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Review Article

The Efficacy of Iranian Traditional and Folk Medicinal Plants for Some Gastroduodenal Disorders

Malihe Safavi[1], Mohammad Reza Shams-Ardakani[2], Maryam Sadat Seyedbagheri[3], Alireza Foroumadi[1]

[1] *Pharmaceutical Sciences Research Center AND Persian Medicines and Pharmacy Research Center, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Persian Medicines and Pharmacy Research Center AND Department of Pharmacognosy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*

[3] *Persian Medicines and Pharmacy Research Center, Tehran University of Medical Sciences, Tehran, Iran*

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Abstract

Peptic ulcer and gastritis are common and universal disease which affect up to 50% of the world's adult population. *Helicobacter pylori* is a major cause of chronic-active gastritis and primary duodenal ulcers, and is strongly linked to gastric cancer. *H. pylori* induce chronic gastritis in virtually all infected patients. Chronic gastritis induced by *H. pylori* increases the risk for a wide spectrum of clinical outcomes, ranging from peptic ulcer disease and atrophic gastritis to gastric adenocarcinoma and gastric mucosal lymph proliferative diseases. Extracts of several plants including *Cinnamomum zeylanicum, Coriandrum sativum, Malus domestica, Phyllanthus emblica, Pistacia lentiscus, Portulaca oleracea, Punica granatum, and Terminalia chebula* have been used in Iranian traditional medicine as therapeutic agents for gastritis and peptic ulcer diseases. The information on all of these remedies was derived from all available old sources such as traditional books. According to new database the mechanisms of action for some of these plants are known. For example *T. chebula* causes improvement in the secretory status of Brunner's gland and also, aqueous extracts of this plant have anti-bacterial activity against *H. pylori*. The information of more recent studied Iranian folk medicinal plants such as *Camellia sinensis, Geum iranicum, Rheum ribes, Salvia mirzayanii, Sambucus ebulus, Stachys lavandulifoli*a, *Stachys setifera, Trachyspermum copticum, and Zataria multiflora* are presented in this review. The medicinal properties of these folk plants are attributed mainly to the presence of natural anti-oxidants and potent anti *H. pylori* activity. It is suggested that an evaluation of the effects of these plants on different aspects of gastric disorders should be performed and further studies are necessary on the other traditional and folk medicinal plants of Iran.

Keywords: Traditional Medicine, Gastritis, Peptic Ulcer, *Helicobacter pylori*, Iran, Medicinal Plant

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Corresponding Author: Alireza Foroumadi
Email: aforoumadi@yahoo.com

1. INTRODUCTION

Traditional uses of plants for medicinal purposes are as old as human civilization [1]. Nature has been a source of medicinal agents since antiquity to date and an impressive number of modern drugs have been isolated from natural sources [2]. Isolation and biochemical characterization of pharmacologically active compounds from medicinal plants continue today. Many of these isolations were based on the uses of the agents in traditional medicine [1], [3]. The past century, however, microorganisms and marine organisms have proved to be a prolific source of structurally diverse bioactive metabolites and a rich source of novel bioactive agents. The plant-based, traditional medicine systems will continue to play an essential role in health care, with about 80% of the world's inhabitants relying mainly on traditional medicines for their primary health care [4], [5], [6].

Disorders of the stomach are very common and induce a significant amount of morbidity in the suffering population. Gastritis, the inflammation of the mucosa of the stomach is a common disorder of a gastrointestinal system and still remains a serious medical problem for many people worldwide [7]. A gastroduodenal ulcer occurs when the gastric mucosa becomes eroded and perforations lead to bleeding [8]. Complications such as peptic ulcer and gastric cancer will result from untreated gastritis [9].

Peptic ulcer and gastric cancer were associated with increased acid production, stress, diet, and anxiety. However, after the discovery of *Helicobacter pylori*, there is authentic evidence to show an association between *H. pylori* – infection and the development of gastric cancer [10]. Gastric ulcer disease and gastric cancer have etiologic factors in common, and are closely associated with *H. pylori* infection [11].

