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Plants against *Helicobacter pylori* to combat resistance: An ethnopharmacological review

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ABSTRACT

Worldwide, *Helicobacter pylori* (*H. pylori*) is regarded as the major etiological agent of peptic ulcer and gastric carcinoma. Claiming about 50 percent of the world population is infected with *H. pylori* while therapies for its eradication have failed because of many reasons including the acquired resistance against its antibiotics. Hence, the need to find new anti-*H.pylori* medications has become a hotspot with the urge of searching for alternative, more potent and safer inhibitors. In the recent drug technology scenario, medicinal plants are suggested as repositories for novel synthetic substances. Hitherto, is considered as ecofriendly, simple, more secure, easy, quick, and less toxic traditional treatment technique. This review is to highlight the anti-*H. pylori* medicinal plants, secondary metabolites and their mode of action with the aim of documenting such plants before they are effected by cultures and traditions that is expected as necessity.

1. Introduction

Helicobacter pylori (*H. pylori*) is a spiral-shaped Gram-negative bacteria colonized in the gastrointestinal tract. *H. pylori* infection leads to peptic ulceration, gastritis, and gastric carcinoma [1]. About 50 % of the world population is estimated to be infected by this bacterium [2]. The colonization of *H. pylori* is caused by its infectious agents as shown in Fig. 1 and Table 1.

2. Pharmacological therapies

Numerous pharmacological studies have been reported for the eradication of *H. pylori*. Proton-pump inhibitors, antibiotics, bismuth saltsand H2-blockers (intragastric pH control drug) are recommended standard therapies [3]. A few issues may arise upon those eradication therapies, for example, the cost, the high global prevalence and the uprising resistance to available antibiotics. Consequently, some patients undergoing many of these drug regimens experience therapeutic failure [3]. Moreover, these therapies include getting too many medications which might cause side effects that, along with significant cost regarding the treatment, promote inadequate patient compliance. It is extremely desirable to explore for alternative strategies with agents to prevent or manage *H. pylori*-associated gastric tumor.

The quest regarding new anti-*H. pylori* therapies has driven exploration in the field of therapeutic plants. Many studies have been performed on a great number of plant varieties. Natural products exhibit their own anti-*H. pylori* actions via different mechanisms. While therapeutic agents have either antisecretory or healing effects, prophylactic compounds produce their effect via their antioxidant and anti-inflammatory mechanisms.

3. Mechanisms of medicinal plants as anti-*H. pylori*

Many natural products have anti-*H. pylori* potentials. The mechanisms of such potentials include urease inhibition, DNA damage, protein synthesis inhibition, and anti-inflammatory effects. In addition to the anti-*H. pylori* effects due to some enzymes like dihydrofolate reductase and myeloperoxidase *N*-acetyltransferase.

3.1. Urease inhibition

The potent effect of resveratrol as anti-*H. pylori* is mainly owing to ureaseinhibition [4]. The anti- *H. pylori* actions of *Paeonia lactiflora* roots is due to the hydrophobicity of 1,2,3,4,6-penta-*O*-galloyl-β-D-glucopyranose which facilitates thebinding to membranes leading to the loss of membrane integrity as well as urease inhibition [5]. Both the $CHCl_3$ fraction and EtOH extract of *Calophyllum brasiliense* stem bark has been reported to decrease *H. pylori* and urease activity in Wistar rats as confirmed by

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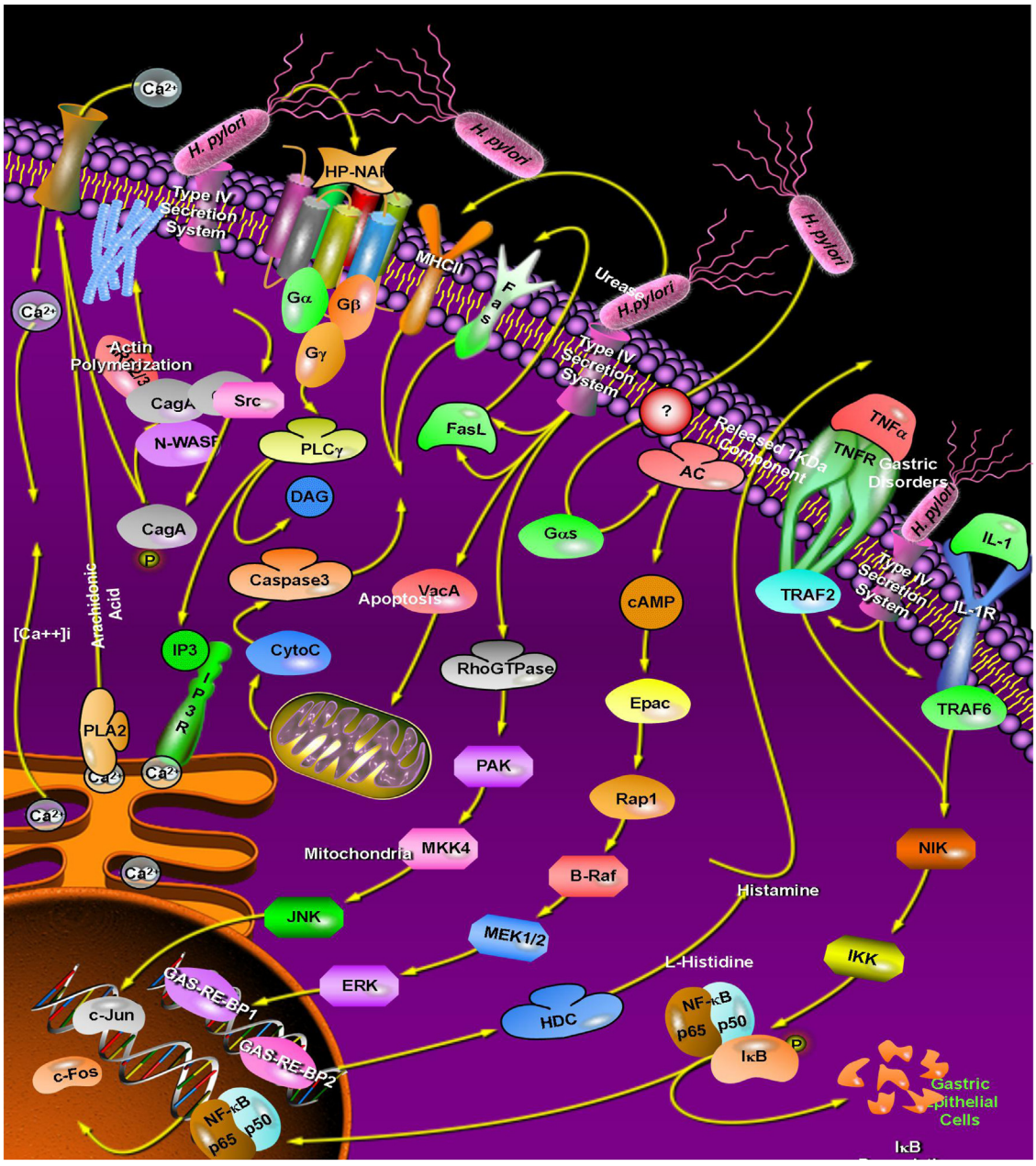

