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REVIEW ARTICLE

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Herbal medicine as an auspicious therapeutic approach for the eradication of *Helicobacter pylori* infection: A concise review

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Abstract

Helicobacter pylori (*H. pylori*) causes gastric mucosa inflammation and gastric cancer mostly via several virulence factors. Induction of proinflammatory pathways plays a crucial role in chronic inflammation, gastric carcinoma, and *H. pylori* pathogenesis. Herbal medicines (HMs) are nontoxic, inexpensive, and mostly anti-inflammatory reminding meticulous emphasis on the elimination of *H. pylori* and gastric cancer. Several HM has exerted paramount anti-*H. pylori* traits. In addition, they exert anti-inflammatory effects through several cellular circuits such as inhibition of 5′-adenosine monophosphate-activated protein kinase, nuclear factor-κB, and activator protein-1 pathway activation leading to the inhibition of proinflammatory cytokines (interleukin 1α [IL-1α], IL-1β, IL-6, IL-8, IL-12, interferon γ, and tumor necrosis factor-α) expression. Furthermore, they inhibit nitrous oxide release and COX-2 and iNOS activity. The apoptosis induction in Th1 and Th17-polarized lymphocytes and M2-macrophagic polarization and STAT6 activation has also been exhibited. Thus, their exact consumable amount has not been revealed, and clinical trials are needed to achieve optimal concentration and their pharmacokinetics. In the aspect of bioavailability, solubility, absorption, and metabolism of herbal compounds, nanocarriers such as poly lactideco-glycolide-based loading and related formulations are helpful. Noticeably, combined therapies accompanied by probiotics can also be examined for better clearance of gastric mucosa. In addition, downregulation of inflammatory microRNAs (miRNAs) by HMs and upregulation of those anti-inflammatory miRNAs is proposed to protect the gastric mucosa. Thus there is anticipation that in near future HM-based formulations and proper delivery systems are possibly applicable against gastric cancer or other ailments because of *H. pylori*.

KEYWORDS
gastric cancer, *Helicobacter pylori*, inflammation, phytomedicine, therapeutic regimens

1 | INTRODUCTION

Helicobacter pylori (*H. pylori*) is a Gram-negative spiral-shaped microorganism, which grows in microaerophilic conditions and is capable of colonizing the epithelial lining of the human stomach (Forgacs, 1996; Hill, 1997). Along the years, *H. pylori* have coevolved within the human host and retained its adaptation to survive under the acidic gastric milieu of the human stomach. It has been estimated that almost half of

the world's population are infected with *H. pylori*, as a Class I carcinogen accentuating its pervasiveness throughout the society. Very recently, a meta-analysis on the worldwide prevalence of *H. pylori* has revealed that the infection was more prevalent in developing countries as compared with the developed countries. Although being widespread worldwide, the highest *H. pylori* infection rate has been reported from Latin America and the Caribbean, whereas Northern America had the lowest rate of infection. Although the exact route of transmission for *H. pylori* infection remains unclear, a mounting body of evidence bolsters person to person or the contents of the stomach aerosol transmission either via oral–oral or fecal–oral (Naumann, Sokolova, Tegtmeyer, & Backert, 2017). Eventually, the pathogen colonizes both the corpus and antrum simultaneously within the stomach. In this respect, chronic infection with *H. pylori* may lead to serious complications such as gastritis, peptic ulcer disease, gastric cancer, mucosa-associated lymphoid tissue, B-cell lymphoma, and gastric adenocarcinoma (Thorell et al., 2017). *H. pylori* is resistant to gastric acid and its pathogenesis is exerted via urease, lipopolysaccharide, and toxins such as vacuolating toxin (vacA), carcinogenic toxin (cagA) and some other proteins, which lead to the gastric inflammation and epithelial damage or two types of gastric cancer (Malekzadeh et al., 2000; Malfertheiner et al., 2002; Press, 2009). Therefore, hindering of the process of *H. pylori* pathogenesis using efficient therapeutic approaches is a chief requirement. Because *H. pylori* infection leads to increase in proinflammatory cytokines/chemokines (interleukin 1 [IL-1], IL-6, IL-8, interferon γ [INF-γ], tumor necrosis factor α [TNF-α]) and proteins, hence the application of anti-inflammatory compounds play a pivotal role in chronic gastritis and cancer prevention. In general, *H. pylori* strains are susceptible to some antibiotics in vitro but only a small number of these antibiotics, such as Clarithromycin, Metronidazole, Amoxicillin, Tetracycline, etc., are used in vitro to successfully eradicate this bacterium (Megraud, 1997). Probably the reason for this is the presence of bacteria that remained under the mucin so that only antibiotics, which can penetrate the infected mucosa are effective (Szajewska, Horvath, & Kołodziej, 2015). Although this bacterium is susceptible to some antimicrobial agents in vitro, the successful eradication of this bacterium is considered a major challenge (Feng, Wen, Zhu, Men, & Yang, 2016). Noticeably, application of gastroprotective herbal medicine (HM) bioactive compounds (particularly tannins, acting as a protective layer over epithelial cells) is a promising approach owing to limitations in long-term consumption of synthetic drugs. Very little is known regarding anticancer and anti-inflammatory HM bioactive compounds with anti-*H. pylori* properties.

