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Traditional Persian topical medications for gastrointestinal diseases

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ABSTRACT

Drug delivery across the skin is used for several millennia to ease gastrointestinal (GI) ailments in Traditional Persian Medicine (TPM). TPM topical remedies are generally being applied on the stomach, lower abdomen, lower back and liver to alleviate GI illnesses such as dyspepsia, gastritis, GI ulcers, inflammatory bowel disease, intestinal worms and infections. The aim of the present study is to survey the topical GI remedies and plant species used as ingredients for these remedies in TPM. In addition, pharmacological activities of the mentioned plants have been discussed. For this, we searched major TPM textbooks to find plants used to cure GI problems in topical use. Additionally, scientific databases were searched to obtain pharmacological data supporting the use of TPM plants in GI diseases. *Rosa × damascena, Pistacia lentiscus, Malus domestica, Olea europaea* and *Artemisia absinthium* are among the most frequently mentioned ingredients of TPM remedies. β-asarone, amygdalin, boswellic acids, guggulsterone, crocin, crocetin, isomasticadienolic acid, and cyclotides are the most important phytochemicals present in TPM plants with GI-protective activities. Pharmacological studies demonstrated GI activities for TPM plants supporting their extensive traditional use. These plants play pivotal role in alleviating GI disorders through exhibiting numerous activities including antispasmodic, anti-ulcer, anti-secretory, anti-colitis, anti-diarrheal, antibacterial and anthelmintic properties. Several mechanisms underlie these activities including the alleviation of oxidative stress, exhibiting cytoprotective activity, down-regulation of the inflammatory cytokines, suppression of the cellular signaling pathways of inflammatory responses, improving re-epithelialization and angiogenesis, down-regulation of anti-angiogenic factors, blocking activity of acetylcholine, *etc*.

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Introduction

The evidence of herbal medicines dates back over 5,000 years. The application of medications to the skin to cure illnesses is a practice that has been utilized by humankind for thousands of years and has included the application of poultices, oils, gels, ointments, pastes, and lotions (1). Skin which is known as the largest organ of the human body plays important role in drug delivery. Three important modes including topical, regional and transdermal are used for delivery of various dosage forms. Topical delivery is used mainly to directly affect cutaneous disorders while regional delivery requires deeper penetration than topical delivery and is used to alleviate disease symptoms in deep tissues such as muscles and vasculature joints, beneath or near the site of application (2). Regional delivery is also applied to reduce drug toxicity, as it is established that systemic delivery, can produce inadequate doses of the drug in target tissue, as well as toxicity in healthy tissue. Transdermal delivery is applied to the skin to achieve systemically active levels of the drug to cure systemic disease (2-4). Transdermal delivery has also several advantages over other routes of administration. It is used to bypass hepatic first-pass effect and other variables associated with the gastrointestinal (GI) tract such as pH and gastric emptying time that can prematurely metabolize or degrade drugs. Moreover, transdermal systems also are non-invasive and can be self-administered. They also improve patient compliance and would cause fewer systemic adverse effects (5-7). Particularly, transdermal administration of medicines has been shown to reduce GI track related side effects (8).

Drug delivery across the skin is used for several millennia to ease GI ailments in various traditional medicine systems. In Traditional Persian Medicine (TPM), which is based on quadratic elements (9), a majority of GI remedies are being applied to skin and mostly aimed at regional and/or transdermal delivery (10). These remedies are especially administrated for the treatment of gastric weakness and dyspepsia, gastritis,

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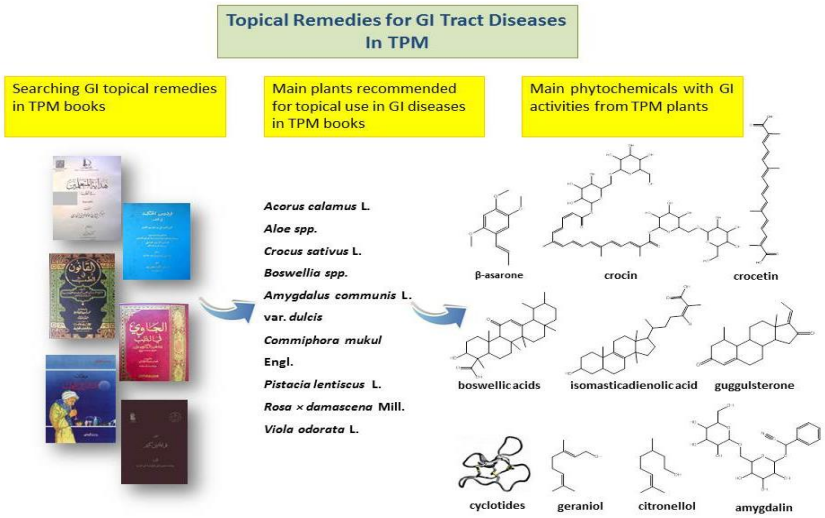

Figure 1. Different steps of the present research

loss of appetite, belching, GI ulcers, colitis, intestinal worms and infections (11, 12). Several medicinal plants, animal products and minerals generally in compound formulations have been recommended to cure these conditions. The recommended formulations are in the forms of poultices, lotions, ointments, rubbing oils, bathes, *etc*. A number of papers have already well studied the medicinal plants used for the treatment of some GI diseases especially peptic ulcer in view of TPM (13, 14). However, there is not any scientific study to specifically survey topical remedies used to alleviate GI problems. Therefore, here we present an overview of the topical GI remedies in TPM and the plant species used as ingredients for these remedies. In addition, relevant pharmacological activities of the mentioned plants in GI tract have been discussed.

Materials and Methods

Firstly, we searched major TPM textbooks to find medicinal plants used for the treatment of GI problems in topical use. These books included *Al-Hawi fi'l-Tebb* (Comprehensive Book of Medicine) by Razi (865-925), *Canon of Medicine* by Ibn Sina (980-1037), *Ferdows al-Hekmah fi'l-Tebb* (Paradise of Wisdom on Medicine) by Tabari (9th century), *Konnash fi'l-Tebb* by Kashkari (9th-10th century), *Hedayat al-Mota'allemin fi'l-Tebb* (An Educational Guide for Medical Students) by Akhawayni (10th century), and *Qarabadin-e-Kabir* by Aqili-Khorasani (16th-17th century). The search was performed using a software namely Jamee al-Tibb containing a majority of TPM books. Afterwards, the scientific names of the retrieved plant names were authenticated using botanical textbooks, including the *Dictionary of Medicinal Plants* (15), *Qamus al-qanun fi'l-tibb* (16), *Illustrated polyglottic dictionary of plant names in Latin, Arabic, Armenian, English, French, German, Italian, and Turkish languages* (17), *Encyclopedia of Medicinal Plants: Arabic-English-French-German-Latin* (18) and *Tafsir kitāb Diyusquiridis* (Explanation of Dioscorides' Book) (19). The scientific names were then entered as key terms for the second search. ScienceDirect, PubMed, Scopus, and Google Scholar databases were searched to obtain pharmacological data supporting the use of TPM plants in GI diseases using the following keywords: Gastrointestinal diseases, peptic ulcer, anti-secretory, gastro-protective effects, anti-inflammatory effects, antibacterial, *Helicobacter pylori*, anti-diarrhea, colitis, *etc*. Different steps of the present research are illustrated schematically in Figure 1.