It is estimated that an infected individual has a 10-20% lifetime risk for the development of peptic ulcer disease, which is at least 3-4 fold higher than in non-infected subjects [12]. *H. pylori* infection were found in 90-100% of duodenal ulcer patients and in 60-100% of gastric ulcer patients [13], [14]. The degree of risk depends on the severity of gastritis, which is determined by various host and bacteria related factors. Subjects infected with a cytotoxin-producing bacterial strain, or a strain possessing CagA, are at a higher risk of peptic ulcer, atrophic gastritis and gastric cancer. Among host factors, most of the evidence focuses on acid production in response to *H. pylori* infection which is increased in duodenal ulcer disease and decreased in gastric ulcer disease [12], [15].

Eradication of *H. pylori* infection is recommended in patients with gastroduodenal diseases such as peptic ulcer disease, atrophic gastritis, and low grade gastric mucosa associated lymphoid tissue (MALT) lymphoma [16], [17]. After eradication of the infection, the risk of recurrence of gastric ulcer disease is usually < 10% and approximately 0% for duodenal ulcer disease [12]. Despite advances in anti-microbial therapy, although there is still no ideal treatment, and indications for therapy continue to evolve [18]. Increasing anti-microbial resistance, side effects, and falling eradication rates underline the importance of the updated guidelines on the management of *H. pylori*. Clinical practice evidence has revealed eradication rates are closer to 80% [19], [20].

Today, for develop new potential anti *H. pylori* candidates, scientists in medicinal chemistry field are also equally concerned with the creation of new synthetic drug compounds [21], [22], [23], [24], [25], [26], [27], [28], [29]. Complementary and alternative modes of treatment, particularly nontoxic, natural, and inexpensive products are attractive. There are many studies on the anti-bacterial properties of vegetables and plant extracts [19]. The focus of this review will be on those Iranian traditional and more recent studied medicinal plants which used to treat gastric disorders.

2. METHODS

In Iranian traditional medicine, there is gastric

disease known as “Bosur” and “varam-e-mede” or “Amas” which seems to be identical to ulcer and gastritis, respectively, regarding the explained symptoms of the disease. Bosur is defined as an increasing stomach pain following consumption of sour substances, such as vinegar and mustard and something like these. The other symptoms include nausea, xerostomia, and regurgitation. The other disease, varam-e-mede or Amas presents with gastralgia, decreased appetite, inflammation, and fever [30], [31]. Various natural remedies have been used in TIM for Bosur and varam-e-mede. Since common causative factor for gastric ulceration and gastritis is an invasion of *H. pylori*, recent studies have focused on this microaerophilic, and Gram-negative, flagellated, a spiral-shaped bacterium.

In this study, information on some of these remedies were derived from available old sources such as documents and books and were added to the information derived from modern medical databases covering all *in vitro*, *in vivo* studies that examined medicinal plants for the treatment of gastric disorders. In addition, medicinal plants that have been studied recently in Iran for the treatment of gastric disease are presented. The information of more recently studied medicinal plants is retrieved from multiple databases, including PubMed, Scopus, EBSCO, and Google scholar.

3. Results

3.1 Pathophysiology of Peptic Ulcer and Gastritis

Atrophic gastritis is an inflammation of the stomach lining which defined as a loss of the glandular structures and a collapse of the reticulin skeleton of the stomach mucosa [32]. Gastritis caused by a number of different factors. Infection with *H. pylori* plays a crucial role in the etiology of atrophic gastritis [33]. In patients with persistent infection, chronic active gastritis develops, leading finally to glandular atrophy, a risk factor for gastric adenoma, and cancer [7], [9].

The pathophysiology of peptic ulcer disease has centered on an imbalance between mucosal aggressive and protective factors in the stomach [34]. The stomach is lined by a complex epithelium that forms a selective barrier between the external environment (lumen) and the body [35]. The gastric mucosal barrier is continuously challenged by a variety of aggressive factors of both endogenous and exogenous nature, including excess secretion of gastric acids and pepsin, reactive oxygen species (ROS), use of alcohol and non-steroidal anti-inflammatory drugs (NSAIDs), as well as infection with *H. pylori*. On the other hand, mucus secretion, bicarbonate production, gastro protective prostaglandin synthesis, and normal tissue microcirculation protect against ulcer formation. The etiology of peptic ulcer is unknown in most of the cases, yet it is generally accepted that gastric ulcers are multifactorial and develop when aggressive factors (endogenous, exogenous and/or infectious agents) overcome mucosal defense mechanisms [36], [37], [38].