2 | THE RECOMMENDED TREATMENT REGIMENS FOR *H. pylori*

First-line treatment regimen: A triple regimen/therapy (TT) containing proton pump inhibitor (PPI) + clarithromycin + amoxicillin or metronidazole, which was first introduced by Maestricht I as an effective treatment regimen for the eradication of *H. pylori* infection worldwide (Malfertheiner et al., 2006; Osato, Reddy, Reddy, Penland, & Graham, 2001). Second line treatment regimen: A quadruple therapy containing PPI + bismuth + tetracycline + metronidazole and third-line treatment regimen, which is based on the antibiotic susceptibility testing though not responding in 20–30% of patients (Gerrits, de Zoete, Arents, Kuipers, & Kusters, 2002; Kwon et al., 2000).

2.1 | First-line treatment

If the resistance to clarithromycin is low 15–20% it is better to use the first-line treatment regimen (Lochmannova, 2010). If metronidazole tested for resistance be less than 40%, then metronidazole can be used instead of amoxicillin. The success of the 14-day course of the first-line of treatment is more than that of the 7-day period (Howden & Hunt, 1998; Malfertheiner et al., 2006). Although the treatment is considered first-line treatment, today the amount of eradication is low and not very effective. The most important factor is the antibiotic resistance of *H. pylori* especially to the clarithromycin antibiotic in recent decades (Mégraud & Lamouliatte, 2003; O'Connor, Gisbert, McNamara, & O'Morain, 2010). Metronidazole has a therapeutic advantage compared with clarithromycin, which is beneficial in eliminating the infection, despite the increased resistance of *H. pylori* to this antibiotic. In addition, the possibility of resistance to clarithromycin and therapeutic failure is very high. Among other factors effective in *H. pylori* eradication, the patient's intolerance to the drug, low gastric pH, and high number accumulation of bacteria in the stomach and duodenum can be stated (Mégraud & Lamouliatte, 2003; O'Connor et al., 2010). Approximately 5–35% of patients with *H. pylori* infection do not respond to treatment with first-line antibiotics (Leung & Graham, 2002; Mégraud & Lamouliatte, 2003). In this case, a quadruple therapy regimen containing bismuth (Lemos et al., 2012) instead of the first-line treatment can be used (Howden & Hunt, 1998; Leung & Graham, 2002). In case of resistance, an antibiotic susceptibility testing is advantageous following the first-line failure (Fallahi & Maleknejad, 2007). Generally, first-line treatment should be simple, tolerable, and affordable (Malfertheiner et al., 2002).

2.2 | Second-line treatment

The second-line treatment after the first-line treatment failure or in the case of allergy to penicillin compounds, the quadruple therapy regimen containing bismuth plus tetracycline, metronidazole, and acid inhibitors (PPI) are the best choice (Howden & Hunt, 1998). Bismuth-based diets, especially when prescribed with PPI, may also be sufficient for 1 week. This diet is widely used in Iran with regard to affordable and effective effects. Bismuth acts on its antimicrobial effects by disturbing the cell wall and increasing its permeability. Changing the color of the tongue, feces, and possible neurological toxicity during the course of its consumption is a complication that can be improved by the discontinuation of the drug. But some believe that the diet is not a good regimen because of the long course of treatment, side effects, high levels of tablets per day, and the lack of available bismuth. If bismuth is not available, then the drug can be converted into a three-dimensional regimen and can be used as second-line (Malfertheiner et al., 2002;

Vaz Coelho, Friche Passos, Chausson, & Castro, 1991). In the absence of tetracycline, it can be replaced by amoxicillin (Howden & Hunt, 1998). If a second-line treatment in primary care failed by a general practitioner, the patient should be referred to a specialist to be diagnosed with antibiotics with a sample taken from the mucosa and antibacterial testing and adoption of antibiotic choice (Malfertheiner et al., 2002).