Topical GI dosage forms in TPM

The use of topical remedies is probably coeval with the appearance of medical knowledge. In TPM, topical medications are almost as applicable as internal formulations (20). In GI problems, topical remedies mostly in the forms of poultices or *zemad*, ointments or *marham*, bathes or *notul*, lotions or *tali* and compresses or *kemad*, are being applied on the stomach area, lower abdomen, lower back and liver.

Poultices are topical preparations usually containing whole fresh medicinal plants or herbal powders occasionally in mixture with herbal distillates, infusions or oils. These dosage forms are directly applied to the skin near the affected area (12).

Herbal oils are common ingredients of topical remedies. In TPM, herbal oils are mostly extracted by maceration method through which the flowers and other herbal tissues are soaked in a base oil (commonly olive, almond or sesame oils), then filtered (12). This process is repeated several times to obtain rich herbal oils containing essential oils and other lipophilic phytpchemicals. Traditional ointments are defined as mixtures of herbal or animal oil and bees wax as a base for bioactive herbal extracts and powders (21). The hydrophobic nature of ointment bases offers an improved percutaneous absorption of herbal extracts. Ointment bases influence drug bioavailability due to their occlusive properties of the stratum corneum, which increases the flux of drug across the skin.

Moreover, they affect drug dissolution and drug partitioning within or from the ointment to the skin (2). Oleo-gum-resins such as mastic, olibanum, guggul, opobalsam, *etc.* which are rich sources of essential oils are important ingredients of TPM cutaneous GI formulations (12). A number of essential oils have been reported to exert GI protective activities (22, 23). Terpenes, the primary constituents of the essential oils obtained from many types of plants and flowers have been shown to have percutaneous permeation through the intact skin (24). Moreover, some terpene-containing essential oils such as fennel oil, peppermint oil, cardamom oil and sweet basil oil are capable of accelerating the percutaneous absorption of co-administered drugs probably due to the increased skin-vehicle partitioning by the oils (25). Various sesquiterpenes have also been found to enhance percutaneous penetration of the drugs possibly by disrupting the intercellular lipid bilayers in the stratum corneum, thus improving co-administered drugs diffusivity, and/or increasing drug partitioning. Some other phytochemicals present in TPM formulations such as fixed oils and fatty acids, aloe juice and α-tocopherol also have percutaneous penetration enhancing effects (26). Thus, these phytochemicals exert multidimensional activities in TPM topical remedies. For instance, the presence of aloe juice in a multi-herbal preparation not only offers multiple GI activities such as anti-ulcerogenic, anti-*H. pylori*, anti-diarrheal, anthelminthic and anti-ulcerative colitis (UC) effects (27-31), but also act as a base or carrier and penetration enhancing agent for other ingredient of the preparation (26).

TPM cutaneous GI formulations aimed at developing percutaneous absorption and deposition of bioactive phytochemicals as well as offering higher regional concentrations than systemic administration at the same total body exposure to the drug. Cutaneous application of these formulations along with oral preparations offers a multifaceted therapeutic strategy for the treatment of GI diseases.

TPM recommended medicinal plants for topical use in gastrointestinal diseases

Around 60 plant species from 34 families have been frequently noted in TPM textbooks to be topically active in the treatment of GI diseases. Most of these species belong to the Apiaceae (eight species) and Rosaceae (four species) families. *Rosa × damascena. Mill.* flowers, *Pistacia lentiscus* L. oleo-gum-resin, *Malus domestica* Baumg. fruits, *Olea europaea* L. fruit oil and aerial parts of *Artemisia absinthium* L. are among the most frequently mentioned herbal ingredients of TPM-recommended remedies. A wide spectrum of GI diseases including GI ulcers, gastric inflammations and swellings, diarrheal illnesses caused by gastric dysfunction, bacterial infections and intestinal problems such as inflammatory bowel disease (IBD) and colitis has been traditionally treated by a combination of internal and topical medications (16, 20, 32). Medicinal plants used to alleviate or cure GI diseases and their TPM information are listed in Table 1.

Table 1. TPM suggested medicinal plants used to treat GI diseases in topical application

Scientific names	Family	Traditional names	Plant part	Medicinal uses	References
Acacia arabica (Lam.) Muhl. ex Willd.	Fabaceae	Aqaqia	dried extract of the leaves and legumes	Gastritis, vomiting caused by yellow bile	(10, 21, 32)
Acorus calamus L.	Acoraceae	Vaj	Rhizome	Stomach weakness, loss of appetite, cholera	(10, 21, 32)
Aloe spp.	Asphodelaceae	Sabr	Dried sap	Stomach weakness, gastritis, stomach swelling	(10-12)
Althaea officinalis L.	Malvaceae	Khatmi	Flowers, seeds	Gastritis, stomach swelling, gastric abscess	(10, 11)
Amygdalus communis L. var. *dulcis*	Rosaceae	Badam talkh	Seeds	Stomach swelling and inflammation	(32)
Anethum graveolens L.	Apiaceae	shebet	Seeds, leaves	Gastritis, stomach swelling, Nausea and vomiting, IBD	(10, 11, 20)
Apium graveolens L.	Apiaceae	Karafs	Seeds	Stomach swelling	(20)
Aquilaria agallocha Roxb.	Thymelaeaceae	Ood	Stem wood	Loss of appetite, diarrhea, digestive aid, stomach tonic, cholera	(10, 20, 21, 32)
Artemisia absinthium L.	Asteraceae	Afsantin	Aerial parts	Stomach weakness, stomach swelling and pain, gastric abscess, vomiting, diarrhea, intestinal worms	(10-12, 20, 21, 32)
Boswellia spp.	Burseraceae	Kondor	Oleo-gum-resin	Stomach weakness, gastritis, Stomach swelling, loss of appetite, diarrhea, intestinal worms	(10-12, 20, 21, 32)
Brassica oleracea L.	Brassicaceae	Kalam	Leaves, seeds	Gastrointestinal swellings, colic, hemorrhoids	(10, 21, 32)
Carum carvi L.	Apiaceae	Zireh	Fruits	Stomach weakness, gastric swellings, flatulence	(10, 20, 21)
Carum copticum Benth. & Hook.f.	Apiaceae	Zenyan	Fruits	gastric swellings	(20)
Cissus quadrangularis L.	Vitaceae	Hamama	Berries	Stomach weakness, gastric swelling caused by phlegm	(10-12, 21)