Common causative factor for gastric ulceration and gastritis is an invasion of *H. pylori*. About half of all gastric ulcer cases are associated with infection by *H. pylori* [39], [40]. The gastric mucosa is well-protected against bacterial infections due to the acidic pH of the lumen, the production of mucus, and rapid epithelial cell turnover [41], [42]. *H. pylori* is highly adapted to its unusual ecological niche in the human stomach, with a unique array of features that permit entry into the mucus, oriented swimming and multiplication in the mucus, attachment to epithelial cells, evasion of the immune response, and as a result, persistent colonization and transmission [43].

Based on earlier documents in response to *H. pylori* colonization of the antral mucosa, G endocrine cells in the distal antral region of the stomach are activated to release the hormone gastrin, which circulates and stimulates parietal cells in the corpus (body) region of the stomach to hyper secrete acid. This increased acid production is likely to play a key role in the pathophysiology of duodenal ulcer disease [44], [45], [46].

Recent studies have shown that *H. pylori* bacteria mainly release specific cytotoxins causing a duodenal ulcer. Several infection-associated factors of *H. pylori*, such as urease, catalase, lipase, adhesion molecules, cytotoxin-associated gene protein (CagA), a homologue of the *Bordetella pertussis* toxin secretion protein (picB) and vacuolating cytotoxin (VacA), contribute to gastric mucosal surface, and the induction of disease [47], [48].

The successful treatment leads to the fall in rates of *H. pylori* infection, on the other hand, the proportion of peptic ulcer disease not related to this organism has risen which will affect the management of peptic ulcer [34]. Stress, smoking, nutritional deficiencies and ingestion of NSAIDs, augment gastric ulcer incidences [49].

3.2 Medicinal Plants and Gastric Disorders

3.2.1 Some medicinal plants in TIM used for peptic ulcer and gastritis

The *in vitro* and *in vivo* studies on plants used in TIM for the treatment of gastric disease are summarized in table 1.

Table 1. *In vitro* and *in vivo* studies on plants used in traditional Iranian medicine for the treatment of gastric disease

Plants	Part	Gastric disease treatment	References
Cinnamomum zeylanicum	Essential oils of dry bark	*C. zeylanicum* essential oil exhibited potent anti *H. pylori* effect IZD: 24.8 mm at 0.5 µl/ml MIC: 0.3 µl/ml	Hosseininejad et al. [57]
Coriandrum sativum	Aqueous suspension of seeds	Pretreatment at oral doses of 250 and 500 mg/kg provide a dose-dependent protection against the i) ulcerogenic effects of different necrotizing agents; ii) ethanol-induced histopathological lesions; iii) pylorus ligated accumulation of gastric acid secretions and ethanol related decrease of nonprotein sulfhydryl groups	Al-Mofleh et al. [59]
Malus domestica	Freeze dried apple flesh extract	i) Apple extracts decreased xanthine-xanthine oxidase or indomethacin induced injury to gastric epithelial cells by 50%; ii) catechin or chlorogenic acid (the main phenolic components of apple extracts) were equally effective as apple extracts in preventing oxidative injury to gastric cells; and iii) apple extracts increased fourfold intracellular anti-oxidant activity, prevented its decrease induced by xanthine-xanthine oxidase, inhibited ROS dependent lipid peroxidation and decreased indomethacin injury to the rat gastric mucosa by 40%	Graziani et al. [61]
Phyllanthus emblica	Ethanol extract of dried fruits	Oral administration of Amla extract at doses 250 mg/kg and 500 mg/kg significantly inhibited the development of gastric lesions in all test models used including pylorus ligation Shay rats, indomethacin, hypothermic restraint stress-induced gastric ulcer and necrotizing agents	Al-Rehaily et al. [69]
	Butanol extract of the water fraction of fresh fruits	Oral pretreatment, with the extract *P. emblica* fruits at the dose of 100 mg/kg body-weight, was found to enhance secretion of gastric mucus and hexosamine in the indomethacin induced ulceration of rats. The morphological observations also supported a protective effect of the stomach wall from lesion induced by indomethacin	Bandyopadhyay et al. [70]

Table 1. *In vitro* and *in vivo* studies on plants used in traditional Iranian medicine for the treatment of gastric disease (Continue)

