. coccifera* leaves have protective effect on ethanol-induced gastric lesions in mice by inhibition of lipid peroxidation (Khennouf *et al*., 2003). Modern investigation also demonstrated antioxidant activity of *Q. ilex* leaves via *in vitro* assay (Chevolleau *et al*., 1993). *Q. infectoria* leaf has revealed wound healing properties through its antioxidant activity (Umachigi *et al*., 2008). *Q. infectoria* gall inhibited *H. pylori* growth *in vitro* (Voravuthikunchai *et al*., 2006).

***Rosa* species:** *R. damascena* Mill. flowers and green leaves showed antioxidant activity *in vitro* (Baydar and Baydar, 2013). *The* flower oil revealed gastroprotective activity (Maleev *et al*., 1972). The flower boiled extract demonstrated laxative activity via osmotic infiltration and transition time reduction in rat intestine (Arezoomandan *et al*., 2011). *R. canina* fruits protected against ethanol-induced gastric ulcer and inhibited 100% of the ulcers in rat (Gurbuz *et al*., 2003). Tellimagrandin I and rugosin isolated from *R. rugosa* were effective against *H. pylori in vitro* (Funatogawa *et al*., 2004).

***Symphytum* species:** Topical preparation from aerial parts of *Symphytum×uplandicum* Nyman. showed wound healing activity in different clinical trials (Barna *et al*., 2007, 2012). Wound healing activity of topical formulations from the leaves of *S. officinale* L. was demonstrated in rat model via reducing infiltration of cellular inflammatory agents and induction of collagen deposition (Araújo *et al*., 2012). Allantoin and pyrrolizidine alkaloids-free composition of *S. asperum* roots which containing crude polysaccharides and biopolymer from poly [3-(3,4 dihydroxyphenyl)glyceric acid] exhibited antioxidant and wound healing activities (Barbakadze *et al*., 2009).

***Tragopogon graminifolius* DC.:** Antioxidant activity of *T. porrifolius* aerial parts has been demonstrated *in vitro* (Mroueh *et al*., 2011). *T. collinus* DC. aerial part demonstrated protective effect on ethanol-induced gastric ulcers in rat (Farzaei *et al*., 2012). *T. graminifolius* aerial parts showed gastroprotective activity against ethanol-induced ulcer in rat (Farzaei *et al*., 2013). Flavonoids including apigenin, luteolin, quercetin and vitexin are the main constituent of *Tragopogon* genus (Kroschewsky *et al*., 1969; Sareedenchai *et al*., 2009). Quercetin showed protective activity against HCl/ethanol-induced gastric ulcer and healing activity against acetic acid-induced chronic gastric ulcer with inhibition of gastric tissue lipid peroxidation (Suzuki *et al*., 1998). *Helicobacter pylori* (*H. pylori*) urease inhibitory function of quercein has been proven (Xiao *et al*., 2012). Quercetin-3-O-α-D-glucuronopyranoside protected gastric mucus against indomethacin-induced ulcer by increasing gastric mucus secretion, reduction of myeloperoxidase (MPO) activity and free radical production, preventing the expression of intercellular adhesion molecule protein and down regulation of the pro-inflammatory cytokines (Yan *et al*., 2011).

Gallic acid is one of the major phenolic compounds of *T. pratensis* (Kucekova *et al*., 2011). Gallic acid protects against indomethacin-and also diclofenac-induced gastric ulcer in rat. Moreover, it demonstrated healing effect on indomethacin-induced gastric ulcer. Mechanism of its antiulcer activity is blocking the oxidative stress and lipid peroxidation. It showed *in vitro* antioxidant activity and suppressed gastric mucosal cell apoptosis (Pal *et al*., 2010).

***Zizyphus spina-christi* L.:** There is no scientific report confirming anti-PU activity of fruits. Although, the leaves showed antioxidant properties in various *in vitro* models (Abalaka *et al*., 2011) and stem bark demonstrated antidiarrheal activity and reduced intestinal transit in rat (Adzu *et al*., 2003).