Cistus ladaniferus Curtis	Cistaceae	Ladan	Sap	Stomach weakness, gastric swelling, gastric trauma, bulimia, diarrhea, diarrhea caused by stomach coldness and weakness	(10-12, 20, 21, 32)
Commiphora mukul Engl.	Burseraceae	Moql azraq	Oleo-gum-resin	Stomach weakness, distention and swelling, belching, intestinal ulcers, IBD, hemorrhoids	(10-12, 20, 21)
Commiphora opobalsamum Engl.	Burseraceae	Balsan	Oleo-gum-resin	Stomach weakness, distention and coldness, gastritis	(10, 11, 21)
Costus speciosus (J.Koenig) Sm.	Costaceae	Qost	Rhizome	Stomach coldness, diarrhea, colic	(11, 12, 32)
Crocus sativus L.	Iridaceae	Zaafaran	Stigma	Cold stomach, gastric distension and swelling, gastritis, nausea, vomiting, diarrhea	(10-12, 20, 21, 32)
Cucurbita pepo L.	Cucurbits	Kadu	Fruits, seeds, peel	Gastric weakness in pregnancy, hot and dry stomach, gastritis, heart burn, peptic ulcer, nausea, thirst, diarrhea	(10, 20, 21, 32)
Cupressus sempervirens L.	Cupressaceae	Sarv	Berries, leaves	Gastric weakness, swelling and distension, cholera, intestinal ulcers, rectal prolapse	(10, 11, 21, 32)
Cydonia oblonga Mill.	Rosaceae	Beh	Fruits, leaves, oil	Poor digestion, nausea, vomiting, gastritis, heartburn, diarrhea, flatulence, cholera	(10, 20, 21)
Cymbopogon schoenanthus (L.) Spreng.	Poaceae	Ezkher	Roots, flowers	Gastric weakness, swelling and distension, diarrhea	(20, 21, 32)
Cyperus rotundus L. *Cyperus longus* L.	Cyperacea	Soad	Rhizome	Stomach weakness, coldness and swelling, dyspepsia, gastritis, nausea, vomiting, diarrhea	(10-12, 20, 21, 32)
Dorema ammoniacum D. Don	Apiaceae	Oshaq	Oleo-gum-resin	Stomach weakness, coldness, swelling and hardness, gastritis, belching, gastric abscess	(10, 11, 21, 32)
Eugenia caryophyllata Thunb.	Myrtaceae	Mikhak	Flowers	Dyspepsia, stomach weakness, severe nausea, diarrhea, cholera	(11, 20, 21, 32)
Foeniculum vulgare L.	Apiaceae	Razianeh	Fruits	Hard swelling of stomach	(20)
Glossostemon bruguieri Desf.	Sterculiaceae	Moghat	Roots, fruits	Hard swelling of stomach	(10, 11)
Hordeum vulgare L.	Poaceae	Jo	Seeds flour	Stomach swelling, gastritis, peptic ulcer, nausea, thirst, chronic diarrhea, gripe, flatulence, rectal prolapse, anal fissure	(10-12, 20, 21, 32)
Hyoscyamus niger L.	Solanaceae	Bangdaneh	Seeds, leaves, flowers	Diarrhea, intestinal ulcers, hemorrhoids pain and inflammation, anal fissure	(10, 12, 21, 32)
Iris florentina L.	Iridaceae	Irsa	Rhizome	Chronic vomiting, belching, hemorrhoids	(21, 32)
Lawsonia inermis L.	Lythraceae	Hana	Leaves, flowers, oil	Coldness of stomach, belching, gastritis, IBD, anal fissure, colic	(10, 21)
Linum usitatissimum L.	Linaceae	Katan	Seeds	Gastritis, gastric hard swelling, vomiting, chronic diarrhea, flatulence, IBD, colic, ileus, hemorrhoids	(10-12, 21, 32)
Malus domestica Baumg.	Rosaceae	Seeb	Fruits, fruits oil	Gastric hard swellings, gastric trauma, stomach weakness, pain and inflammation, loss of appetite, intestinal worms, nausea, cholera, chronic diarrhea	(10, 11, 20, 21, 32)
Matricaria Chamomila L.	Asteraceae	Babuneh	Flowers	Gastric hard swelling, burning and inflammation, flatulence, belching,	(10, 11, 20, 21, 32)

				vomiting, colic, proctitis	
Melilotus officinalis (L.) Lam.	Fabaceae	Eklil al-malek	Legumes	Gastric swelling and inflammation, gastric abscess, dyspepsia, hard swelling, gastric pain, flatulence, vomiting, diarrhea	(11, 20, 21, 32)
Myristica fragrans Houtt.	Myristicaceae	Joz Buya	Seeds, aryls	Nausea, vomiting, diarrhea, hemorrhoids	(10, 32)
Nymphaea alba L. *Nymphaea lotus* L.	Nymphaeaceae	Nilufar	Flowers	Gastritis	(21)
Olea europaea L.	Oleaceae	Zeytun	Fruit oil	Gastric pain and inflammation, bulimia, abdominal pain caused by flatulence, hiccups, dyspepsia, nausea, vomiting, cholera, IBD, hemorrhoids	(10-12, 21)
Opopanax chironium W.D.J.Koch	Apiaceae	Gavshir	Oleo-gum-resin	Gastric swelling and inflammation, belching	(11, 20, 21)
Phoenix dactylifera L.	Arecaceae	Khorma	Fruits	Diarrhea, cholera,	(10, 21)
Pimpinella anisum L.	Apiaceae	Anisun	Fruits	Intestinal ulcers	(21)
Pistacia atlantica Desf. *Pistacia terebinthus* L.	Anacardiaceae	Botm	Oleo-gum-resin	Gastric hard swelling, anal pain, gastric weakness, belching, gastric abscess, colic, hemorrhoids, anal fissure	(10, 12, 21)
Pistacia lentiscus L.	Anacardiaceae	Mastaki	Oleo-gum-resin	Gastric weakness, hard swelling, pain and inflammation, loss of appetite, dyspepsia, hiccups, severe nausea, intestinal ulcers, diarrhea, cholera	(21)
Portulaca oleracea L.	Portulacaceae	Khorfeh	Aerial parts	Gastric weakness, vomiting, excessive thirst, hemorrhagic hemorrhoids	(11, 12, 21)
Punica granatum L.	Punicaceae	Golnar	Flowers	Gastric weakness and inflammation, loss of appetite, excessive vomiting, diarrhea, cholera, intestinal ulcers, anal fissure, rectal prolapse	(10, 20, 21, 32)
Rhus coriaria L.	Anacardiaceae	Somaq	Fruits	Gastric diarrhea, nausea, intestinal ulcers, rectal prolapse, diarrhea, hemorrhoids	(10, 20, 21)
Rosa × damascena Mill.	Rosaceae	Gol-e-sorkh	Flowers, seeds, oil	Gastric hard swelling, pain and inflammation, chronic hiccups, dyspepsia, excessive thirst, bulimia, gastric diarrhea, nausea, intestinal ulcers, cholera, IBD, anal inflammation, anal fissure and fistula, rectal prolapse	(10-12, 20, 21, 32)
Santalum album L.	Santalaceae	Sandal	Wood	Gastric hard swelling and inflammation, nausea, hiccups, loss of appetite, diarrhea, cholera, colic	(10-12, 20, 21, 32)
Tragopogon graminifolius DC *Tragopogon pratensis* L.	Asteraceae	Lehyat al-tees	Aerial parts	Gastric diarrhea, intestinal ulcers	(21, 32)
Trigonella foenum-graecum L.	Fabaceae	Holbeh	Aerial parts	Gastric hard swelling, gastric abscess, gastritis, IBD, ileus, hemorrhoids	(10, 11, 20, 21, 32)
Valeriana celtica L. *Nardostachys jatamansi* DC.	Caprifoliaceae	Nardin	Rhizome	Gastric weakness, hard swelling and inflammation, loss of appetite, belching, colic	(10, 12, 20, 21, 32)
Viola odorata L.	Violaceae	Banafsheh	Aerial parts	Gastric weakness, swelling and inflammation, vomiting, thirst, colic, hemorrhoids	(10, 11, 20, 21)

Pharmacological activities of TPM recommended GI plants

Pharmacological GI activities of TPM recommended medicinal plants have been shown by a large number of *in vitro* and animal investigations as well as some clinical trials.