2.3 | Third-line treatment

The antimicrobial susceptibility test is expensive and not performed extensively in all areas, and more important this test is performed during the upper gastrointestinal endoscopy, which is costly, well tolerated by all patients and not indicated in many cases (such as uninvestigated indigestion). Therefore, in the current clinical practice, the role of antimicrobial susceptibility test is drawn to the margin. However, because of the increasing prevalence of antibiotic resistance, the successful eradication of these organisms requires the consumption of low-resistance antibiotics, which requires extensive research to determine the antibiotic resistance of *H. pylori* in different geographical areas and antibiotic susceptibility testing. The rate of eradication of *H. pylori* with the experimental and nonscientific diets is lower than the optimal and desirable level. On the other hand, according to studies, the rate of eradication of this bacterium by performing antibiotic susceptibility tests is high (83–99%), highlighting the need for antibiotic susceptibility testing to successfully eradicate *H. pylori*. According to the published guidelines, antibiotic susceptibility testing is performed if the treatment fails twice. Treatment of the third-line after antibiotic susceptibility testing should contain twice daily PPI and at least two effective antibiotics for 1 to 2 weeks. Bismuth subsalicylate can also be used as a fourth-line treatment (Gisbert & Pajares, 2005; Nishizawa, Suzuki, & Hibi, 2009; O'Connor et al., 2010; Roghani, Massarrat, Shirekhoda, & Butorab, 2003). Novel therapeutic and vaccination approaches such as bismuth-containing quadruple therapy with metronidazole and amoxicillin (Q. Chen et al., 2016), herbal extracts, such as berberine (Huang et al., 2015) and other traditional medicines, probiotics combination therapies, nanoparticles, novel drug-delivery methods have been evaluated in this regard (Safavi, Sabourian, & Foroumadi, 2016). Phytotherapy is a promising alternative therapy, particularly due to its naturality, least side effects, low toxicity, and inexpensiveness as compared over the chemical therapy.

3 | EFFICACY OF HM AGAINST *H. pylori* HIGHLIGHTING THEIR ANTI-INFLAMMATORY AND ANTICANCER CELLULAR PATHWAYS

HM has been applied for centuries and has recently been used in the treatment of various diseases in the development of new anticancer drugs as plant antibiotics and even prebiotics. According to studies, the most potent anti-*H. pylori* HM in vitro were *Carum carvi L.* and ethanolic extract of *Thymus zygis L.* each with minimum inhibitory concentration (MIC) of 0.3 µl/ml, followed by ethanolic extract of *Hydrastis canadensis L* (MIC = 0.78–50 µg/ml), and chloroform extract of *Centaurea solstitialis L* and *Chromolaena odorata L* (MIC for each being 1.95 µg/ml). In addition, two studies have evaluated minimum bactericidal concentrations (MBCs) including *Camellia sinensis* (L.) Kuntze (MBC = 4 mg/ml) and *Chenopodium ambrosioides* L. (MBC = 5 mg/ml; Cogo et al., 2010; Nariman, Eftekhar, Habibi, Massarrat, & Malekzadeh, 2009; Nostro et al., 2005). Noticeably, apart from all the discomforts and illnesses, HMs are even used as inexpensive, safe, and nontoxic complementary or alternative anti-*H. pylori* formulations, particularly against those drug-resistant strains. It was found that conventional therapy by Chinese herbal medicine had reduced the mortality rate due to gastric cancer by 45% (Hung et al., 2017). The major mechanisms exerted by HM include blocking the serotonin 2b/2c receptor pathway (Japanese formula), suppression of the signaling circuits of nuclear factor-κB (NF-κB), and mitogen-activated protein kinases in lipopolysaccharide-induced macrophage cells (Radix Astragali and Os Sepiae and Kampo medicine), *hefA* efflux pump gene suppression (emodin, baicalin, schizandrin, and berberine), cell membrane disruption, and hindering the bacterial DNA, RNA, and protein biosynthesis, and degradation of endotoxins (*Radix scutellariae*), inhibiting bacterial proliferation and respiration, suppressing the oxidation of glucose and sugar metabolic intermediates (*Rhizoma coptidis*), *H. pylori* amine-*N*-acetyl transferase inhibition (emodin), destroying the proton motive force and enzymes (by hydroxyl group of carvacrol in (*Satureja bachtiarica*; Falsafi et al., 2015).