CONCLUSION

Current stalemates of modern medicine in the management of various ailments incline research tendencies to traditional medicine. In this respect, traditional medicine has introduced good protocols for treatment of various gastrointestinal disorders including inflammatory bowel disease (Rahimi *et al*., 2010; Rastegarpanah *et al*., 2011), irritable bowel disease (Rahimi and Abdollahi, 2012a), hemorrhoids (Rahimi and Abdollahi, 2012b; Rahimi and Abdollahi, 2013) and peptic ulcer as presented in this article. All of the remedies presented here had adequate evidence from traditional or scientific source for their efficacy in management of PU. As shown in Table 1, the plants used in TIM for management of PU are from different families and there is no exact relationship between the family of plants investigated and their efficacy. For many of these herbs, various studies which demonstrating their usefulness on PU were found. These studies were mainly *in vitro* and *in vivo* which are summarized in details in the Table 2 and 3, respectively.

As shown in Table 4, only 4 clinical trials were found; 2 on Symphytum x uplandicum (Barna *et al*., 2007; Barna *et al*., 2012) and 2 on Pistacia l entiscus (Al-Habbal *et al*., 1984; Dabos *et al*., 2010). As shown in Table 5, these remedies have shown their effectiveness on PU via several mechanisms of action including prostaglandin enhancement, modulation of inflammatory mediators and antioxidant, anti *H. pylori*, wound healing, cytoprotective and antisecretory activities. For some of these plants including *Zizyphus spina-christi*, *Alisma plantago-aquatica*, *Rosa* species, *Cupressus sempervirens*, *Acacia Arabica*, *Cyperus* species, *Bambusa arundinacea*, *Althaea officinalis* and *Dolichos lablab*, just one or two study on the efficacy and relevant mechanisms has been carried out. Advanced scientific studies for evaluation of these herbs on PU and their possible mechanisms are suggested. In comparison, some of these plants such as *Boswellia carterii* and *B. serrata*, *Melissa officinalis*, *Myrtus communis*, *Polygonum* species and *Tragopogon graminifolius* show their beneficial effects in PU by affecting various associated mechanisms. According to published investigations, these medicinal plants probably are more effective in the management of PU than the other ones. As mentioned above, despite many *in vitro* and *in vivo* evidences, there are few supportive clinical findings. Therefore, conducting clinical trials on the efficacy and safety of mentioned medicinal plants in the management of PU is