Fig. 1. Virulence agents of *H. pylori*. IL: Interleukin; TLR4: Toll-like receptor 4; NF-κB: Nuclear factor-kappaB; NIK: NF-κB-inducing kinase; VacA: Vacuolating cytotoxin A; CagA: Cytotoxin-associated gene antigen; PAK1: p21-activated kinase; IKKα/β: IκB kinase α/β; MAPK: Mitogen-activated protein kinase; MEK1/2: MAPK/ERK kinase 1/2; INF-γ: Interferon-γ; NOD1: Nucleotide-binding oligomerisation domain protein 1; ICAM-1: Intercellular adhesion molecule-1; iNOS: Inducible nitric oxide synthase, COX-2: Cyclooxygenase-2; MKK4: MAPK kinase 4; LPS: Lipopolysaccharide; TNF-α: Tumor necrosis factor-α.

histopathology [6]. The mode of action of mixed cranberry and oregano water extract may be due to inhibition of proline dehydrogenase and urease activvity [7]. Both*Calotropis procera* and *Acacia nilotica* extracts inhibit urease activity through competitive mechanisms [8].

3.2. Oxidative stress

2-Methoxy-1,4-naphthoquinoneexhibits strong anti *H. pylori* action. 2-methoxy-1,4-naphthoquinone is metabolized in *H. pylori* membrane by flavoenzymes and produces a high amount of free radicals that may damage cellular macromolecules and may lead to *H. pylori* death [9].

3.3. Anti-adhesion activity

Borage, parsley, and turmeric water extracts are found to be able to decrease adhesion of *H. pylori* [10]. The Liquoriceroot aqueous extract and polysaccharides exhibite strong anti-adhesive activity of human gastric mucosa aliquots with fluorescent-labeled *H. pylori* [11]. The *Pelargonium sidoides* root extract display antiadhesive activity [12]. The diterpene Plaunotol, isolated from the plau-noi leaves, is also found to inhibit adhesion of *H. pylori* as well as inhibition of IL-8 secretion [13].

4. Structure activity relationship

Plantswith anti H. pylori activityconsist of various phytocompounds, such as alkaloids, flavonoids, saponins, terpenes, and

Table 1
Virulence agents of *H. pylori*.

Vrulence agent	*H. pylori* Function
Vacuolating cytotoxin A (VacA)	Induce Cyto C release Cytotoxicity
Cag Pathogenicity Island (CagPAI)	Induce inflammation
Cag genes (Cag E,G,I,H, L and M)	Coding for 40-kb is a major virulence factor of *H. pylori*.
Urease	Causing epithelium cells toxicity Disrupting cell tight junctions Buffers stomach acid Sheathing antigen
Duodenal ulcer promoting A (DupA)	Induce inflammation
Outer inflammatory protein A (OipA)	Induce inflammation for IL-8
H. pylori neutrophil activation protein (HP-NAP)	Activation of neutrophil
BabA	Adhesin
Flagella	Movements through mucin

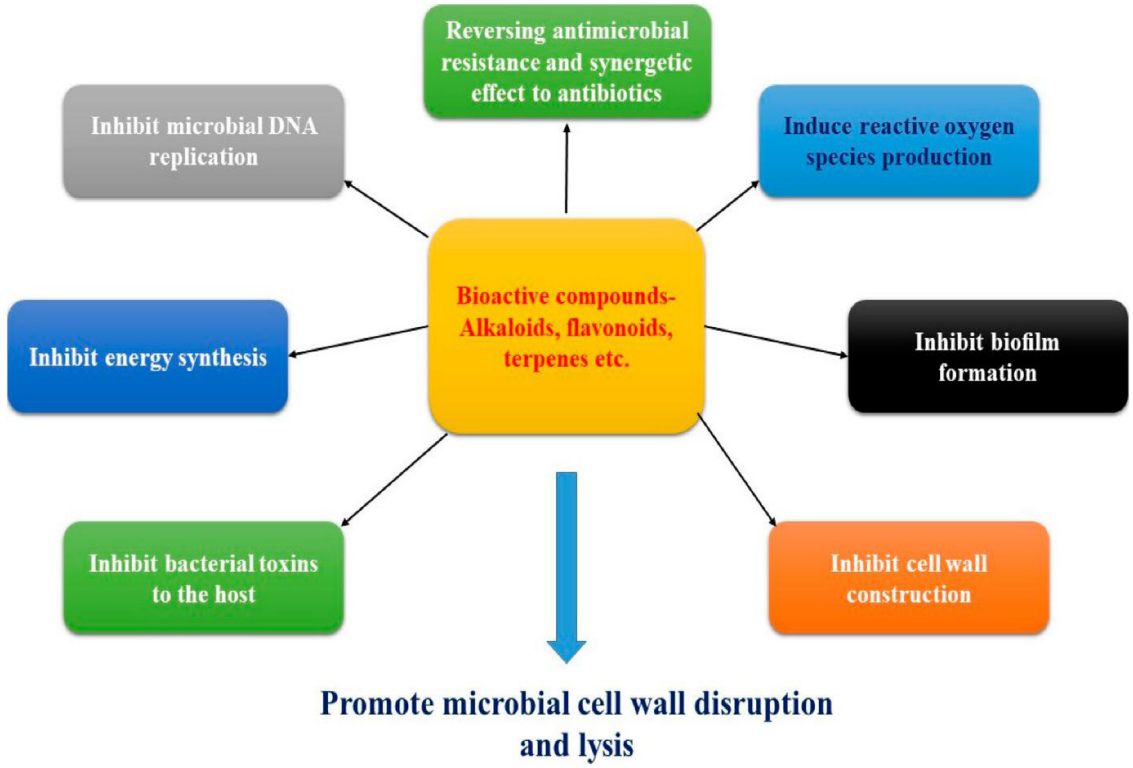

Fig. 2. Mechanisms of action of phytocompounds against microorganisms.

polysaccharides, which responsible for antimicrobial activity (Fig. 2) are discussed within this review in Table 2.