Plants	Part	Gastric disease treatment	References
Pistacia lentiscus	TMEWP and isolated pure triterpenic acids fraction	Administration of TMEWP to mice infected with the *H. pylori* SS1 strain over the period of 3 months with an average dose of 0.75 mg/day led to an approximately 30-fold reduction in the *H. pylori* colonization The acid fraction was found to be the most active extract against a panel of 11 *H. pylori* clinical strains MBC: 0.139 mg/ml	Paraschos et al. 2007 [75]
Portulaca oleracea	Aqueous and ethanol extracts of leaves	Both *P. oleracea* extracts decreased total gastric acidity not only upon oral administration but also by intra-peritoneal route. Since gastric acid and pH are important factors for ulceration of pylorus-ligation, these results suggest that *P. oleracea* has gastro protective action	Karimi et al. [77]
Punica granatum	Methanol extract peel of fruit	Among 23 Iranian plants, the extracts of *P. granatum* and *Juglans regia* had remarkable anti *H. pylori* activity. In view of the results obtained with *P. granatum* the peel extracts of nine cultivars of pomegranate were further assayed against the clinical isolates of *H. pylori*. Iranian pomegranate cultivars, except one of them, showed significant *in vitro* anti *H. pylori* activity against the clinical isolates of *H. pylori.* *P. granatum* IZD: 39.0 ± 3.4 mm at 100 mg/disc cultivars of pomegranate IZD: 16-40 mm at 50 mg/disc	Hajimahmoodi et al. [87]
	Methanol extract peel of fruit	Methanol extracts of pomegranate rind showed the highest inhibition against *H. pylori* clinical isolates. Aqueous and butanol fractions of pomegranate peel showed good activity on *H. pylori* clinical isolates. Chloroform fraction had no activity against tested *H. pylori* isolates. Methanol extract IZD: 27.96 ± 0.97 mm at 2 mg/disc Aqueous fractions MIC: 156 µg/ml Butanol fractions MIC: 195.12 µg/ml	Nakhaei Moghaddam et al. [88]
Terminalia chebula	Ether, alcoholic and water extracts of fruit	Aqueous extracts of the plant were significantly more active than other extracts. The aqueous extract of *T. chebula* showed uniform anti-bacterial activity against 10 clinical strains of *H. pylori* MIC: 125 mg/l MBC:150 mg/l	Malekzadeh et al. [92]

H. pylori: *Helicobacter pylori*, IZD: Inhibition zone diameter, MIC: Minimum inhibitory concentration, MBC: Minimum bactericidal concentration, TMEWP: Total mastic extract without polymer, ROS: Reactive oxygen species

Cinnamomum zeylanicum known as "Darchin" is an efficacious remedy for the treatment of gastritis in TIM [30] and has widely used as a common condiment in Iranian food diets. The anti-microbial effects of plant essential oil and its two major components, cinnamic aldehyde and eugenol, has been shown. Previous studies have reported the high

in vitro anti-bacterial, anti-fungal and anti-tumor activities of *C. zeylanicum* essential oil [50], [51], [52], [53]. Cinnamaldehyde is an aromatic aldehyde and main component of bark extract of cinnamon which inhibited the growth of all the 30 *H. pylori* strains tested, at a concentration of 2 μg/ml [54]. It should also be mentioned that *C. zeylanicum* can inhibit urease activity and prevent gastric upsets [55]. Tabak et al. [56] demonstrated methylene chloride extract of cinnamon is able to inhibit the growth of *H. pylori*, while ethanol extract counteracted its urease activity. The inhibitory effect of the essential oils of *C. zeylanicum* against clinical isolate of *H. pylori* are presented in table 1 [57].

Coriandrum sativum (Coriander) known as "Geshniz" is another natural product used in TIM for gastritis [58]. The seeds of coriander are used as an anti-spasmodic, carminative, stomachic, and against gastrointestinal complaints such as dyspepsia, flatulence, and gastralgia. The seeds are also used as an ingredient in herbal preparations to prevent stomach griping [59]. *C. sativum* demonstrated significant suppression of ROS from *H. pylori*-infected cells. Anti-inflammatory and cytoprotective effects of this plant which could partially validate the traditional use of these plants in gastrointestinal disorders particularly associated with *H. pylori* [60]. Results of a study clearly demonstrate that aqueous suspension of coriander confers a dose-dependent protection against gross damaging action of ethanol and other necrotizing agents on gastric mucosa of rats [59].