Mastic gum (oleo-gum-resin from *Pistacia lentiscus* L.) as one of the most emphatic TPM recommended GI plants has been found to exert anti-*Helicobacter pylori* activities *in vivo* (33). In a randomized clinical trial (RCT) in 148 patients with functional dyspepsia, administration of 350 mg mastic gum three times daily for 3 weeks significantly improved symptoms of functional dyspepsia when compared to placebo (34). Mastic gum decreased histological damage in trinitrobenzene sulfonic acid (TNBS)-induced colitis, regulated oxidant/antioxidant balance and modulated inflammation (35). It improved the clinical features of Chron's disease (CD)(36). Additionally, mastic gum exhibited antibacterial activity against *Escherichia coli, Staphylococcus aureus, and Bacillus subtilis* (37).

Artemisia absinthium L. another important GI active TPM plant could induce a significant decrease in volume of gastric juice, acid output and peptic activity in rats. It also decreased the ulcer index significantly (38). In a 6 weeks controlled clinical trial in patients with CD, administration of *A. absinthium* improved symptoms of CD by increased production of pro-inflammatory cytokines such as TNF-α (39). *A. absinthium* also exhibited anti-inflammatory, anti-nociceptive, anthelmintic activities properties and antibacterial activities against GI pathogens (40-42).

Olive oil has traditionally been applied to relieve gastric pain and inflammation, dyspepsia, abdominal pain caused by flatulence, bulimia, hiccups, nausea and vomiting, cholera, IBD and hemorrhoids (11, 20, 32). Odabasoglu *et al* demonstrated that olive oil could prevent the indomethacin-induced gastric damages in rats, enhanced the efficacy of indomethacin for reducing carrageenan-induced paw edema and exerted anti-inflammatory activity against paw edema (43). In a human study, a 30-day olive oil containing diet resulted in attenuating gastric secretory function, suppression of serum gastrin and higher levels of peptide YY in patients with gallstones (44). Olive oil also exhibited strong anti-*H. pylori* activity, decreased acid secretion in the GI tract and reduced the size of peptic ulcers (45).

Additionally, olive oil phenols inhibited the NF-κB driven transcription in a concentration-dependent manner supporting its use in gastric inflammation (46).

Guggul gum (oleo-gum-resin from *Commiphora mukul*) has been widely applied in TPM to alleviate stomach distention and swelling, belching, intestinal ulcers, IBD and hemorrhoids (10, 21). In a randomized controlled trial in 99 patients with hemorrhoids, administration of 3 g/day guggul gum for 4 weeks decreased flatulence, dyspepsia, gastro-esophageal reflux, and colonoscopic grading scores significantly compared to control. The rate of constipation, and proctorrhagia were also significantly improved after 4-weak follow-up (47). Guggulsterone, a steroid found in guggul gum, exhibited anti-inflammatory activities in mouse models of colitis by targeting lamina propria T cells (48). In addition, guggulsterone significantly increased apoptosis in HT-29 cells through activating caspases-3 and -8. It decreased cIAP-1 and 2, and Bcl-2 levels and increased the levels of truncated Bid, Fas, p-c-Jun, and p-JNK. The size of HT-29 xenograft tumors in guggulsterone-treated mice was significantly smaller than control group (49).

Pharmacological activities of other TPM GI recommended plants are shown in Table 2. Most of the mentioned plants exhibited various GI activities which support their extended application in TPM. Nonetheless, the majority of studies have investigated the effects of internal administration of the plants and there is scarcity in studies dealing with their topical application as it is recommended in TPM. Therefore, future studies are needed to elucidate GI effects of TPM plants in topical use. Interestingly, some of the mentioned plants like saffron are traditionally used in depression, tension, anxiety and insomnia even in topical use (21, 50, 51). These effects can exert additional relieving effects on stress-related GI diseases such as peptic ulcers, IBD, *etc*.

Essential oils from aromatic plants have components with antibacterial activities. Cinnamaldehyde, thymol analogues, geraniol, menthol and carvacrol are examples of these components which mostly derive from terpenes and terpenoids (52, 53). Topical use of plants containing antibacterial essential oils may reduce bacterial pathogens in GI track especially in the intestines. Interestingly, phenolic monoterpenes and phenylpropanoids (typically showing strong antimicrobial activities) in combination with other components were found to increase the bioactivities of these mixtures which support the application of the combination of herbal oils in TPM (12, 54). It is well-established that the combination of phenolics such as thymol and carvacrol, with monoterpenes alcohols like eugenol produced synergistic effects on several microorganisms. There are some generally accepted mechanisms of antimicrobial interaction that produce synergistic effects. These mechanisms include the sequential inhibition of a common biochemical pathway, inhibition of protective enzymes of microorganisms; and the use of cell wall active agents to enhance the uptake of other antimicrobials (54). Polyphenols have been found to exhibit numerous beneficial activities in the gastrointestinal tract, including antispasmodic, anti-ulcer, anti-secretory, anti-colitis, anti-diarrheal, and anti-oxidative stress properties (55). For instance, flavonoids and other phenolic compounds such as flavone, quercetin and naringenin which are present in many TPM plants have

been found to be effective in inhibiting the growth of the microorganisms (56). In addition, a number of polyphenolic compounds including oleuropein, cinnamic acid, baicalein, rutin, quercetin, and tephrosin have been reported to exhibit anti-ulcerogenic activity with a good level of gastric protection (57). Generally, polyphenols possess anti-ulcer activities through improving cytoprotection, re-epithelialization, angiogenesis, and neovascularization which are mediated by the up-regulation of tissue growth factors, PGs, and vWF/ factor VIII complex, together with the down-regulation of anti-angiogenic factors. Moreover, polyphenols have been shown to suppress vascular permeability and leukocyte-endothelium interaction mediated by the down-regulation of cellular and intercellular adhesion agents. Polyphenols can palliate inflammatory responses and down-regulate pro-inflammatory cytokines within mucosal ulcers by inhibiting intracellular signaling pathways of the inflammatory process (ERK, JNK, and MAPK), as well as modulating intracellular transcriptional factors (55). Besides their action as gastroprotectives, flavonoids also can be alternative agents for alleviating peptic ulcers associated with *H. pylori* (58).