4.1. Sterol

The presence of a free OH group in C-3 is necessary for the antiulcer action of triterpenoids and sterols consistently, the only structural difference between the active 3a-hydroxymasticadienonic acid (Fig. 3, 1) and the inactive masticadienonic acid (Fig. 3, 2) is the presence of an OH group and a C=O group in the C-3 [14,15].

4.2. Flavonoids

Flavonoids have been used in the treatment of countless diseases [16–21]. Flavonoids (Fig. 4) are found to display as antisecretory and cytoprotective agents by increasing PG levels, inhibiting *H. pylori*, decreasing histamine, and antioxidants [22]. The structure activity relationship shows that the presence of OCH_3 group in the C-5 or C-7 positions, the double bonds at C-2 and C-3 and the presence pof an intact C-ring appear to increase gastroprotection potential. On the other hand, substitution with OH or OCH_3 groups at C-3, C-6, or C-8 diminish the gastroprotective action.

Flavonoids can kill microbs by 1) membrane disruption by apigenin, catechin, naringenin, quercetin, and rhamnetin and inhibition of nucleic acid synthesis 2) inhibit dihydrofolate reductase by epicatechin, 3) inhibithelicase by luteolin and myricetin, d) inhibitgyrase/topoisomerase by apigenin, kaempferol and quercetin, 4) inhibit bacterial virulence by quercetin and kaempferol 5) inhibit quorum sensing by epicatechin, naringenin, quercetin and kaempferol 6) inhibit fatty acid synthase and peptidoglycan synthesis by taxifolin, kaempferol, luteolin, myricetin and quercetin7) inhibit Ala–Ala dipeptide synthesis by gaiangin, kaempferol, and kaempferol-3-*O*-glucoside, 8) inhibitpeptidoglycan crosslinking by apigenin and quercetin. 9) inhibit

Table 2
Restorative herbs having anti-*H. pylori* action.

Plant Names	Part and extract	Active ingredients responsible for the activity	Activity	Refs.
Aesculus hippocastanum	EtOH extract	Saponin (Aescine)	Antisecretory effect	[31]
Acacia nilotica	flower aceton extract	Not identified	Urease inhibitor	[8]
Achillea millefolium	MeOH extract of aerial parts	Not identified	Antioxidant	[45,46]
Ageratina pichinchensis	EtOH extract	3,5-diprenyl-4-hydroxyacetophenone	Maintaenence NO, PG, SH release	[47]
Ageratum conyzoides	MeOH extract of the entire plant	Not identified	Not detected	[48]
Agrimonia pilosa Ledeb.	Aqueous extract of whole plant	Not identified	Not detected	[49]
Alchornea triplinervia	MeOH and EtOAc extracts	Not identified	Antisecretory Increase PGE2 Decrease gastric injuries Increase mucus Promote epithelial cell	[50,51]
Allium sativum	Oil and aqeous extract	Thiosulfinates Diallyl disulfide	Interfere with cell wall Causing cell lysis and Triggering autolysis	[52,53,54,55,56]
Aloe vera	Polysachharide fraction	Lectins	Increase mucus Inhibit aminopyrin uptake Reduce TNF-α	[57]
Alpinia speciosa	EtOH extract of root	Not identified	Inhibit H.pylori	[58]
Amphipterygium adstringens.	CH_2Cl_2 extract	3a-hydroxymasticadienonic acid, b-sitosterol 3-*epi*-oleanolic acid	Gastroprotective	[59]
Angelica sinensis	EtOH extract	Polysaccharide indomethacin	Inhibition of MPO activity	[60]
Anisomeles indica	Stem and leaves EtOH extract	Not identified	Inhibit IL-12 and TNF-α,	[58]
Annona cherimola	Stem and leaves MeOH extract	Not identified	Not detected	[61]
Anthemis altissima	Isolated compounds from arial part	Sesquiterpene lactones Tatridin-A, sivasinolide, 1-epi-tatridin B, altissin, desacetyl-β-cyclopyrethrosin,	Not detected	[62]
Aralia elata	Root bark	Araloside A	Gastric lesion inhibitor ulcer formation inhibitor	[33]
Arrabidaea chica	HydroEtOHic extract of leaves	Flavones and flavonols	Inhibit H. pylori	[63]
Artemisia ludoviciana	Leaves and stem aqueous extract	Artemisin	Bactericidal kinetics Morphological degeneration	[61]
Atractylodes ovata	EtOH extract	Sesquiterpenoid Atractylenolide III	-Inhibition of MMP-2 -MMP-9 expression	[64]
Bixa orellana	EtOH extract of seeds	Not identified	Not detected	[65]
Boesenbergia rotunda	EtOH extract	Flavanone Pinostrobin	Antioxidant Decrease gastric motility	[66]
Bombax malabaricum	EtOH extract of root	Not identified	Not detected	[58]
Boronia pinnata	Whole shrub extract	Cinnamic acid derivative (boropinic acid)	Anti-ulcer agent	[67]
Brassica oleracea	Broccoli sprouts	Not identified	On human volunteers	[68]
Brazilian propolis	Propolis extract	3-hydroxy-2,2dimethyl-8-prenylchromane-propenoic acid	Anti-H.pylori invitro	[69]
Bridelia micrantha	Acetone and EtOAc extracts of stem bark	Not identified	Anti-inflammatory	[70,71]
Byrsonima crassa	Leaves MeOH and $CHCl_3$ extracts	Not identified	Immunostimulatory	[72]
Byrsonima fagifolia	Leaves MeOH extract	Not identified	Gastroprotective Antidiarrheal Antibacterial Immunomodulatory	[73]
Byrsonima intermedia	Leaves MeOH extract	Not identified	Antioxidant	[74]
Calophyllum b8rasiliense	Hexane, HydroEtOH extract and Ch_2Cl_2 fraction of stem bark	Mixture of chromanone	Decreased urease, Reduce H. pylori in pathological analysis	[6,75]
Calotropis procera	Acetone and MeOH extracts of leaves and flowers	Not identified	Urease inhibitor	[8]
Camellia sinensis	MeOH and water extracts of young shoots	Catechin	Urease inhibitor Anti-inflammatory	[27,76,77]
Carum carvi L.	Fruit MeOH	Not identified	Not detected	[78]
Casearia sylvestris	Leaves EtOH extract	Terpenoids	Decrease ulcerative size Eradicate *H. pylori*	[79]
Chamomilla recutita	Oil extract of flowers 70 % aqueous MeOH 96 % ethanol	Catechin	Urease inhibitor Decreasegastric mucosal injury	[65,80,81,82]
Cinnamomum cassia	Bark aqueous EtOH	Not identified	Suppression of IL-8	[46]
Cinnamomum verum	Essential oils of dry bark	Cinnamaldehyde	Urease inhibitor	[83,84,85,86]