Malus domestica, with the common name as apple, is another natural product for the treatment of gastric ulcer and gastritis in TIM [59]. In general, dietary anti-oxidants play a crucial role in the maintenance of gastric homeostasis by preventing the potentially mucosal damaging effects exerted by ROS. Accordingly, a diet rich in apple anti-oxidants (phenolic compounds) might exert a beneficial effect in gastric ulcer and prevent gastric mucosal lesions brought by a number of ulcerogens [61]. In addition, *in vitro* strong inhibition of tumor cell proliferation by apple extract is attributed to the presence of phytochemicals (phenolic acids and flavonoids) [62]. Polyphenol extract with powerful anti-oxidant activity may be useful in the prevention and/or treatment of NSAIDs-associated side effects [63]. In the other study, apple polyphenol extract reduces aspirin-induced gastric injury independently of gastric acid secretion inhibition [64]. Apple peel polyphenol-rich extract also displayed an *in vitro* anti-adhesive effect against *H. pylori*. This study also demonstrated orally administered apple peel polyphenols showed an anti-inflammatory effect on *H. pylori*-associated gastritis, lowering malondialdehyde levels, and gastritis scores [65]. The results of Graziani et al. [61] study are summarized in table 1. The data of this study revealed apple polyphenol extracts prevent exogenous damage to human gastric epithelial cells *in vitro* and to the rat gastric mucosa *in vivo*.

Phyllanthus emblica known as "Amla"or "Amlaj" is one of the important herbal drugs used in TIM for the treatment of gastritis [66]. Amla fruits are anabolic, anti-bacterial and are also used for the treatment of various gastric ailments including dyspepsia [67]. Novel anti *H. pylori* activity of ethanol extract of Amla fruit pulp has been reported [68].

Al-Rehaily et al. [69] demonstrated that Amla extract showed protection against ethanol-induced depletion of stomach wall mucus and reduction in non-protein sulfhydryl concentration. The results of this study offer that Amla extract possesses anti-secretory, anti-ulcer, and cytoprotective properties. According to data of another study butanol extract of the water soluble fraction of the fruits of *P. emblica* exerts cytoprotective action on gastric ulcer formation predominantly by its anti-oxidant property [70].

Pistacia lentiscus resin known as "Mastaki" has traditionally been used in the treatment of gastritis in Iran [71]. Mastaki has been referred to over centuries as having medicinal properties to treat a variety of diseases like diverse gastric malfunctions.

Mastaki at an oral dose of 500 mg/kg produced a significant reduction in the intensity of gastric mucosal damage on experimentally-induced gastric and duodenal ulcers in rats. These observations support the effectiveness of mastic in the therapy of duodenal ulcer [72]. The other study results suggest that mastic has definite anti-bacterial activity against *H. pylori*. This activity may at least partly explain the anti-peptic ulcer properties of mastic [73]. The results of an evaluation of the anti-bacterial activity of Mastaki against a panel of clinical isolates of *H. pylori* revealed it can kill 50% of the strains tested at a concentration of 125 µg/ml and 90% at a concentration of 500 µg/ml [74]. Paraschos et al. [75] showed that administration of total mastic extract without polymer may be effective in reducing *H. pylori* colonization and that the major triterpenic acids in the acid extract may be responsible for such an activity.

Portulaca oleracea called "khorfeh" is an annual plant, which is grown as a vegetable in many parts of the world. In TIM, this plant is utilized in the treatment of gastric mucosal diseases [31]. It is commonly used in Iranian folk medicine in gastro esophageal reflux [76]. In the recent investigation, the aqueous and ethanol extracts were studied in mice for their ability to inhibit gastric lesions induced by HCl or absolute ethanol. The extracts of *P. oleracea* showed a dose-dependent reduction in the severity of ulcers. This beneficial preventive effect on gastric ulcers may be an acid neutralizing action or anti-secretory activity through antagonizing muscarinic or H2 receptors. The anti-ulcer activity of the extracts of this plant may be is due to flavonoids, tannins, and anti-oxidants which present in extracts. Furthermore, this plant comprises some mucilages [77]. Gastro protective effect of flavonoids is explained with an increase of mucosal prostaglandin content, decrease of histamine secretion, and free radical scavenging activity [78]. Tannins render the outermost layer of the mucosa less permeable and more resistant to chemical and mechanical injury or irritation [79].