Table 1: Medicinal plants used for the treatment of peptic ulcer in traditional Iranian medicine

Scientific names	Family	Name(s) in TIM resources	Uses in TIM
Acacia arabica	Leguminosae	Samghe arabi (gum)	Gastric tonic, respiratory disorders, diarrhea, PU, IBD
Acorus calamus	Acoraceae	Vaj, Agir torki	Carminative, improvement of memory function, PU, stuttering
Alisma plantago-aquatica	Alismataceae	Mezmar-o-raei, Ghashogh wash	Inflammation, diarrhea, PU
Althœa officinalis	Malvaceae	Khatmi	Rerspiratory disorders, PU, IBD
Bambusa arundinacea	Poaceae	Tabashir	Gastric and liver tonic, PU, dysentery, aphthous
Boswellia carterii and *B. serrata*	Burseraceae	Kondor	Improvement of memory function, gastric tonic, PU, IBD
Cupressus sempervireus	Cupressaceae	Joz-al-sarv (fruit)	Gastric and liver and spleen tonic, hemorrhage, PU, improvement of memory function
Cyperus species	Cyperaceae	Soad	Diuretic, gastric tonic, dyspepsia, PU, appetizer
Dolichos lablab	Leguminosae	Ashaghe	Purgative, inflammation, PU, obstmctive disorders of liver
Hyssopus officinalis	Labiatae	Zoufa	Respiratory disorders, PU
Laurus nobilis	Lauraceae	Barge bou, Hab-al-ghar (seed)	Antidepressant, diuretic, PU
Melissa officinalis	Labiatae	Badranjbouye	Anexiolytic, antidepressant, carminative, PU
Myrtus communis	Myrtaceae	Mourd, Aas	Antidepressant, diarrhea, polymenorrhera, bruise
Nymphaea alba	Nymphaeaceae	Niloufar	Palpitation, diarrhea, PU
Oxalis species	Oxalidaceae	Hammaz, Torshe	Liver tonic, appetizer, PU, IBD
Pistacia lentiscus	Anacardiaceae	Mastaki	Gastric tonic, diarrhea, PU, IBD
Plantago major and *P. lanceolata*	Plantaginaceae	Barhang, Lesan-al-hamal	Hemorrhage, diarrhea, IBD
Plantago ovata and *P. psyllium*	Plantaginaceae	Esfarze, Bazr-e-ghatouna,	Laxative, softening, inflammation, PU, IBD
Polygonum spp.	Polygonaceae	Alaf haft band, Asi-al-raei	PU, hemoptysis, hemorrhage, chronic diarrhea, wound healer
Portulaca oleracea	Portulacaceae	Khorfe, Baghle-al-homgha	Gastric tonic, urinary tract iufections, lithontropic, diabetes, PU
Quercus species	Fagaceae	Balout, Jaft (fruit husk), Afes and Majou (gall)	Diarrhea, hemorrhage, PU, IBD
Rosa species	Rosaceae	Gole sorkh,Vard	Antidepressant, wound healer, Gastric tonic, PU,
Symphytum sp.	Boraginaceae	Samghouton,	Inflammation, IBD, PU, polymenorrhea
Tragopogon graminifolius	Composiatae	Sheng, Lahyat-al-tis,	Gastric tonic, dydpepsia, PU, IBD, hemorrhage, polymenorrhea, wound healer
Zizyphus spina-christi	Rhamnaceae	Sedr, Konar	Diarrhea, PU