Table 2 (*Continued*)

Plant Names	Part and extract	Active ingredients responsible for the activity	Activity	Refs.
Cistus laurifolius	Flowers $CHCl_3$ fraction	Isorhamnetin Kaempferol 3,7-dimethyl ether, quercetin 3,7-dimethyl ether	Inhibit ulcer Eradicate *H.pylori*	[87,88]
Citrus aurantium	EtOH extract	Monoterpene b-Myrcene	indomethacin, ischemia reperfusion	[89]
Citrus lemon	Essential oil	Monoterpene Indomethacin Limonene	Mucus production HSP-70 activation Vasoactive intestinal peptide and NO release Maintenance of PGE2 and glutathione levels	[90]
Cocculus hirsutus	EtOH extract of leaves	Alkaloids	Anti *H. pylori*	[91]
Cochlospermum tinctorium	Acidified EtOH	Polysaccharide Arabinogalactans II	Antioxidant Immunomodulatory	[40]
Combretum molle	Stem bark acetone extract was the best	Flavonoids	Gastroprotective	[92]
Coptis chinensis	Rhizome aqueous extract	Alkaloid	Inhibit ulcer Eradicate *H.pylori*	[93]
Croton reflexifolius	EtOH extract	Diterpenoid Polyalthic acid	Gastroprotective Block sulfhydryl groups Inhibit NO synthase	[94]
Croton sublyratus	Leaves extract	Terpenoid (Plaunotol)	Suppress IL-8 secretion	[95]
Cuminum cyminum	EtOH extracts of seeds	Phenolic compounds	Antioxidant	[96]
Cuphea aequipetala	Leaves aqueous extract	Phenolic compounds	Reduce gastric lesions Inhibit ulcer	[61]
Curcuma amada	Rhizome 70 % EtOH	Curcumin	Inhibit proton potassium ATPase	[97]
Cupressus sempervirens	Essential oil	Monoterpenes	Not detected	[98]
Curcuma longa	Polyphenolic rich extract of the root	Curcumin	Chemo-preventative	[99]
Cymbopogon citratus	Essential oil	Terpenes	Inhibit COX Inhibit NO synthase Activate K^+ATP channel and α2 receptors.	[98]
Cyrtocarpa procera	Hexane extracts from stem bark	Not identified	Gastroprotective Anti-inflammatory	[59,61,100]
Davilla elliptica	Leaves MeOH extract	Not identified	Anti-inflammatory Gastroprotective	[101]
Davilla nítida	Leaves MeOH extract	Not identified	Anti-inflammatory Gastroprotective	[101]
Daucus carota	Essential oil of seed	Carvacrol and nerol	Decrease pH	[102]
Derris trifoliate	Petroleum ether and stem$CHCl_3$ extracts	Not identified	Eradicate *H. Pylori* Gastroprotective	[103]
Desmostachya bipinnata	Wholeplant Diethyl ether extract	Flavonoids (4-methoxy quercetin-7-O-glucoside)	Chemopreventive agent	[104,105]
Dittrichia viscosa	Aerial parts essential oil (Oxygenated fractions)	3-methoxy cuminyl isobutyrate	Antibacterial action	[81,106]
Eucalyptus torelliana	Hexane extract of leaves	Saponin and taninns	Decrease gastric acid Increase pH gastric juice	[107]
Eugenia caryophillus	EtOH extracts of flowers	Eugenol	Increase activity at acidic pH	[84,108]
Eugenia caryophyllata	Flowers aqueous extract	Essential oil	Anti-inflammatory	[49]
Eupatorium aschenbornianum	EtOH extract	Chromene Encecanescin	Antioxidant activity	[109]
Evodia rutaecarpa	Alkaloids rich extract	1-Methyl-2-[(Z)-7-tridecenyl]-4-(1 H)-quinolone	Anti-inflammatory Very strong Anti-H.pylori	[110]
Feijoa sellowiana	Fruit Acetone Extract	Flavone	Inhibit H^+/K^+ATPase activity and Increase PGE_2	[111]
Ferulago campestris	Root extract	Coumarins (Aegelinol and Benzoyl aegelinol)	Not detected	[112,113,114,115]
Foeniculum vulgare	MeOH extract of the seeds	Not identified	Antioxidant	[45,46]
Garcinia achachairu	Acidified ethanol of the seeds	Polyisoprenylated benzophenone Guttiferone A	Gastroprotective	[116]
Geranium wilfordii	EtOH extracts and EtOAc fraction	1,2,3,6-tetra-O-galloyl-β-D-glucose and corilagin	Not detected	[117]
Geum iranicum	Aqueous fraction of the roots	Tannins Eugenol	Gastroprotective	[118]
Glycyrrhiza glabra	Water extract of the root	Polysaccharide Flavonoids (glabridin)	Anti-adhesive activity Inhibit dihydrofolate reductase Inhibit DNA gyrase	[11,29]
Glycyrrhiza uralensis	MeOH extract of roots	licoricidin licoisoflavone B licoric	Chemopreventive agents	[119,120]
Guaiacum coulteri	Bark MeOH extract	Not identified	Antibacterial action	[61]
Hancornia speciose	Hydroalcoholic extract of the bark	Not identified	Antibacterial action	[121]
Hericium erinaceus	Hydroalcoholic extract of bark	Not identified	Antibacterial action	[122]
Hydrastis canadensis	MeOH extract of rhizome	Isoquinoline alkaloids		[123,124,125,126]