Alkaloids have been also isolated from a number of TPM recommended plants. Isocorydine alkaloid found in some *Aquilaria spp*. which are used in TPM GI remedies exhibited spasmolytic effects and weak gastric H^+/K^+-ATPase activity (59). Tropane alkaloids such as atropine and scopolamine which are found in Solanaceae family are used to block the muscarinic activity of acetylcholine showing anti-secretory and antispasmodic effects in the treatment of peptic ulcer, gastroenteritis, and spastic colitis (60). Anthocyanins also possess beneficial activities in the management of many GI disorders such as IBD by alleviating oxidative stress, exhibiting cytoprotective activity, down-regulating the inflammatory cytokines and suppressing cellular signaling pathways of inflammatory responses (61). Gastrointestinal activities of a number of phytochemicals present in TPM plants have been shown in Table 2. As seen in Table 2, several phytochemicals from TPM plants have been found to be effective in GI ailments. β-asarone from *Acorus calamus* L. (potent anthelmintic, anti-amoebic and antibacterial activities), amygdalin from *Amygdalus communis* L. var. *dulcis* (anti-gastric ulcer activity), boswellic acids from *Boswellia serrata* (gastric ulcer protective effect, protecting the colonic mucosa against tissue injury, and reducing colitis activity), guggulsterone from *C. mukul* (anti-inflammatory, apoptogenic properties in colon cancer cells), crocin from *Crocus sativus* L. (inhibiting the growth of colorectal cancer cells), crocetin (ameliorating UC and anti-*H. pylori* effects), isomasticadienolic acid from *P. lentiscus* (Reducing *H. pylori* colonization), and cyclotides from *Viola odorata* L. (anti-gastrointestinal nematodes) are among the most GI bioactive phytochemicals. Accordingly, above-mentioned compounds are potential active principles with GI tract actions as well as good candidates for future pharmacological and clinical studies and developing new GI protective medicines.

The most emphatic TPM topical GI formulations

Numerous multi-herbal topical formulations are used in TPM for the treatment of GI diseases. Some of these formulations have been frequently mentioned in many TPM textbooks indicating their extensive effectiveness and safety in traditional medicine observations. The following formulations are examples of the most frequently applied topical TPM formulations for the treatment of GI ailments.

A topical preparation containing *Valeriana celtica* L., mastic oil, aloe sap and verjuice is recommended to apply on stomach area to relieve gastritis and gastric burning and discomfort. As seen in Table 2, some of the ingredients of this remedy have been found to be strongly GI-protective supporting their use in TPM. A poultice consist of barley flour in combination with diverse gastroprotective anti-ulcer plants such as pureed quince, squash, purslane, mastic, sandalwood powder, *etc.* has also been frequently used to alleviate gastric inflammation, pain and burning (10, 21). An ointment containing *Commiphora opobalsamum* Engl. oleo-gum-resin, aloe and bees wax is used to relieve symptoms of gastritis (10). Another well-experienced topical prescription for gastric discomfort, nausea and vomiting is a mixture of crushed squash, purslane, barley flour and vinegar (10).

Rubbing a mixture of rose oil and mastic oil on stomach has been frequently recommended for terminating prolonged episodes of hiccups (21). A poultice containing olibanum, mastic gum, agarwood, sweet flag, pomegranate flowers, quince juice and wine is noted in many TPM books for the treatment of poor appetite (10, 21).

An ointment containing guggul gum in mixture with dill and fenugreek seeds, henna leaves, olive oil and rose oil has been used as a potent remedy to alleviate IBD symptoms (10).

The above-mentioned prescriptions along with many other TPM remedies as invaluable sources of experienced traditional knowledge offer new horizons for future studies to find bioactive phytochemicals and develop new phytopharmaceuticals and therapeutic strategies for the treatment of GI diseases.

Conclusion

With around 60 different plant species from 34 families frequently used in hundreds of recipes of TPM for topical application to cure a wide variety of GI ailments, we can conclude that these plants (in simple use or in combination recipes) can be

potential alternatives for GI medications. These medications are generally applied in forms of poultices, ointments, bathes and lotions on the stomach area, lower abdomen, lower back and liver to achieve regional and/or systemic delivery of the plant's biologically active compounds. β-asarone from *A. calamus*, amygdalin from *A. communis* L. *var. dulcis*, boswellic acids from *B. serrate*, guggulsterone from *C. mukul*, crocin and crocetin from *C. sativus*, isomasticadienolic acid from *P. lentiscus*, and cyclotides from *V. odorata* are among the most important phytochemicals present in TPM plants with GI protective activities. These phytochemicals along with many other bioactive compounds play pivotal role in alleviating GI disorders through exhibiting numerous activities including anti-spasmodic, anti-ulcer, anti-secretory, anti-colitis, anti-diarrheal, antibacterial, anthelmintic, anti-inflammatory and anti-oxidative stress properties. Several mechanisms underlie these activities including the alleviation of oxidative stress, exhibiting cytoprotective activity, down-regulation of the inflammatory cytokines, suppression of the cellular signaling pathways of inflammatory responses, improving re-epithelialization, angiogenesis, and neovascularization mediated by the up-regulation of tissue growth factors, PGs, and vWF/ factor VIII complex, together with the down-regulation of anti-angiogenic factors, blocking muscarinic activity of acetylcholine (resulting in antisecretory effects), *etc*. TPM topical GI remedies commonly contain a combination of herbal powders, oils, oleo-gum-resins and extracts which may have synergistic effects with different mechanisms. Mastic gum, aloe, absinthe and olive oil are the most frequent herbal ingredients of TPM GI recipes. Although pharmacological investigations well support the use of TPM plants, data on topical application of these plants are scarce. Accordingly, there is a need to investigate pharmacological activities, clinical efficacy, pharmacokinetic aspects as well as possible skin reactions and other adverse effects of recommended plants in topical use. In conclusion, TPM topical GI remedies, the mentioned medicinal plants and their active compounds are useful pharmacological tools to discover new active principles with GI tract actions.