Table 2: *In vitro* studies on plants used in traditional Iranian medicine for the treatment of peptic ulcer

Plant	Part/extract	Active constituent	Result	Reference
Acacia arabica	Bark/ various extracts and fractions	-	Antioxidant activity, lipid peroxidation inhibition, the strongest antioxidant Activity with ethyl acetate fraction	Sundaram and Mitra (2007)
Acorus calamus	Rhizome/methanol extract		Antioxidant activity and inhibition of lipid peroxidation	Ilaiyaraja and Khanum (2011)
	Rhizome/water extract	-	No inhibitory action on *H. pylori*	Babarikina *et al.* (2011)
Alisma	Rhizome/aqueous extract	-	Inhibition of iNOS expression	Kim *et al.* (1999)
plantago-aquatica	Rhizome	-	Antioxidant activity	Kim et al., 2007
Althaea officinalis	Flower/50% methanol extract	-	*H. pylori* urease enzyme inhibition	Nabati *et al.* (2012)
	Flower/hydroalcoholic extract	-	Antioxidant	Jahed Khaniki *et al.* (2012)
Bambusa vulgaris	Secretions/50% methanol extract	-	*H. pylori* urease enzyme inhibition	Nabati *et al.* (2012)
Bambusa arundinacea	Leaves/various extract	-	Antioxidant	Naz *et al.* (2012)
Cupressus sempervirens	Essential oil	-	Anti *H. pylori*	Ohno *et al.* (2003)
Cyperus esculentus	Seeds/oil	-	Antioxidant activity	Jing *et al.* (2013)
Cyperus papyrus, *C. esculentus* and *C. rotundus*	Tuber/various extracts	-	Antioxidant activity *in vitro* and also in cell line	Hamed *et al.* (2012)
Dolichos lablab	Seeds in polyherbal formulation decoction	-	Antacid	Wu *et al.* (2010)
	Beans/80% methanol extract	-	Antioxidant	Marathe *et al.* (2011)
	Seeds/methanol extract	-	No anti *H. pylori* activity	Lee *et al.* (2003)
Hyssopus officinalis	Aerial part/ethanol extract	-	Wound healing function, enhancement of collagen in cell culture, antioxidant activity	Alexandru *et al.* (2011)
Laurus nobilis	Leaves/chloroform and methanol extract	-	Antioxidant	Speroni *et al.* (2011)
	Leaves/methanol extract	-	Anti *H. pylori*	Mahady *et al.* (2005)
Melissa officinalis	Aerialparts/petroleum ether, chloroform, ethyl acetate, n-butanol and water extracts	-	Antioxidant, ↓lipid peroxidation Canadanovic-	Brunet *et al.* (2008)
	Leaves/methanol extract	-	Anti *H. pylori*	Mahady *et al.* (2005)
	Essential oil	-	Anti *H. pylori*	Weseler *et al.* (2005)
	Essential oil	Citral	Inhibition on KCl, acetyl choline and 5-HT induced contraction of isolated rat ileum	Sadraei *et al.* (2003)
Myrtus communis	Leaf/essential oil	-	Strong anti *H. pylori* activity	Deriu *et al.* (2007)
	Leaf, stem and flower/essential oil and methanol extract	-	Antioxidant activity	Wannes *et al.* (2010)
Nymphea alba	Rhizome/ethanol extract	-	Antioxidant	Bose *et al.* (2012b)
	Flower/methanol extract	-	Inhibition of *H. pylori* urease enzyme	Nabati *et al.* (2012)
Pistacia lentiscus	Oleo gum resin	-	Anti *H. pylori*	Marone *et al.* (2001)
	oleo gum resin/total extract without polymers and its different fractions	Major triterepenic acids particularly iso masticadienolic acid	Anti *H. pylori*	Paraschos *et al.* (2007)
	Aerial parts/ methanol extract	-	Anti-*H. pylori*	Castillo-Juarez *et al.* (2009)
Plantago major	Seed husk	Water soluble polysaccharides	↑Proliferation of human epithelial cells (skin keratinocytes and fibroblasts), ↑growth factor receptors	Deters *et al.* (2005)
	seed husk/ crude extract	-	↑NO synthase	Mehmood *et al.* (2011)
Polygonum tinctorium	-	Tryptanthrin, kaempferol	Anti *H. pylori*	Kataoka *et al.* (2001)
Polygonum minus	Aerial parts/water extract	-	Antioxidant	Huda-Faujan *et al.* (2007)
Portulaca oleacea	whole part/ water and 80% ethanol extract	-	Anti *H. pylori*, antioxidant	Cho *et al.* (2008)
Quercus ilex	Leaves/hexane extract	-	Antioxidant	Chevolleau *et al.* (1993)
Quercus infectoria	Gall/Ethanol extract	-	Anti *H. pylori*	Voravuthikunchai *et al.* (2006)
Rosa damascena	Flowers and green leaves/hot and cold methanol extracts	-	Antioxidant	Baydar and Baydar (2013)
Rosa rugosa	-	Tellimagrandin I and rugosin	Anti *H. pylori*	Funatogawa *et al.* (2004)
Tragopogon graminifolius	Aerial part/methanol extract	-	Antioxidant	Mroueh *et al.* (2011)
		Quercetin	Antioxidant	Suzuki *et al.* (1998)
		Quercetin	*H. pylori* urease inhibition	Xiao *et al.* (2012)
		Gallic acid	Antioxidant function, gastric mucosal cell apoptosis inhibition	Pal *et al.* (2010)
	Leaves/ ethanol and hexane extracts	-	Antioxidant	Abalaka *et al.* (2011)