Punica granatum called "Anar" in TIM has been used for the treatment of gastritis [80], [81]. Anti-bacterial, anti-parasitic, and anti-viral effects have been reported for pomegranate peel, up to now [82], [83]. Furthermore, this plant can minimize the problem of anti-biotic resistance of *H. pylori* by increasing the cell surface hydrophobicity of *H. pylori* strains and inhibiting the attachment of this bacterium to the gastric mucosa [84]. The evidence strongly suggests that *P. granatum* has a potential preventative effect on *H. pylori* induced gastric disease by eradicating *H. pylori* as well as showing anti-inflammatory and anti-cancer effects [85]. Repeated oral administration of 400 mg:kg of *P. granatum* significantly lowered the severity of ethanol-induced gastric damage [86]. Hajimahmoodi et al. [87] showed a significant *in vitro* susceptibility of clinical strains of *H. pylori* to the extracts of several native Iranian pomegranate cultivars. The other study revealed that methanol extracts, butanol and aqueous fractions of *P. granatum* were capable of inhibiting the *in vitro* growth of 27 clinical isolates of *H. pylori*. It is possible that some of anti *H. pylori* activity of pomegranate peel is related to the presence tannin and phenolic compounds [88].

Terminalia chebula known as "Halile siah" has been used in TIM in southern and central parts of Iran as a remedy for human gastritis and peptic ulcers [89]. *T. chebula* has a strong laxative effect and increases the gastric emptying time. It seems that this action is balanced with a protective effect on the gastrointestinal mucosa, with the improvement in the secretory status of Brunner's gland involved in the protection against duodenal ulcer [90]. Chebulinic acid isolated from *T. chebula* fruit has gastro protective effect. Chebulinic acid significantly reduced free acidity, total acidity and upregulated mucin secretion and also, inhibited H(+) K(+)-ATPase activity *in vitro* [91]. Water extracts of *T. chebula* showed significant anti-bacterial activity. It is concluded that the traditional Iranian folk medicinal use of this plant to treat gastric infections is substantiated by the anti-bacterial

activity of its extracts against *H. pylori* [92].

3.2.2 Some recent studied Iranian medicinal plants, used for peptic ulcer and gastritis

The results of some Iranian researcher studies on folk medicinal plants in the treatment of gastric disorders are presented in table 2.

Table 2. Selected potent Iranian medicinal plants in treatment of gastric disorders

Study	Plant	Part	Results
Hassani et al. [97]	*Camellia sinensis*	Methanol/water extracts of young shoots	Both nonfermented and semifermented extracts had inhibitory effects against *H. pylori* and urease production. A concentration of 4 mg/ml nonfermented and 5.5 mg/ml semifermented extract were bactericidal for *H. pylori*
Shahani et al. [98]	*Geum iranicum* Khatamsaz	Methanol extract of the roots	The methanol extract of *G. iranicum* plant showed significant activity against one of the clinical isolates of *H. pylori* which was resistant to metronidazole. The aqueous fraction was the most effective fraction of the extract against all clinical isolates of *H. pylori*. The subfraction which contained Tannins were the effective fraction. It appeared that tannins were probably the active compounds responsible for the anti *H. pylori* activity of *G. iranicum* aqueous fraction IZD: 24-35 mm at 100 µg/ml
Nabati et al. [55]	*Rheum ribes*	50% methanol/water extract of root	Among 137 Iranian traditional medicinal plants which were tested for urease inhibitory activity, *R. ribes* extract inhibit urease enzyme. Urease inhibition IC50:92 µg/ml
Atapour et al. [106]	*Salvia mirzayanii*	Methanol extract of leaves	Among the 12 Iranian medicinal plants used in folk medicine for the treatment of gastric ailments including peptic ulcers disease *S. mirzayanii* was the most active plant, with strong anti-bacterial activity against 12 clinical isolates of *H. pylori* MIC: 32-64 µg/ml
Nabati et al. [55]	*Sambucus ebulus*	50% methanol/water extract of fruit	Among 137 Iranian traditional medicinal plants which were examined against Jack bean urease activity, the most potent urease inhibitory was observed for *S. ebulus* Urease inhibition IC50: 57 µg/ml
Nabavizadeh et al. [114]	*Stachys lavandulifolia*	Aqueous extract aerial parts	The *S. lavandulifolia* extract, protected gastric mucosa from an alcohol-induced gastric ulcer in rats. This gastro protection may mediate via gastric mucosal nitric oxide production
Khanavi et al. [117]	*Stachys setifera*	methanol extracts aerial parts	*S. setifera* among 10 species of *Stachys* and *Melia* showed the most potent anti *H. pylori* activity on the 12 isolates IZD: 38.3 at 8 mg/disc
Nariman et al. [119]	*Trachyspermum copticum*	Equal mixture of methanol/petroleum Benzene/diethyl ether extract of aerial parts	Extracts of *T. copticum* showed anti *H. pylori* activity against 70 clinical isolates from children. Over 93% of *H. pylori* isolates were sensitive to the extracts of *T. copticum* MIC: 31.25-250 µg/ml
Hosseininejad et al. [57]	*Zataria multiflora*	Essential oils of aerial parts	The essential oils of *Z. multiflora* demonstrated potent anti *H. pylori* effect IZD: 23.6 mm at 0.5 µl/ml MIC: 0.3 µl/ml