Table 2. Gastrointestinal activities of TPM-recommended plants for topical use and their main phytochemicals

Scientific name	Common name	Extract/phytochemical/plant part	Pharmacological activities	Model	Reference
Acacia arabica (Lam.) Muhl. ex Willd.	Gum arabic tree	Gum arabic-supplemented oral rehydration solution	Anti-diarrhea	*in vivo*	(62)
Acorus calamus L.	Sweet flag	Crude extract/ n-hexane fraction	Spasmolytic activity by inhibition of spontaneous and high K^+-induced contractions through Ca^{2+} channel blockade in the isolated rabbit jejunum preparation	*ex vivo*	(63)
		Methanol extract	Anti-diarrhoeal effect	*in vivo*	(64)
		Ethanol extract of rhizome containing β-asarone	Potent anthelmintic activity, anti-amoebic and antibacterial activity	*in vitro*	(65)
		Ethanol extract of rhizome	Anti-secretory, anti-ulcer, cytoprotective	*in vivo*	(66)
Aloe spp.	Aloes	Aqueous extract of the leaves of *A. ferox* Mill	Improving intestinal motility, increasing fecal volume in loperamide-induced constipation	*in vivo*	(27)
		A. vera gel	Inhibitory effects on colorectal prostaglandin E2 and interleukin-8 production	*in vitro*	(28)
		Aqueous extract of *A. vera* leaves	Inhibition of gastric acid secretion	*in vivo*	(30)
		A. vera extract	Strong anti-*H. pylori* activity, ulcer healing properties	*in vitro, in vivo*	(29)
		Aqueous extract of leaves of *A. ferox*	Anthelminthic activity	*in vitro*	(67)
		Ethanolic extract of *A. barbadensis*	Antimicrobial activity	*in vitro*	(68)
Althaea officinalis L.	Marsh mallow	Hydro-ethanolic extract of aerial parts	Antibacterial against *Escherichia coli*	*in vitro*	(69)
		Aqueous extract of aerial parts	Antiulcer activity: reduction of the ulcer number, ulcer index and peptic activity after pyloric ligation, reduction of oxidative stress and histamine release	*in vivo*	(70)
Amygdalus communis L. var. *dulcis*	Bitter almond	Amygdalin	Protection against gastric ulcer	*in vivo*	(71)
		Ethanol extract of seeds	Laxative effect	*in vivo*	(72)
Anethum	Dill	Seed ethanolic extract	Inhibiting acid secretion and the	*in vivo*	(73)

graveolens L.			occurrence of lesions in stomach		
		Aqueous and ethanolic extracts of seeds	Protection against gastric ulcer, attenuation in the changes in gastric juice volume, pH, acid-output and ulcer index, acid buffering activities pepsin binding activity	*in vitro* *in vivo*	(74)
		Seeds powder			
		Hydroalcoholic extract	Potent spasmolytic activity in ileum	*ex vivo*	(75)
		Hot water and acetone extracts of seed	Antibacterial activity	*in vitro*	(76)
Apium graveolens L.	Celery	Methanolic and aqueous extracts of aerial part and seeds	Inhibition of gastric ulcers	*in vivo*	(77)
		Methanolic and aqueous extracts of leaves	Antimicrobial activity against enteric pathogens	*in vitro*	(78)
		Ethanolic and aqueous extracts of leaves	Inhibition of spontaneous rat ileum contractions	*ex vivo*	(79)
Aquilaria agallocha Roxb.	Agarwood	Ethyl acetate extract	Analgesic, anti-inflammatory	*in vivo*	(80)
Artemisia absinthium L.	Absinthe	Essential oil containing trans-sabinyl acetate, myrcene, β-thujone	Anti-fungal, antibacterial activity	*in vitro*	(81)
		Ethanol extract of aerial parts	Anti-gastric ulcer effects, decrease in volume of gastric juice and acid output	*in vivo*	(38)
		Powder	TNF-α suppression, remission of symptoms of CD	RCT	(39)
		Methanol extract	Anti-inflammatory	*in vivo*	(82)
		Methanol extracts	Antibacterial (GI pathogens)	*in vitro*	(40)
		Essential oil, aqueous extract	Anti-inflammatory, anti-nociceptive	*in vivo*	(41)
		Aqueous extracts ethanolic extracts	Anthelmintic	*in vitro* *in vivo*	(42)
		A multiherbal preparation containing ethanolic-aqueous extracts	Cure upper abdominal complaints	RCT	(83)
Boswellia spp.	Olibanum	*B. serrate* oleo-gum-resin	Complete resolution of ulcers in chronic colitis, loss of friability of mucosa, and granulation, loss of hypercellularity of lamina propria without distorted crypt architecture in rectal mucosa, healing of ulcers and loss of fibrous tissue and chronic inflammatory cells	clinical trial	(84)
		B. serrata gum-resin hydroalcoholic extract	Antidiarrheal activity, inhibition of acetylcholine- and electrical field stimulation-induced contractions in the isolated guinea-pig ileum	*in vivo, ex vivo*	(85)
		Boswellic acids	Gastric ulcer protective effect	*in vivo*	(86)
		B. serrata gum-resin extract, acetyl-11-keto-β-boswellic acid	Attenuating leu-kocyte–endothelial cell adhesive interactions, ameliorating inflammation-associated tissue injury in a rat model of experimental IBD	*in vivo*	(87)
		Boswellic acids	Attenuating the recruitment of both leukocytes and platelets, blunting P-selectin expression, protecting the colonic mucosa against tissue injury, and reducing colitis activity	*in vivo*	(88)
		β-boswellic acid derivatives	*H. pylori* urease inhibitory activities	*in vitro*	(89)
Brassica oleracea	Cabbage	Hydroalcoholic extract of leaves	Protection against gastric ulcer	*in vivo*	(90)

L.					
Carum carvi L.	Persian cumin	Methanol extract of seeds	Anti-*H. pylori*	*in vitro*	(91)
		Essential oil	Treatment of intestinal dysbiosis	*in vitro*	(92)
		Ethanol extract of the seeds	Inhibiting the response of intestinal smooth muscle cells to acetylcholine	*ex vivo*	(93)
		Powdered seeds	Modulatory role on tissue lipid peroxidation, antioxidant profile and preventing 1,2-dimethylhydrazine-induced histopathological lesions in colon cancer rats	*in vivo*	(94)
		Alcoholic extract	anti-ulcerogenic activity: reducing acid output, increasing mucin secretion, increasing prostaglandin E2 release, decrease in leukotrienes, protection against gastric ulceration	*in vivo*	(95)
Carum copticum Benth. & Hook.f.	Ajwain	Ethanol and aqueous extract of fruits	Antidiarrhoeal activity	*in vivo*	(96)
		Aqueous extract of fruits	Inhibitory effect on ACh-induced contraction in rat's ileum	*ex vivo*	(97)
		Aqueous extract	Treatment of peptic ulcer	*in vivo*	(98)
		An equal mixture of methanol, diethyl ether and petroleum benzene extract	Anti-*H. pylori*	*in vitro*	(99)
Cissus quadrangularis L.	Veldt grape	Methanol extract of stem	Attenuation in levels of TNF-α, IL-1β), microvascular permeability, activity of nitric oxide synthase-2, mitochondrial antioxidants, lipid peroxidation, DNA damage, Decrease in tissue damage glutathione, superoxide dismutase and catalase, reducing size of NSAID induced ulcer crater, restoration of mucosal epithelium	*in vivo*	(100, 101)
		Stem extract	Attenuation in aspirin-induced gastric lesions, an increase in uric acid, antioxidative enzymes, SH groups, decrease in lipid peroxidase, TNF-α, xanthine oxidase, myeloperoxidase activities	*in vivo*	(102)
		Methanolic extract	Increase in the mucosal defensive factors like mucin secretion, mucosal cell proliferation, glycoproteins, and life span of cells in experimentally induced gastric ulcer	*in vivo*	(103)
		Chloroform extract	Potent anti-*H.Pylori*	*in vitro*	(104)
Cistus ladaniferus Curtis	Labdanum	Aqueous extract of aerial parts	Effective against reserpine- and serotonin-induced mucosal congestion and haemorrhagic ulcers	*in vivo*	(105)
		Aqueous extract of leaves and stems	Antispasmodic action in the rabbit jejunum through calcium channel blockade	*ex vivo*	(106)
		aerial parts aqueous extract	Anti-diarrhoeal activity in castor oil-induced diarrhoea	*in vivo*	(107)
Commiphora mukul Engl.	Guggul	Guggulsterone	Anti-inflammatory activities in mouse models of colitis by targeting lamina propria T cells	*in vivo*	(48)
		Guggulsterone	Activation of the mitochondria-dependent pathway and the extrinsic pathway of apoptosis in colon cancer cells, inhibition of the growth of HT-29 xenografts	*in vitro*	(49)
		Guggulsterone	Inducing apoptosis, inhibition of angiogenesis and metastasis in colon cancer cells through	*in vitro*	(108)