The decrease in MIC of amoxicillin and tetracycline (by emodin baicalin, schizandrin, and berberine; Huang et al., 2015) and the decrease of resistance rate against clarithromycin (*Myrtus communis*, *Teucrium polium* extracts) have been also observed. The latter extracts inhibit mutations and thereby hinder resistance development. An ellagitannin-rich fraction from *Eucalyptus citriodora* (ECF) exerted marked gastroprotective effect by reducing the proinflammatory markers; IL-1β, TNF-α, 5-LO, and COX-2 and also caspases-3 tissue levels in rat model study.

HMs contain some major active compounds including alkaloids (nitrogen-bearing molecules acting as anti-infective agents), anthocyanins (for blood vessel health), anthraquinones (in Chinese herbs for large intestine health), bitters (for GI function improvement), triterpenoids (anticancer and anti-inflammatory), glycosides (remarkable effect on cardiac function), coumarins (for muscle function), coumarins (anticancer and anti-inflammatory), flavonoids (anti-inflammatory effects), glucosilinates (wound and joint healing), phenols (such as that in thyme acting as antiseptic and anti-inflammatory), tannins (anti-infective agents), vitamins (remarkable health effects), taxol (anticancer), vincristine (anticancer), terpenes (anti-infective), Antimicrobial peptides, and volatile oils (various effects such as anti-infective and anti-inflammatory; Liu et al., 2018). Those major anticancer compounds entered in clinical trials include taxanes, camptothecins, vinca (or Catharanthus), and epipodophyllotoxins. The vinca alkaloids, taxanes (including paclitaxel), and other semisynthetic fractions disrupt tubulins the mitosis in metaphase of the cell cycle (R. C. Wang et al., 2017). In addition, a recent mass spectroscopy analysis demonstrated major compounds

TABLE 1 Anti-inflammatory and anticancer mechanisms of curcumin in vitro and in vivo

Antioxidant effects	Inhibition and eradication of free radicals. Inhibition of iNOS gene at low concentration.
Inflammatory signals	IKBα phosphorylation inhibition and NF-κB formation or its transmission. Curcumin is not able to exert this effect in the form of a complex with the UPS system. Inhibition of NF-κB, MAPK, ERK, PI3K, and protein kinase B expression.
Cell cycle regulation	Via CDKs, Cki(P27, P21), cyclin D, CDK1, CDK2, and CD25. Inhibition and cleavage of CD1 promoter and Rb phosphorylation, preventing EF-2 target genes expression. Expression of antiapoptotic proteins IAP, XI, BCL, and BCL2. Inhibition of IL-1, IL-16, IL-18, chemokines, TNF-α, and MMPs. Inhibition of cdc25A phosphatase.
Repair in enzyme functions	LOX and COX-2.
Adhesins	Inhibition of adhesin molecules such as ICAM-1, VCAM, E-selectin, and MMPs.

Note. ERK: extracellular signal-regulated kinase; IL-1: interleukin 1; MAPK: mitogen-activated protein kinase; MMP: matrix metalloproteinase; NF-κB: nuclear factor-κB; PI3K: phosphoinositide 3-kinase; TNF-α: tumor necrosis factor α; UPS: XXX; VCAM: vascular cell adhesion molecule.

of HMs including niaziridin, glycyrrhizin, piperine, *zingiber officinale*, *Cuminum cyminum*, *C. carvi*, *Stevia rebaudiana*, lysergol, allicin, *Aloe vera*, curcumin, genistein, ammannia multiflora, naringin, quercetin, capsaicin, and sinomenine (A. Zhang, Sun, & Wang, 2018). Furthermore, some major anti-inflammatory HM compounds with clinical trial included Qingchang Wenzhong Decoction, which alleviated colitis-associated inflammation, Erchen decoction (ECD), and Linguizhugan decoction acting by TNF-? and insulin pathway, macrophage-stimulating protein (MSP) upregulation, Recepteur d'Origine Nantais expression, reducing the protein kinase B/ (pAkt/Akt, phosphorylated [p] Akt) levels and claudin-2 expression and enhance the zona occluden 1 expression. Moreover, the regulation of inflammatory pathways or cytokines was exerted by roots of *Glycyrrhiza uralensis* Fisch *Scutellaria baicalensis* Georgi, the fruit of *Ziziphus jujuba* Mill and *Paeonia lactiflora* Pall.