Table 3: *In vivo* studies on plants used in traditional Iranian medicine for the treatment of peptic ulcer

Plant	Part/extract	Active Constituent	Model	Species	Result	Reference
Acacia arabica	Gum/aqueous extract	-	Meloxicam-induced intestinal damage	Rat	↓Intestinal damage, Attenuation of intestinal enzymes (lipase, amylase, alkaline phosphatase and lactate dehydrogenase) increase	Abd El-Mawla and Eldien (2011)
Acacia senegal	Gum	-	Cold restraint stress-induced gastric ulcer	Rat	↓Gastric ulcer	Omayma *et al*. (2011)
Acorus calamus	Rhizome/methanolic extract	-	Ethanol-induced oxidative stress	Rat	↑Antioxidant activity and enzymes, lipid peroxidation prevention	Ilaiyaraja and Khanum (2011)
	Leaves/80% ethanol extract	-	Excision and incision wound	Rat	Wound healing activity	Jain *et al*. (2010)
Alisma plantago-aquatica	Rhizome/ethanolic extract	-	Pyloric ligation-, indomethacin-and reserpine-induced gastric ulcer, duodenal ulcer induced by cysteamine, cytoprotection model induced by cytodestructive agents (80% ethanol, 0.6 M HCl, 0.2 M NaOH and 25% NaCl),	Rat	↓Gastric ulcer in all gastric ulcer models, ↓gastric juice and acidity in pylorus ligation model, ↓intestinal ulcer, protection against cytodestructive agents (cytoprotective activity)	Rafatullah *et al*. (1994)
	Rhizome/boiled extract in polyherbal formulation	-	Ethanol-induced gastric ulcer	Rat	↓Gastric ulcer, ↓lipid peroxidation, activation of antioxidant enzymes such as GSH	Jeon *et al*. (2012)
Althaea officinalis	Flower/aqueous extract	-	Ethanol-induced gastric ulcer	Rat	↓Gastric ulcer	Hage-Sleiman *et al*. (2011)
Bambusa arundinacea	Leaf/methanol extract	Hydrolysate β-(1-3)-glucan	Aspirin-and pylorus ligation-induced gastric ulcer	Rat	↓Gastric ulcer in both experimental models, no significant effect on gastric juice secretion and acidity	MuniappanandSundararaj(2003)
Boswellia serrata	Oleo gum resin	Boswellic acids	acute and chronic ethanol/HCl-, cold restraint stress-, aspirin, pyloric ligation-induced ulcer	Rat	↓Gastric ulcer in all experimental models, production of Pgs, ↑pH and ↓volume of gastric juice, inhibition of leukotriene synthesis and improvement of gastric cytoprotection	Singh *et al*. (2008)
	Bark/petroleum ether and aqueous extracts	-	Aspirin-induced gastric ulcer	Rat	↓Gastric ulcer	Zeeyauddin *et al*. (2011)
	oleo gum resin topical formulation	-	Excision wound	Rat	Wound healing activity	Mallik *et al*. (2010)
Boswellia serrata and *B. carterii*	oleo gum resin	Triterpenoids	Acetic acid-induced chronic gastric ulcer	Rat	↓Gastric ulcer healing, enhancement the regeneration of mucosal ulcers	Mei and Zeng (2012)
Cupressus sempervirens	Fruits/essential oil topical formulation	-	Incision and excision wound	Rat	No remarkabale wound healing activity	Tumen *et al*. (2012)
Cyperus esculentus	Seeds/oil		antioxidant assay	Mouse	Antioxidant activity	Jing *et al*. (2013)
	Rhizome/90% ethanol extract	Catechin and chlorogenic acid	Excision and incision wounds	Rat	Wound healing activity	Puratchikody *et al*. (2006)
	hizome/50% methanol extract		Celiac artery clamping-induced ischemia and reperfusion gastric damage	Rat	↓Gastric damage, ↑antioxidant enzymes (Gpx) and ↓free radicals (MDA)	Guldur *et al*. (2010)
Dolichos lablab	Leaf/methanol extracts	-	Aspirin-and ethanol-induced gastric ulcer	Mouse	↓Gastric ulcer in both experimental models	Tarin and Chichioco-Hernandez (2011)
	Seed/aqueous and		Ethanol-induced gastric ulcer oily fraction	Rat	↓Gastric ulcer	Afifi *et al*. (1997)
Laurus nobilis	Fruits/boiling water and methanol extract	-	Ethanol-induced gastric ulcer	Rat	↓Gastric ulcer, effect of boiling water extract as well as misoprostol	Gurbuz *et al*. (2002)
	Leaves/aqueous extract		Excision and incision wound	Rat	Wound healing function	Nayak *et al*. (2006)