			blocking STAT3 and VEGF expression		
		Oleo-gum-resin powder	Reduction in symptoms of uncomplicated hemorrhoids grade 1 and 2.	RCT	(47)
Commiphora opobalsamum Engl.	Arabian balsam tree	Oleo-gum-resin ethanol extract	Protecting against gastric ulcers, anti-secretion	*in vivo*	(109)
		Methalonic extract of aerial parts	analgesic and anti-inflammatory activity	*in vivo*	(110)
		Essential oil	Antimicrobial activity	*in vitro*	(111)
Costus speciosus (J.Koenig) Sm.	Crêpe ginger	-	-	-	-
Crocus sativus L.	Saffron	Extract of stigma, crocin	Inhibiting the growth of colorectal cancer cells	*in vitro*	(112)
		Methanol and aqueous extracts, crocin and safranal	Anti-*H. pylori* effects	*in vitro*	(113)
		Crocetin	Ameliorating UC by down-regulation of NFkB	*in vivo*	(114)
		Aqueous extract	Inhibition of gastric cancer progression	*in vivo*	(115)
		Hydro-ethanol extract	Strong inhibitor of IL-8 secretion from *H. pylori*-infected epithelial cells	*in vitro*	(116)
Cucurbita pepo L.	Pumpkin, squash	Aqueous extract of pulp	Anti-ulcer activity by enhancement of gastric adherent mucus in aspirin-induced gastric and duodenal ulcer	*in vivo*	(117)
Cupressus sempervirens L.	Mediterranean cypress	Essential oil	Inhibition of the growth of *H. pylori*	*in vitro*	(118)
		Ethanolic extract of leaves, cupressuflavone	Anti-ulcerogenic activity through enhancement of endogenous antioxidant enzymes, disposal of free radicals and anti-apoptotic activity	*in vivo*	(119)
		Essential oil	Antimicrobial	*in vitro*	(120)
Cydonia oblonga Mill.	Quince	Juice	Diminishing inflammation and ulcer indices in TNBS-induced ulcerative colitis	*in vivo*	(121)
		Polyphenol extract of peel	Potent anti-inflammatory effect	*in vitro*	(122)
		Ethanolic extract of seeds aqueous extract	Anti-*E.coli,* anti- *Enterobacter aerogenes*	*in vitro, in vivo*	(123)
		A fruit preparation	Inhibiting the gastrointestinal content advance, reducing castor oil-induced diarrhea	*in vivo*	(124)
Cymbopogon schoenanthus (L.) Spreng.	Camel grass	-	-	-	-
Cyperus rotundus L.	Java grass	Decoction of rhizome	Gastric ulcer inhibitory effect	*in vivo*	(125)
		Hydro-methanol extract of whole plant	Antinociceptive effect	*in vivo*	(126)
Dorema ammoniacum D. Don	Gum ammoniac tree	-	-	-	-
Eugenia caryophyllata Thunb.	Clove	Hydro-ethanolic extract of flowers	Anti-*H.pylori*	*In vitro*	(127)
		Essential oil/ eugenol	Protection against gastric ulcer	*in vivo*	(128)
		Essential oil/ eugenol	Anti-*Giardia* activity	*in vitro*	(129)
Foeniculum vulgare L.	Fennel	Aqueous-ethanol extract of seeds	Suppressing ROS generation in *H. pylori*-infected gastric epithelial cells	*in vitro*	(116)
		aqueous extract of seeds	Anti-ulcerogenic and antioxidant effects	*in vivo*	(77)
Glossostemon bruguieri Desf.	Dombeya arabica	-	-	-	-
Hordeum vulgare L.	Barley	Seeds	Antiinflammtory	*in-vitro, in-vivo*	(130, 131)
Hyoscyamus niger L.	Henbane	Crude extract of seeds/ β-sitosterol	GI antispasmodic effect through a combination of anticholinergic and Ca^{2+}antagonist mechanisms.	*in-vivo*	(132)
Iris florentina L.	Iris	-	-	-	-
Lawsonia inermis	Henna	Aqueous, ethanol and	Decrease in the volume of gastric	*in vivo*	(133)