Table 2 (*Continued*)

Plant Names	Part and extract	Active ingredients responsible for the activity	Activity	Refs.
			Inhibit bacterial efflux pumps, Inhibit of nucleic acid synthesis, Inhibite the enzyme dihydrofolate reductase	
		Berberine Hydrastine		
Hyptis suaveolens	EtOH extract	Diterpene, Indomethacin Suaveolol	NO, PGE2, SH compounds	[127]
Impatiens balsamina	Pod acetone, EtoAc, terpenoid fraction	2Methoxy1,4naphthoquinone Stigmasta7,22-diene3βol	Produce ROS to damage *H pylori* cell membrane	[9]
Ixeris chinensis	Boiling water,EtOH and $CHCl_3$ extract was the active one	Not identified	Antibacterial	[128]
			Antiadhesive Anti-inflammatory Inhibit IL-8, NO, TNF-α	
Jatropha isabelli	Acidified EtOH	Monoterpene 1,4-Epoxy-ρ-menthan- 2-ol Sesquiterpene Cyperenoic acid Triterpene Acetyl aleuritolic acid 9b,13a- Dihydroxyisabellione Diterpene Jatropholone A Jatropholone B Jatrophone	Gastroprotective	[129]
Juglans regia	Fruit MeOH extract	Xanthanolide	Not detected	[130]
Larrea divaricata	Branches and leaves aqueous extract	Nordihydroguaiaretic acid	Anti-inflammatory Gastroprotective Anti-gastric cancer	[131]
Lycopodium cernua	Whole plant hexane extract	The powerful compound was found in hexane fraction	Not detected	[48]
Magnoliae officinalis	Ether fraction of cortex	Magnolol	Antigastritic, antioxidant, neutralize acid, inhibit the secretion of gastric acid	[132]
Mallotus phillipinesis	70 % EtOH extract of fruit	Isorottlerin, rottlerin 3′-prenylrubranine, 5,7-dihydroxy-8-methyl-6-prenylflavanone	Not detected	[97]
Malva sylvestris	Inflorescence and leaves EtOH Extract	Not identified	Not detected	[65]
Mangifera indica	Pet-ether and EtOH extracts of leaves	Mangiferin	Gastroprotective Antisecretory, antioxidant	[133,134]
Mentha piperita	Leaves andstem aqueous extract	Essential oil Menthol	antisecretory,antioxidant, anti-inflammatory, and antiapoptotic actions	[61]
Mentha sp.	EtOH extract	Monoterpene Indomethacin pyloric ligature Menthol	Increase PGE2 Antiapoptotic,Antioxidant Anti-inflammatory	[38,39]
Morus alba	leaves EtOH extract	Steroid, Albosteroid Pyloric ligature	Antisecretory Antioxidant	[135,136]
Mitrella kentii	EtOH extract	Chalcone Desmosdumotin C	Antiapoptotic, antioxidant Inhibit COX-2	[137]
Musa acuminata	Crude flavonoids extract	Flavonoids Leucocyanidin	Increase mucus	[138,139]
Myristica fragrans	MeOH extracts of seeds and aerial parts	Not identified	Gastroprotective	[97,140]
Myroxylon peruiferum	Isolated compound	Isoflavone Cabreuvin	Inhibit NADH oxidation	[141]
Myrtus communis	Essential oil	Monoterpenes	Inhibit urease	[86,142]
Olea europaea	Leaves MeOH extract	Not identified	Increase gastric flora Reduce H. pylori	[143]
Ocimum sanctum	Fixed oil	Not identified	Inhibit lipoxygenase Antisecretory Histamine antagonistic	[144]
Origanum majorana L.	Aerial parts MeOH extract	Phenolic compounds	Enhance protective host defence	[45]
Oroxylum indicum	Crude Flavone glycosides	7-*O*-methylchrysin, 5-hydroxy-749-dimethoxyflavone, oroxylin A, chrysin, and baicalein	Gastroprotective	[145, 146]
Paeonia lactiflora	Root lipid fraction	Lysophosphatidic acid Paeonol benzoic acid methyl gallate,1,2,3,4,6-penta- *O*-galloyl-β -D-glucopyranose	Increase PG E2 Decrease membrane integrity Inhibit urease Inhibit UreB (an adhesin)	[5,147]
Panax ginseng	Polysaccharides fraction	Galacturonic acid	Anti-adhesive	[148,149]
Papaver somniferum	Alkaloids	Porphine	Not detected	[150]
Pausinystalia yohimbe	Alkaloids	Yohimbine	Decrease ulcer	[44]

Table 2 (*Continued*)