H. pylori: *Helicobacter pylori*, IZD: Inhibition zone diameter, MIC: Minimum inhibitory concentration

Camellia sinensis (green tea) is the species of plant whose leaves and leaf buds are the source of tea, the commonest beverage in the world. There are several reports of *in vivo* and *in vitro* anti-bacterial effects of *C. sinensis* extracts [93], [94]. In 1994 Diker and Hascelik [95] showed extracts of black and green tea inhibited *in vitro* growth of six clinical isolates of *H. pylori* in an agar diffusion assay. The results of a recent study revealed the protective effect of green tea against stomach cancer [96]. More recently, it has been shown methanol: water mixture extracts of young shoots of *C. sinensis* can inhibit the growth of *H. pylori* and in lower concentrations inhibit the function and the production of enzyme urease that is a major colonization factor for this bacterium. Decrease in *H. pylori* numbers and low urease production affect *H. pylori* colonization and therefore decrease the risk of chronic gastritis, peptic ulceration, MALT lymphoma, and gastric adenocarcinoma [97].

Geum iranicum Khatamsaz, belongs to the Rosaceae family. The genus *Geum*, is a perennial rhizomatous herb with five species in Iran of which *G. iranicum* Khatamsaz is an endemic one [98]. Some *Geum* species are used as medicinal plants in folk medicine. In Iranian folk remedy, the infusion of the root of *G. iranicum* is employed to treat gastrointestinal disorders like diarrhea, and a decoction of the whole plant is mixed with wheat flour and used as a poultice for frostbite [99]. In a study, the activity of various extracts, sub-fractions, and main components of *G. iranicum* against clinical isolates of *H. pylori* (resistant to metronidazole) has been evaluated [98].

Rheum ribes known as “Rivas” grows in Iran and Turkey, cultivated in some temperate countries for its edible red leaf stalks. Traditionally, *R. ribes* has been used in Iran as sedative and mood enhancer [100]. Chrysophanol, physcion, rhein, aloe-emodin, physcion-8-oglucoside, aloe-emodin-8-O-glucoside, sennoside A, rhaponticin, and flavonoids are the content of this plant [101]. A study revealed the methanolic extract of *R. ribes* has anti-ulcer activity comparable with standard drugs cimetidine [102]. The urease inhibitory activity was observed for *R. ribes* with IC50 values > 100 μg/ml. This plant has the ability to prevail *H. pylori*. The survival of *H. pylori* in the acidic stomach is dependent on urease, so specific inhibition or reduction of urease enzyme activity would result in an increased sensitivity of the bacteria in acidic medium [55].