Table 3: Continue

Plant	Part/extract	Active Constituent	Model	Species	Result	Reference
Melissa officinalis	Leaf/30% alcohol extract	-	Indomethacin-and pylorus ligation-induced gastric ulcer	Rat	↓Gastric ulcer in both model, ↓gastric acidity and gastric secretion, ↓leukotriene in gastric juice, ↓mucin and pepsin and PGE2 in gastric juice	Khayyal *et al*. (2006)
Myrtus communis	Leaf/topical formulation		Excision wounds	Rat	Wound healing activity in low doses	Rezaie *et al*. (2012)
	Fruit/methanol and aqueous extract		Ethanol-induced, indomethacin-induced and pyloric ligation-induced gastric ulcer	Rat	↓Gastric ulcer in all experimental models, suppression of gastric secretion and acidity and ↓mucosal barrier significantly	Sumbul *et al*. (2010)
Nymhaea alba	Rhizome/ethanol extract	-	Castor oil-induced diarrhea	Rat	Antidiarrheal action, ↓fluid infiltration, ↓gastrointestinal transition	Bose *et al*. (2012a)
Oxalis corniculat	Whole plant/ethanol and petroleum ether extract		Excision wound	Rat	Wound healing activity	Taranalli *et al*. (2004)
	Leaves/aqueous and ethanol extract		Pyloric ligation-and ethanol -induced ulcer	Rat	↓Gastric ulcer in both experimental models, ↓Gastric juice secretion and acidity in pylorus ligation model, ↓antioxidant enzymes (SOD and catalase) and lipid peroxidation inhibition	Patil *et al*. (2011)
	Whole plant/methanol extract		Pylorus ligation-and indomethacin -induced gastric ulcer	Rat	↓Gastric ulcer in both experimental models, ↓gastric secretion and free and total acidity in pylorus ligation model	Sakat *et al*. (2012)
Pistacia lentiscus	Virgin fatty oil/topical administration	-	Burn-induced wound	Rabbit	Wound healing activity	Djerrou *et al*. (2010)
	Oleo-gum resin	-	Ethanol-, pyloric ligation-, aspirin-, phenylbutazone-, reserpine-and cold restraint stress-induced gastric ulcer and cysteamine-induced duodenal ulcers	Rat	↓Gastric ulcer in all experimental models, ↓gastric free acidity in pylorus-ligated rats, no significant effect on cysteamine-induced duodenal ulcers Nymphaea alba	Al-Said *et al*. (1986)
	Oleo-gum resin	-	Chronic *H. pylori* infection	Mouse	↓*H. pylori* growth in stomach of the infected Mouse, no significant suppression in chronic gastritis and inflammation associated with *H. pylori*	Paraschos *et al*. (2007)
	Oleo-gum resin	-	*H. pylori* infection	Mouse	No *H. pylori* eradication in animal stomach, no significant reduction in the gastric bacterial load	Loughlin *et al*. (2003)
Plantago lanceolate	Leaves/boiled water extract		-		acetic acid-, indomethacin-and pylorus	
			ligation-induced gastric ulcer, cysteamine-induced duodenal ulcer	Mousee and rat	Amelioration of ulcer in acetic acid chronic gastric ulcer, ↓Gastric ulcer in indomethacin gastric ulcer, ↓intestinal ulcer in cysteamine-induced duodenal ulcer, ↓Gastric ulcer and gastric secretion and ↓mucus secretion in pylorus ligation gastric ulcer	Melese *et al*. (2011)
Plantago major	Leaf/methanol extract		Aspirin-and ethanol-induced gastric ulcer	Rat	↓Gastric ulcer in asprin-induced ulcer, ↓Gastric ulcer and gastric acidity in ethanol-induced ulcer	Atta *et al*. (2005)
	Leaf/aqueous extract	-	Incision wound	Rat	Wound healing activity	Mahmood and Phipps (2006)
	Leaf/aqueous extract	-	Ethanol-induced gastric ulcer	Rat	↓Gastric ulcer	Phipps and Mahmood (2006)
	Leaf/aqueous extract	-	Aspirin-induced gastric ulcer	Rat	↓Gastric ulcer	Than *et al*. (1996)
	Seed husk/crude extract	-	Caster oil induced experimental Diarrhea	Mouse	Secretion stimulating and muscarinic activity at 100 and 300 mg kg^{-1} dose, antisecretory and antidiarrheal activity at higher doses	Mehmood *et al*. (2011)