Plant Names	Part and extract	Active ingredients responsible for the activity	Activity	Refs.
Peperomia pellucida	EtOH extract	Allylbenzene Dillapiole	Gastroprotective	[151]
Persea americana	MeOH extracts of leaf	Procyanidins	Inhibit urease	[61]
Piper carpunya	Flavonoids rich extract of the leaves	Vitexin Isovitexin Rhamnopyranosylvitexin Isoembigenin	Releasemyeloperoxidase Inhibite H+,K + ATPase activity *N*-Acetylation	[154]
Piper multiplinervium	Hydroxybenzoic acid prenylated derivative	3-farnesyl-2-hydroxybenzoic acid	Treat stomach aches	[155]
Pistacia lentiscus	Mastic gum	Triterpenic acids	Induce blebbing Cellular fragmentation Morphological abnormalities in H. pylori cells	[156,157,158,159]
Plectranthus grandis	EtOH extract	Diterpenes 3b-Hydroxy-3- deoxibarbatusin Barbatusin	K^+ATP channel NO, TRPV1 channels	[160]
Plumbago zeylanica	EtOAc of rhizome	Naphthoquinone Plumbagin	Bactericidal activity	[58,161]
Polygala cyparissias	EtOH extract	Xantone	Anti-ulcer Gastroprotective	[162]
Polygonum tinctorium	Leaf juice	Tryptanthrin Kaempferol	decrease numbers of colonies in gerbils stomachs	[163]
Polygala cyparissias	EtOH extract	Sterol a-Spinasterol	Reduce percentage of lesion area Reduce ulcer index	[162]
Potentilla fruticose	Aqueous extracts of aerial part	Not identified	Antibacterial action	[164]
Prunus dulcis	Polyphenol-rich extracts of skin	Protocatechuic acid	Post gastric plus duodenal digestion	[165]
Prumnopitys andina	Acidified EtOH	Diterpene, acetic acid Ferruginol	PGE2 production Inhibit lipoperoxidation	[37]
Psoralea corylifolia	Seeds extract	Psoracorylifols	Antibacterial	[166]
Pteleopsis suberosa	MeOH extract of stem bark	Oleanane saponine Arjunglucoside I	Anti*vacA/cagA* positive and metronidazole-resistant strains	[167]
Punica granatum	EtOH, MeOH, BuOH and aqueous extracts from fruit peel	Phenolic compounds	Chang hydrophobicity of *H. pylori* cell surface	[130,168,169]
Phyllanthus niruri	Aqueous extracts of leaves	Ellagic acid Hydroxycinnamic acid	Damage *H.pylori* cell membrane	[103,152]
Physalis alkekengi	EtOAc extract of the aerial parts	Quercetin Physalindicanols A kaempferol Blumenol A	Antiinflammatory Antiulcer invivo Analgesic	[153]
Qualea parviflora	MeOH extract of bark	Triterpenes Saponins	Maintaine GSH levels Increase SH compounds Stimulate PGE2 synthesis	[170]
Rabdosia trichocarpa	MeOH extract from entire plants	Diterpene Trichorabdal A	Strong antibacterial action	[171]
Rhei Rhizoma	Rhizome	Emodin	Damage DNA *H. Pylori*	[30]
Rheum palmatum	Rhizome	Rhein	Inhibite *N*-acetyltransferase	[172]
Rheum rhaponticum L.	Root EtOH Extract	Not identified	Anti-inflammatory	[56]
Rosmarinus officinalis	Leaves MeOH extract	Not identified	Antiulcer, vasodilator Gastroprotective	[45]
Rubus imperialis	EtOH extract	Triterpene 2b,3b-19a-Trihydroxy ursolic acid	Not detected	[173]
Rubus ulmifolius	Leaves extract Flavonoids	Ellagic Kampferol	Reduce gastric PH Participate No and SH	[26]
Ruta graveolens	Aqueous EtOH extract of leaves	Polyphenols	Antioxidant Anti-inflammatory Inhibit IL-8 secretion	[46]
Salvia mirzayanii	MeOH extract of leaves	Not identified	Not detected	[174]
Sanguinaria Canadensis	MeOH extracts of rhizome	Sanguinarine, chelerythrine, two benzophenanthridine alkaloids	Anti ulcer	[123,175]
Santalum album	hydro-alcoholic extract of stem	(Z)-R-santalol (7), (Z)-β-santalol, (Z)-lanceol	Strong antiulcer	[176]
Schinus molle	EtOH extract	Flavonol, Rutin	Antioxidant	[177]
Sclerocarya birrea	Essential oil	Terpinen- 4-ol	Decrease membrane integrity	[110,178]
Senecio brasiliensis	Inflorescences Pyrrolizidine alkaloids	Integerrimine, retrorsine, senecionine, usaramine, and seneciphylline	Increase mucus Increase PG	[42,43]
Simaba ferruginea	Rhizome fractions	Alkaloid Canthin-6-one	Antiulcerogenic Reduce myeloperoxidase malondialdehyde Reduce plasma IL-8	[41]
Scleria striatinux	MeOH extract of roots	Okundoperoxide	Antibacterial	[48]
Solanum paniculatum L.	New isolated steroids saponins	diosgenin 3-*O*-b-d-glucopyranosyl(10 → 69)-*O*-b-d-glucopyranoiside.	Decrease gastric lesion Decrease levels of MPO in the mucosa	[179]
Sphacele chamaedryoide	EtOH extract Diterpene	Horminone, Carnosol Taxoquinone	Gastroprotective Inhibit gastric lesions	[180]
Stachys setifera	MeOH extracts of leaves	Not identified	Not detected	[181]

Table 2 (*Continued*)

Plant Names	Part and extract	Active ingredients responsible for the activity	Activity	Refs.
Strychnos pseudoquina	Leaves MeOH extract	Alkaloid enriched fraction	Increase cell proliferation in gastric mucosa	[182]
Syzygium aromaticum	Flower buds	Flavonoids	Antiulcerogenic	[183,184]
		Tannins	Antisecretory Increase PGE	
Tabebuia impetiginosa	Inner bark	(hydroxymethyl)anthraquin	Strong antibacterial	[185]
		anthraquinone-2-carboxylic Lapachol, plumbagin		
Termitomyces eurhizus	Mushroom	Polysaccharides fraction	Stimulate mucosal regeneration and proliferation Restoring gastric mucus Increase PG E2 Modulate COX-1 and COX-2 Reduce TNF-α and IL-1b	[186]
Terminalia spinosa	Young branches crude extract	Not identified	Not detected	[187]
Terminalia chebula	Aqueous extracts of fruit	Chebulinic acid Ethyl gallate gallic acid	Improve secretory of B runner gland	[188,189,190]
Thymus vulgaris	Essential oils	Monoterpenes	Gastroprotective Anti-inflammatory	[191]
Tithonia diversifolia	EtOH extract	Sesquiterpene Indomethacin, Tagitinin C	Gastroprotective	[192]
Trachyspermum copticum	Mixture of petroleum / MeOH extract of fruit and leaves	Not identified	Antibacterial	[78,193]
Vaccinium macrocarpon	Cranberry juice	Polyphenols	Anti-adhesive	[194,195]
Vitis venefera	Grape seeds Flavonoids	Resveratrol	Chemopreventative Antioxidant	[4]
Xanthium brasilicum	Aerial parts MeOH, diethyl ether and benzene	Not identified	Antimicrobial	[78]
Zataria multiflora	Essential oils of aerial parts	Thymol, carvacrol	Enhance mucosa Cytoprotective	[83,196]
Zingiber officinalis	Root extract	6-gingesulphonic acid	Inhibit thromboxane synthetase	[45,197,198,199,200,201,202]
		6-shogaol, Arcurcumene Gingerols		

Methanol: MeOH; Ethanol: EtOH; Butanol: BuOH; Dichloromethan: CH_2Cl_2; Chloroform:$CHCl_3$; Prostaglandin: PG; Tumor necrosis factor: TNF; Interlokin: IL; Cyclooxiginase: COX; Nitric oxide: NO; sulfhydryl : SH.