Studies have revealed that nontoxic molecule curcumin has a wide spectrum of beneficial properties for example, antioxidant, anticancer, anti-inflammatory, antiproliferative, anti-fungal, and antimicrobial (Akram et al., 2010). Curcumin anti-*H. pylori* properties as a potential therapeutic candidate include anti-carcinogenesis activity through inhibition of I-κB kinase and expression of NF-κB and survival of gastric mucosa and inhibition of cell apoptosis induced by *H. pylori* Type IV secretion system. It exerts astonishing anti-inflammatory power through the inhibition of COX-2, LOX, iNOS, and production of cytokines such as IFN-γ and TNF-α (Sarkar, De, & Mukhopadhyay, 2016). Furthermore, curcumin inhibits production of inflammatory cytokines for example, IL-1β, IL-6, and TNF-α, and downregulates the protein kinase C hindering cancer cell growth. It has also anticancer effects via apoptosis (Caspase activation, p21 expression or p53 signaling and release of cytochrome-C; Haghi, Azimi, & Rahimi, 2017; Larussa et al., 2017).

In addition, curcumin has profound anticancer effects as depicted in Table 1. The curcumin is a major HM exerting remarkable anti-*H. pylori* effects, which exhibit profound anti-inflammatory and anticancer traits as well.

Agrimonia eupatoria L., rich in various polyphenols, exhibited 100% anti- *H. pylori* effect at 50 mg/ml by membrane damaging and suppression of bacterial virulence factors. In addition, an ellagitannin-enriched fraction (hydrolyzable tannins) of *Fragaria vesca* extract could eradicate all the isolates at 25 mg/ml. Notably, these fractions exerted no inhibitory effect on microbial flora but decrease the nitric oxide level as an inflammatory mediator (Cardoso et al., 2018). Noticeably, intervenolin derivative AS-1934 could downregulate *H. pylori* urease (which protects bacteria from gastric acid) and also suppressed the dihydroorotate dehydrogenase enzyme (acting in de novo pyrimidine biosynthesis pathway), therefore the application of compounds with similar inhibitory effects would be promising (Ohishi et al., 2018).

Some similar properties have been observed among most of the other HMs, which also protect gastric mucosa such as ginger, garlic acid, cranberries, broccoli sprouts, green tea, and so forth (Table 2). Several of promising and effective HM against *H. pylori* infection have been exhibited in Table 2. In some biodiversity-rich areas such as China, Africa, India, and Iran the use of traditional herbs is most common. Considering the strong association between gastric cancer and *H. pylori* infection, anticancer properties of these compounds are also promising. It is noteworthy that ethanolic, aqueous, and other compounds of saffron (*Crocus sativus L.*) have exerted remarkable anticancer effects through DNA synthesis inhibition, apoptosis, and arrest of cell cycle both in vitro and in vivo (Abdullaev & Frenkel, 1992; Tavakkol-Afshari, Brook, & Mousavi, 2008). Noticeably, crocin (in vitro against MCF, MDA-MB-231, MCF-7, HL-60, K562, C3H10T1/2, A549, VA13, MIA-PaCa-2, and Ascpc1 cancer cell lines and in vivo on mice, Syrian mice, rats, and Athymic mice), crocetin (in vitro on MCF, MDA-MB-231, MCF-7, HL-60, K562 and in vivo on mice, rats, and Syrian mice), safranal and picrocrocin have displayed anticancer traits (Chryssanthi et al., 2007; Hariri, Moallem, Mahmoudi, & Hosseinzadeh, 2011; Magesh, Singh, Selvendiran, Ekambaram, & Sakthisekaran, 2006; Mousavi, Tavakkol-Afshari, Brook, & Jafari-Anarkooli, 2009; Noureini & Wink, 2012).

The aqueous and ethanolic extracts and other compounds of *Peganum harmala L* seeds have exhibited profound anticancer effects. Alkaloid derivatives, harmine, and harmaline decrease or inhibit the growth of cancer cells by induction of apoptosis in a dose-dependent manner (Bernardo et al., 2012; Hamsa & Kuttan, 2011). In addition, they act as apoptotic inducers through

TABLE 2 Herbal medicines and their active fragments with plausible effects against *H. pylori* infection