Table 3: Continue

Plant	Part/extract	Active Constituent	Model	Species	Result	Reference
	Seed husk	Water soluble polysaccharides	Incision wound	Guinea Mongolian	Wound cleansing and wound healing activity	Westerhof *et al*. (2001)
Polygonum tinc torium	-	Tryptanthrin, kaempferol	*H. pylori*-infected stomach	pig	↓*H. pylori*-iufection in animal stomach gerbils	Kataoka *et al*. (2001)
Polygonum minus	Leaf/aqueous extract	-	Ethanol-induced gastric ulcer	Rat	↓Gastric ulcer, ↓leucocytes infiltration in	Wasman *et al*. (2010)
	Leaf/ethyl acetate:		Ethanol-induced gastric ulcer	Rat	↑SOD, ↑pH of gastric juice, ↑mucus content, ↑hexosamine, ↑PGE2 level in gastric tissue	Qader *et al*. (2012)
Polygonum cuspidutum	Leaf/50% ethanol extract	-	Excision wound	Rat	Wound healing activity, ↓↑TGF-β1	Wu *et al*. (2012)
Portulaca olercea	Fruits/aqueous juice	-	Antioxidant assay	Rat	↓lipid peroxida,tion ↓antioxidant enzymes in different organ of animals such as GSH, GPx, SOD	Dkhil *et al*. (2011)
	Aerial parts/fresh homogenized crnde extract	-	excision wound	Rat	Wound healing activity	Rashed *et al*. (2003)
	Leaves/aqueous and ethanol extracts		HCl-and ethanol-induced gastric ulcer	Mouse	↓Gastric ulcer, ↓gastric acidity, ↓pH of gastric juice	Karimi *et al*. (2004)
Quercus ilex	Root bark/aqueous extract	Tannic acid	Ethanol-induced gastric ulcer	Rat	↓Gastric ulcer	Gharzouli *et al*. (1999)
Quercus infectoria	Leaf/ethanol extract of leaves	-	Incision and excision wound	Rat	Wound healing activity, ↓antioxidant enzymes of the tissue	Umachigi *et al*. (2008)
Quercus and *Q. coccifera*	Leaf/acetone extract	-	Ethanol-induced gastric ulcer	Mouse	↓Gastric ulcer, ↓lipid peroxidation of gastric tissue	Khennouf *et al*. (2003)
Rosa canina	Fruits/aqueous extract	-	Ethanol-induced gastric ulcer	Rat	100% Inhibition in the gastric ulcers	Gurbuz *et al*. (2003)
	Flower/oil	Major triterepenic acids particularly	↓Gastric ulcer	Rat	↓Gastric ulcer	Maleev *et al*. (1972)
	Flower/boiled extract	-	Intestinal transit time and laxative effect in animal	Rat	Laxative activity with ↓osmotic infiltration and ↓transition time in intestine	Arezoomandan *et al*. (2011)
Symphtum asperum	Roots/allantoin and toxic pyrrolizidine alkaloids-free composition	Poly[3-(3,4-dihydroxyphenyl) glyceric acid]	Excision wound, skin burn wound	Mouse	Wound healing activity in both experimental models	Barbakadze *et al*. (2009)
	Leaves/extracts in three topical formulations: Carbomer gel, glycero-alcoholic solution and O/W emulsion	-	Excision wound	Rat	Wound healing activity, ↓cellular inflammatory agents infiltrate, induction of collagen deposition	Araújo *et al*. (2012)
Tragopogon collinius DC	Aerial parts/70% ethanol extract	-	Ethanol-induced gastric ulcer	Rat	↓Gastric ulcer	Farzaei *et al*. (2012)
	Aerial parts/70% ethanol extract	-	Ethanol-induced gastric ulcer	Rat	↓Gastric ulcer	Farzaei *et al*. (2013)
Tragopogon graminifolius	-	Quercetin	HCl/ethanol-induced gastric ulcer, acetic acid-induced chronic gastric ulcer	Rat	↓Gastric ulcer, ↓lipid peroxidation, healing activity in chronic gastric ulcer, ↓lipid peroxidation	Suzuki *et al*., 1998
	-	Quercetin-3-O-β-	Indomethacin-induced gastric ulcer	Rat	↓Gastric ulcer, ↓MPO activity,	Yan *et al*., 2011

Table 3: Continue

Plant	Part/extract	Active Constituent	Model	Species	Result	Reference
		D-glucuronopyranoside			↓gastric mucus secretion, ↓free radical production, ↓expression of intercellular adhesion molecule protein, ↓mRNA expression of TNF-a and IL-1β	
	Aerial parts/70% ethanol extract	-	Ethanol-induced gastric ulcer	Rat	↓Gastric ulcer	-
	-	Gallic acid diclofenac-induced gastric ulcer	Indomethacin-and	Rat	↓Gastric ulcer in both experimental models, healing effect on indomethacin-gastric ulcer, oxidative stress inhibition, ↓lipid peroxidation	Pal *et al*. (2010)
Zizyphus lotus	Root bark, leaf, fruit/aqueous, methanol and ethyl acetate extracts from each part	-	HCl/ethanol-and pylorus ligation-induced gastric ulcer	Rat	↓Gastric ulcer in both ulcer models, ↓gastric juice secretion and acidity	- Wahida *et al*. (2007)
	Stem bark/methanol extract	Tannins	Castor oil-induced diarrhea	Rat	Antidiarrheal function, ↓intestinal transit	Adzu *et al*. (2003)