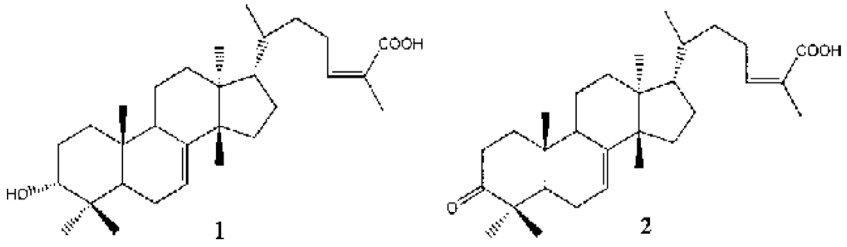

Fig. 3. Chemical structure of 3a-hydroxymasticadienonic acid (1) and masticadienonic acid (2).

refflux pumps by diadzein, genistein, epicatechin and quercetin10) inhibit NADH-cytochrome c reductase activity in the bacterial respiratory chain by chalcon11) inhibit ATP synthase by epicatchin, quercetin, quercetrin, and silymarin [23].

As shown in Fig. 4, quercetin decreases lipid peroxide and neutrophil leukocyte infiltration, in the *H. pylori* colonization [24]. The blend of kaempferol and tryptanthrin reduce the viability of *H. pylori* invivo [25,26]. Upon giving green tea product that is consisted of catechin to *H. pylori*-infected Mongolian gerbils, both of gastritis and the prevalence of *H. pylori* were significantly suppressed [27]. Besides, apigenin treatments effectively eradicated *H. pylori,* atrophic gastritis, and gastric cancer rates in *H. pylori*-infected Mongolian gerbils. Apigenin is reported to have excellent ability to inhibit *H. pylori* as well as possessing potent anti-gastric cancer [28]. As for Glabridin, it possesses a strong inhibitory effect on dihydrofolate reductase and DNA gyrase [29]. While emodin; a major phytocompound of *Rhizoma Rhei* induces *H. pylori* DNA damage [30].

4.3. Steroid saponin

Aescine (Fig. 5) reduces the severity of ulcers by decreasing gastric secretion [31], while Ginsenoside increases the amount of mucus [32].

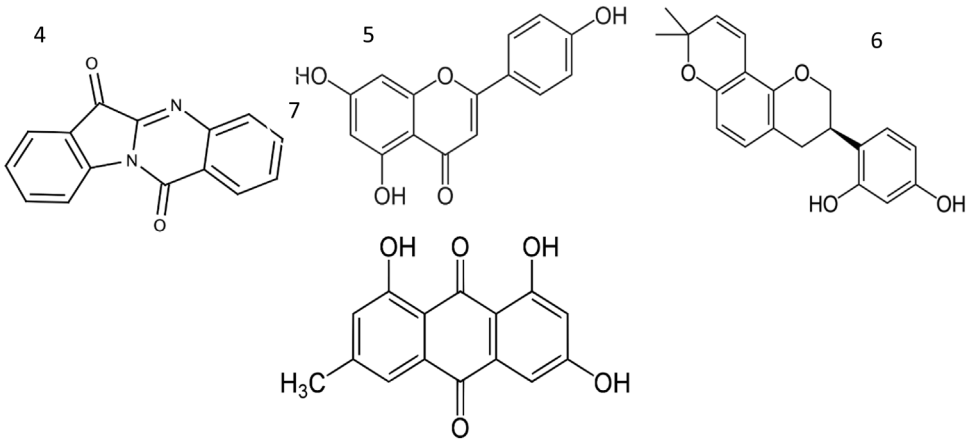

Fig. 4. Chemical structure of anti-H.Pylori flavonoids 1) Quercetin 2) Kampferol 3) Catchin 4) tryptanthrin 5) Apigenin 6) Glabridin 7) Emodin.

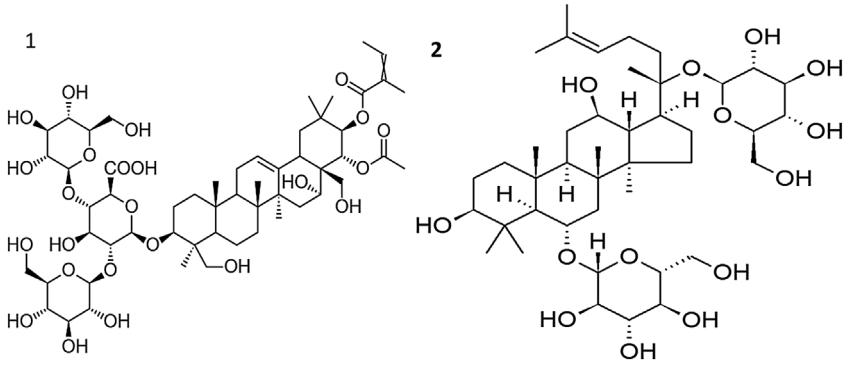

Fig. 5. Chemical structure of Aescine (1) and Ginsenoside (2).