Salvia mirzayanii is known locally as “Moor Talkh” grows in the southern parts of Iran and is widely used in Iranian folk medicine. Decoctions of this plant have many supposed medicinal properties and are used in folk medicine for the treatment of digestive disorders like stomach ache [103]. Several studies have shown the various biological activities of this plant including its anti-bacterial properties [104], free radical scavenging, and anti-oxidant activity [105]. In the screening of 12 Iranian medicinal plants, *S. mirzayanii* had the strongest activity against *H. pylori*, with an MIC of 32 μg/ml [106].

Sambucus ebulus called “Aghti” is a native perennial herb. *S. ebulus* has been shown to have anti-inflammatory, anti-nociceptive, anti-cancer, anti-angiogenic, and anti-oxidative activities. This plant was used in traditional medicines for the treatment of inflammatory reactions [56]. Pharmaceutical and biologically active ingredient of *S. ebulus* are isolated and identified as ebulitin, ebulin 1, flavonoid, anthocyanin, and other components [107]. Anti *H. pylori* effect of the *S. ebulus* chloroform extract was observed by using the agar dilution method [108]. Nabati et al. [55] showed *S. ebulus* have the potency to inhibit urease activity.

Stachys lavandulifolia is a medicinal plant in Iranian folk medicine and popularly known as “chaie koohi” which widely distributed in different regions of Iran [109], [110]. During past years pharmacological studies have confirmed that extracts of *S. lavandulifolia* exert significant anti-inflammatory, anti-bacterial, and wound healing effects [111], [112], [113]. Nabavizadeh et al. [114] investigated the therapeutic and preventive

effects of *S. lavandulifolia* extract on gastric acid-pepsin secretions together with nitric oxides possible role. The data of this study revealed that *S. lavandulifolia* extract has a protective role in alcohol-induced gastric ulcer in rats. The mechanism underlying the anti-ulcerogenic effect may be related to the flavonoid derivatives from luteolin present in *S. lavandulifolia* extract and in active fractions.

Stachys setifera is a native plant of Iran. The genus *Stachys* is as a source of biologically active substances of various classes which are responsible for the broad spectrum of pharmaceutical-therapeutic action of plants of this genus and drugs prepared from them [115]. Some species of this genus exhibited significant anti-bacterial activity [116]. Khanavi et al. [117] showed *S. satifera* exhibited potent anti *H. pylori* activity on the strains isolated from patients.

Trachyspermum copticum is known as "Zenyan" which the inhibitory effect of its essential oil on the growth of *Aspergillus parasiticus* shown in 118. The results of six native Iranian plants screening introduced *T. copticum* as a strong *H. pylorI* inhibitor [119]. Furthermore, the crude organic extracts of *T. copticum* fruit showed the high activity against *H. pylori* among the twenty Iranian plants extracts [120]. However, the results of other study showed that the extract of the fruits of this plant had only very weak anti *H. pylori* activity [106].

Zataria multiflora as "Avishane Shirazi" is an endemic plant to Iran with many traditional uses. For instance this plant has been used for relief of gastric pains and irritable bowel syndrome. The essential oil of the plant has shown high anti-oxidant and free radical scavenging effect in *in vitro* and *in vivo* studies [121]. The inhibitory effects of the essential oil of *Z. multiflora* against a wide range of Gram-positive and Gram-negative bacteria, fungi, and parasites have been reported [122], [123], [124], [125]. The analysis of the plant essential oil showed the presence of thymol and carvacrol as major compounds of the oil [121]. The essential oil of *Z. multiflora* has exhibited the most inhibition in different tested concentration [57].

5. Conclusion

Nowadays, people pay more and more attention to their health and a healthy stomach depends on nourishing. The health preservation concepts of TIM are beneficial to protect and treat the gastric diseases.

TIM has a number of herbal formulations that treat disorders of the digestive system. Some of the plants used in traditional medicine in Iran have been derived from the traditional books. For many of the plants used in TIM, there are various *in vitro* and *in vivo* studies demonstrating their efficacy in gastric disorders. Studies on TIM and some Iranian folk medicinal plants revealed modes of action of these plants. These medicines have shown their usefulness in gastric disease by different mechanisms of action including inhibitory effects against *H. pylori* and urease production, preventing ROS induced injury to gastric epithelial cells, and increasing intracellular anti-oxidant activity. Further evaluations are needed to understand the mechanism of actions of these plants, and on the other traditional and folk medicinal plants of Iran.

6. Conflict of Interests

Authors have no conflict of interests.

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