NO: Nitric oxide, eNOS: Endothelial NO synthase, iNOS: Inducible NO synthase, GSH: Glutathione, GPx: Glutathione peroxidase SOD: Superoxide dismutase, TNF-α: Tumor necrosis factor-alpha, EGF: Endothelial growth factor, VEGF: Vascular endothelial growth factor, HGF: Hepatocyte growth factor, COX1: Cyclooxygenase-1, PGE2: Prostaglandin-E2, MPO: Myeloperoxidase, IL-1β: Interleukine-1ß, MDA: Malondialdehyde, HB-EGF: Heparin binding epidermal-growth-factor-like growth factor, TBARS: Thiobarbituric acid reactive substances

Table 4: Clinical studies on plants used in traditional Iranian medicine for the treatment of peptic ulcer

Plant	Preparations: Treatment group	Preparations: Control group	Study design	Disease	No. of patients	Treatment duration	Result	Reference
Pistacia lentiscus	Oleo-gum resin powder	Placebo powder	Double blind controlled clinical trial	Patients with duodenal ulcer	38	14 day	Symptomatic relief of PU in 80% and endoscopically proven healing in 70% of patients received resin	Al-Habbal *et al.* (1984)
	Oleo-gum resin	Pantoprazole, amoxicillin, clarithromycin	Randomized pilot study	*H. pylori* harbour patients	52	14 days	30.8% eradication of *H. pylori* in patients which received 350 mg resin tid ($p = 0.08$) and 38.5% in patients received 1.05 g resin tid ($p = 0.064$)	Dabos *et al.* (2010)
Symphytum× *uplandicum*	Topically applied preparation of aerial parts	No preparation	Randomized clinical double-blind	Patients with fresh abrasions	278 108	10 days 10 days	Faster initial reduction of wound and complete healing	Barna *et al.* (2007)
	Topically applied preparation of aerial parts	-	Randomized, controlled, clinical double-blind	Children with fresh abrasions			Physicians and children/ parents both rated the efficacy of the 10% cream as significantly better than that of the control preparation	Barna *et al.* (2012)

PU: peptic ulcer; tid: three time a day

Table 5: Mechanisms of action of the plants used for the treatment of peptic ulcer disease in traditional Iranian medicine

Plant	↑PG	NO modulation	Inflammatory modulation	Wound healing	Antisecretory	Mucus protection (cytoprotection)	Antioxidant	Anti *H. pylori*	Antacid	↑ Angiogenesis
Acacia arabica					*					
Acorus calamus						*	*	*		
Alisma plantago-aquatica	*					*				
Althaea officinalis						*	*			
Bambusa arundinacea							*			
Boswellia carterii and *B. serrata*	*		*	*		*			*	
Cupressus sempervireus			*				*			
Cyperus species			*			*				
Dolichos lablab							*	*	*	
Hyssopus officinalis			*			*				
Laurus nobilis				*			*	*		
Melissa officinalis	*						*	*	*	
Myrtus communis			*	*		*	*	*		
Nymphaea alba				*			*	*		
Oxalis species				*	*				*	
Pistacia lentiscus			*			*	*			
Plantago major and *P. lanceolata*				*	*		*			
Plantago ovata and *P. psyllium*	*		*	*						
Polygonum species	*		*	*		*	*	*	*	
Portulaca oleracea			*			*	*	*		
Quercus species			*			*	*			
Rosa species							*	*		
Symphytum species			*			*				
Tragopogon graminifolius and *T. colinus*	*			*	*	*				
Zizyphus spina-christi						*				

PG: Prostaglandin, NO: Nitric oxide, *H. pylori*: *Helicobacter pylori*

recommended. Moreover, combination of many of the mentioned herbs according to the protocols of TIM sources can be assumed to obtain more efficacious complementary and alternative treatment for PU.

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