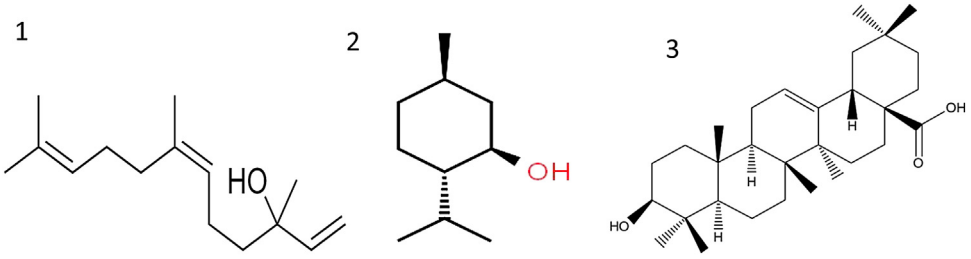

Fig. 6. Chemical structure of anti-H.pylori terpens 1) Nerolidol 2) Menthol 3) Oleanolic acid.

According to Lee et al. [33], the saponins display antisecretory action by inhibiting acid secretion, total acid output, and lowering the pH of gastric juice [34].

4.4. Terpenes

Nerolidol (Fig. 6) has an antiulcerogenic and cytoprotective effect by increasing mucus production via increasing the PG, improving the gastric blood flow, and increasing the secretion of gastric bicarbonate and mucus [35]. In addition, terpenoids act as antioxidants, reduce the lipid peroxidation levels, and increase the activity of antioxidant enzymes in the gastric mucosa [36,37]. Menthol is a monoterpene that increases the maintenance of SH compounds and the amount of mucus and PG production. It also possesses an antisecretory effect, in addition to antioxidant, anti-inflammatory, and antiapoptotic actions [38,39]. Oleanolic acid is a triterpene that improves healing in the ulcer model. The low toxicity and the widespread occurrence in various plants support the potential development of new antiulcer drug based on triterpenes or their derivatives [37].

4.5. Polysaccharides

Arabinogalactan (Fig. 7) has the ability to bind on the gastric mucosa acting as a protective layer, in addition to its antisecretory activity towards gastric juice. The mucosal protective activity of Arabinogalactan is provided by an increased mucus synthesis and free radical scavenging activity. The particular mechanisms of polysaccharides are described by their potential to bind on the surface of the gastrointestinal mucosa, thereby acting as a protective layer, in addition to their antisecretory action. Their mucosal protective potentials are provided by an increased mucus

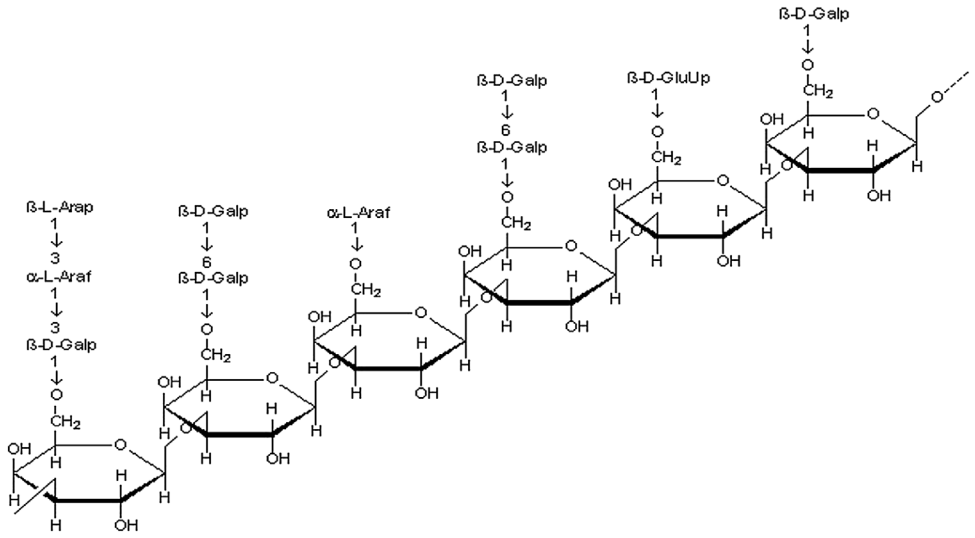

Fig. 7. chemical structure of Arabinogalactan.

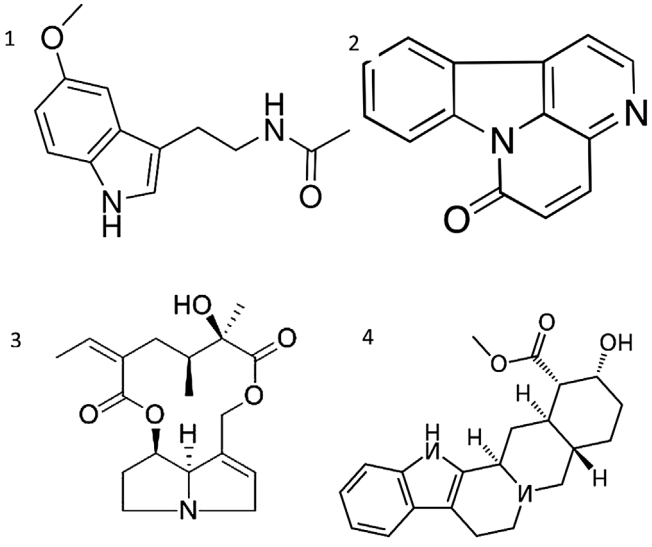

Fig. 8. Chemical structure of Melatonin (1), Canthin-6-one (2), Integerrimine (3), Yohimbine (4).

synthesis and their antioxidant activity. Pectic polysaccharides obtained by aqueous extraction represent examples of the main polysaccharides displaying gastric antiulcer action [40].

4.6. Alkaloids

Canthin-6-one (Fig. 8), isolated from *Simaba ferruginea* rhizome has been shown to be antiulcerogenic [41], while integerrimine isolated from *Senecio brasiliensis* was found to increase mucus and PG levels [42,43]. Melatonin, as a hormone, has the ability to scavenge free radical and ameliorating gastric blood flow [43]. Yohimbine, isolated from *Pausinystalia yohimbe*, decreases ulcers [44].

5. Conclusion

H. pylori inhibition with antibiotic therapies has a limitation mainly owing to antibiotic resistance. Medicinal herbs provide another opportunity to inhibit *H. pylori*. Medicinal herbs might also provide successful approach to decrease stomach cancer. However, potential cytotoxicity and side effects might present from those herbs. Therefore, further cytotoxicity investigation will be required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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