L.		chloroform extract of leaves	acid secretions, free acidity and total acidity and ulcer index in gastric ulcers induced rats.		
		Aqueous extract of leaves	Antibacterial activity	*in vitro*	(134)
Linum usitatissimum L.	Linseed	Crude extract of lignans of seeds	Protection and recovery against gastric ulcers	*in vivo*	(135)
		Seeds oil and mucilage	Protection against gastric ulcers	*in vivo*	(136)
		Aqueous-methanol extract of seeds	Antidiarrheal and antispasmodic activities through inhibition of Ca^{2+} channels	*in vivo, Ex vivo*	(137)
Malus domestica Baumg.	Apple	Methanol extract of fruit flesh containing polyphenols	Preventing aspirin-induced gastric injury, counteracting aspirin-induced up-regulation of HB-EGF and COX-2 expression	*in vivo*	(138)
		Fruit juice	Antiulcerative activity	*in vivo*	(139)
		Fruit sauce	Antidiarrheal activity	*in vivo*	(140)
Matricaria Chamomila L.	Chamomile	Hydroalcoholic extract of aerial parts	Protective effect against ethanol-induced gastric mucosal lesions by reducing gastric lesions and malondialdehyde and increasing glutathione levels in gastric tissue or whole blood	*in vivo*	(141)
		aqueous-methanolic extract of aerial parts	Antidiarrhoeal, antisecretory and antispasmodic activities through K^+-channels activation and weak Ca^{2+} antagonist effect	*in vivo*	(142)
		aqueous extract of aerial parts	Spasmolytic activity by cAMP-cGMP-phosphodiesterases inhibition	*in vitro*	(143)
		decoction of aerial parts	Potent antidiarrheal and antioxidant: protection against castor oil-induced diarrhea and intestinal fluid accumulation	*in vivo*	(144)
Melilotus officinalis (L.) Lam.	Common melilot	Gel and aqueous extract containing catechin and cinnamic acid	Attenuating acetic acid induced UC antioxidant and anti-inflammatory effects	*in vivo*	(145)
Myristica fragrans Houtt.	Nutmeg	Crude suspension and petroleum ether extract of seeds	Antidiarrheal effect	*in vivo*	(146)
		Hydro-ethanolic extract	Anti-*H. pylori* activity	*in vitro*	(147)
Nardostachys jatamansi DC.	Spikenard	-	-	-	-
Nymphaea lotus L.	White lotus	Aqueous extract	Protection against gastric ulcer	*in vivo*	(148)
Nymphaea alba L.	White water rose	Ethanol extract of rhizome	Antioxidant and analgesic	*in vivo, in vitro*	(149)
Olea europaea L.	Olive	Olive oil	Preventing the indomethacin-induced gastric damages in rats, enhancing efficacy of indomethacin for reducing carrageenan-induced paw edema, anti-inflammatory effect against paw edema	*in vivo*	(43)
		A 30-day period of diets containing olive oil	Attenuating gastric secretory function, suppression of serum gastrin and higher levels of peptide YY.	*Patients with gallstones*	(44)
		Polar fraction of extra-virgin olive oil	Inhibition of NF-κB driven transcription and nuclear translocation in AGS cells (a model for gastric inflammation)	*in vitro*	(46)
		Virgin olive oil extracts rich in phenolic compounds especially dialdehydic form of decarboxymethyl ligstroside (Ty-EDA)	Strong anti-*H. pylori* activity, decrease acid secretion in the GI tract, reduction in the size of peptic ulcers	*in vitro*	(45)
		Leaves extract	Attenuation of the ethanol-induced gastric lesions, prevention of an increase in gastric lipid peroxidation, prevention of a decrease in antioxidative enzyme activity	*in vivo*	(150)
Opopanax chironium W.D.J.Koch	Sweet myrrh	-	-	-	-

Phoenix dactylifera L.	Date	Aqueous and ethanolic extracts of fruits	Ameliorative effect on ethanol-induced gastric ulcer	*in vivo*	(151)
		Ethanol and water extracts of the flesh and pits	Enhancing the GI transit	*in vivo*	(152)
Pimpinella anisum L.	Anise	Aqueous suspension of fruits	Cytoprotective and anti-ulcer activities against experimentally-induced gastric lesions	*in vivo*	(153)
		Aqueous and ethanol extracts of fruits	Antioxidant and antimicrobial activities	*in vitro*	(154)
Pistacia atlantica Desf.	Persian turpentine tree	Essential oil of oleo-gum-resin	Antimicrobial activity	*in vitro*	(155)
Pistacia atlantica subsp. *kurdica*	Baneh tree	Oleo-gum-resin, essential oil	Anti-colitis activity	*in vivo*	(156)
Pistacia lentiscus var. *Chia*	Mastic	Oleo-gum-resin	Improving symptoms in patients with functional dyspepsia	RCT	(34)
		Oleo-gum-resin	Antibacterial activity against *H. pylori*	*in vivo*	(157)
		Oleo-gum-resin total extract/ isomasticadienolic acid	Reducing *H. pylori* colonization	*in vivo*	(33)
		Oleo-gum-resin powder	Decreasing histological damage in TNBS-induced colitis, regulating oxidant/ antioxidant balance and modulating inflammation	*in vivo*	(35)
		Oleo-gum-resin powder	Improving the clinical features of CD and regulating inflammation and antioxidant status	RCT	(36)
		Oleo-gum-resin essential oil	Antibacterial activity against *E. coli, Staphylococcus aureus,* and *Bacillus subtilis*	*In vitro*	(37)
Portulaca oleracea L.	Purslane	Aqueous and ethanolic extracts	Gastric anti-ulcerogenic effects	*in vivo*	(158)
Punica granatum L.	Pomegranate	Methanol extract of peel	Potent anti-*H. pylori*	*in vitro*	(159)
		Aqueous-methanolic extract of flowers	Gastric anti-ulcerogenic effects	*in vivo*	(160)
		Ethanolic extract of pericarp: ethyl acetate and n-butanol fractions	Anti-enterohemorrhagic *E. coli*	*in vitro*	(161)
		Aqueous extract of peels	Antidiarrheal effects	*in vivo*	(162)
		Methanol-water extract of flowers and its ellagic acid rich fraction	Attenuation of colonic inflammation in UC, attenuation of histamine, myeloperoxidase and oxidative stress	*in vivo*	(163)
Rosa × damascena Mill.	Damask rose	Hydroalcoholic extract of flowers	Inhibition of ileum contraction at mg concentrations, stimulatory effect on ileum at µg concentrations	*ex vivo*	(164)
		Flowers essential oil containing geraniol and citronellol	Inhibitory effect on ileum contraction	*ex vivo*	(165)
		Hydroalcoholic extract of flowers	Improving macroscopic and histopathological parameters of acetic acid-induced colitis	*in vivo*	(166)
Rhus coriaria L.	Sumac	Crude methanolic extract	Anti-secretory, antidiarrheal and antispasmodic properties through Ca^{2+} blockade	*in vivo, in vitro*	(167)
		Ethanol extract	Anti-*H. pylori* activity	*in vitro*	(168)
		Hydroalcoholic extract of leaves	Analgesic effect	*in vivo*	(169)
Santalum album L.	Indian sandalwood	Methanol extract of wood	Anti-diarrhoeal activity	*in vivo*	(170)
		Hydro-alcoholic extract	Protection against gastric ulcer	*in vivo*	(171)
		Methanolic extract of wood	Analgesic and anti-inflammatory activities	*in vivo*	(172)
Tanacetum balsamita L. subsp. *Balsamitades* (Schultz Bip.) Grierson	Costmary	Essential oil	Antimicrobial activity	*in vitro*	(173)
Tragopogon pratensis L.	Meadow salsify	Ethanol extract of aerial part	Antibacterial properties	*in vitro*	(174)
Tragopogon graminifolius	Goatsbeard	Ethanol extract of aerial part	Alleviating colitis via anti-inflammatory effects	*in vivo*	(175)
		Hydroalcoholic extract of aerial part	Protection against gastric ulcer	*in vivo*	(176)

Trigonella foenum-graecum L.	Fenugreek	Aqueous extract and a gel fraction of seeds	Gastric ulcer protective effects	*in vivo*	(177)
Valeriana celtica L.	Alpine valerian	-	-	-	-
Viola odorata L.	Sweet violet	Aqueous extract of aerial parts	Antibacterial effects	*in vitro*	(178)
		Cyclotides	Anti-gastrointestinal nematodes	*in vitro*	(179)
		Hydro-ethanol extract	Strong inhibitor of IL-8 secretion from *H. pylori*-infected epithelial cells	*in vitro*	(116)
Ziziphus spina-christi (L.) Willd.	Christ's Thorn Jujube	Methanol extract of stem bark	Anti-diarrhoeal effects	*in vivo*	(180)

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