Scientific names	Family	Extract fraction/compound	References
Acacia nilotion	*Fahaceae*	Acetone methanol	Amin, Anwar, Naz, Mehmood, and Saari (2013)
Alchornea triplinervia	*Euphorbiaceae*	methanol	Lima et al. (2008)
Arrabidaea chica	*Bignoniaceae*	Hydroethanolic	Mafioleti, da Silva Junior, Colodel, Flach, and Martins (2013)
Artemisia absinthium	*Asteraceae*	Artemisinin, quercetin, isorhamnetin, camphor, alpha-pinene, saponins, germacrene-D	Samuelsen (2000)
Bridelia micrantha	*Euphorbiaceae*	Acetone, ethyl acetate	Okeleye, Bessong, and Ndip (2011)
Cabphyllum brasiliesnse	*Clusiaceae*	Hydroethanolic, dichloromethane, chromanone acid	Souza et al. (2009); Lemos et al. (2012)
Calotropis procera	*Asclepiadoieae*	Acetone, methanol	Amin et al. (2013)
Camellia sinensis	*Theaceae*	Methanol	Hassani et al. (2009)
Chamomilla recutita	*Asteraceae*	Methanol	Shikov, Pozharitskaya, Makarov, and Kvetnaya (2008)
Cichorium intybus	*Composite*	Lacton sescoetrepens	Meimandi and Yaghoobi (2015); Stamatis et al. (2003)
Cinnamomum verum	*Lauraceae*	Cinnamaldehyde	Ali et al. (2005); Hosseininejad et al. (2011)
Cocculus hirsutus	*Menispermaceae*	Ethanol	Perumal Samy and Chow (2012)
Combretum molle	*Combretceae*	Acetone	Njume, Jide, and Ndip (2011)
Croucus sativus	*Iridaceae*	Carotenoids, monoterpenes, aldehydes, crocetin, crocins, safranal, picrocrocin	Kim et al. (2011); Stamatis et al. (2003)
Cuminum cyminum	*Apiaceae*	Ethanol	Nostro et al. (2005)
Cyrtocarpa procera	*Anacaxliaceae*	dichloromethane, dichloromethane–MeOH methanolic	Escobedo-Hinojosa, del Carpio, Palacios-Espinosa, and Romero (2012)
Daucus carota	*Apiaceae*	Oil	Bergonzelli, Donnicola, Porta, and Corthesy-Theulaz (2003)
Derris trifoliate	*Fahaceae*	Petroleum, chloroform, methanol	Uyub, Nwachukwu, Azlan, and Fariza (2010)
Desmostachya bipinnata	*Poaceae*	Methanol ethyl acetate	Ramadan and Safwat (2009)
Dittrichia viscosa	*Asteraceae*	Methanol	Miguel, Faleiro, Cavaleiro, Salgueiro, and Casanova (2008); Stamatis et al. (2003)
Eucalyptus torelliana	*Myrtaceae*	Chloroform, methanol	Adeniyi, Odufowoke, and Olaleye (2006)
Eugenia caryophillus	*Myrtaceae*	Ethanol	Ali et al. (2005); Li, Xu, Zhang, Liu, and Tan (2005)
Geranium wilfordii	*Geraniaceae*	Ethanol ethyl acetate	X. Q. Zhang et al. (2013)
Glycyrrhiza uralensis	*Fahaceae*	Methanol	Fukai et al. (2002)
Hancornia speciosa	*Apocynaceae*	Hydroalcoholic	Moraes et al. (2008)
Hydrastis canadensis	*Ranunculaceae*	Methanol	Mahady, Pendland, Stoia, and Chadwick (2003)
Lagenaria siceraria	*Cucurbitaceae*	Phocostrol, compserol, saponins	Hajian (2016)
Mallotus phillipinensis	*Euphorbiaceae*	Ethanol	Zaidi, Yamada, Kadowaki, Usmanghani, and Sugiyama (2009)
Myrstica fragrans	*Myristicaceae*	Methanol	Bhamarapravati, Pendland, and Mahady (2003); Mahady et al. (2005)
Myrtus communis	*Myrtaceae*	Oil	Deriu et al. (2007)
Persea americana	*Lauraceae*	Methanol	Castillo-Juárez et al. (2009)
Pistacia lentiscus	*Anacaxliaceae*	Triterpenic acids	Paraschos et al. (2007)
Plantago major	*Plantaginaceae*	Caffeic acid, flavonoids, alkaloids, terpenoids	Chiang, Chiang, Chang, Ng, and Lin (2002)
Plumhago zeylanica	*plumhaginaceae*	Ethanol, acetone, ethyl acetate	Wang and Huang (2005a)
Potentilla fruticosa	*Rosaceae*	Ethanol	Wang and Huang (2005b)
Prunus dulcis	*Rosaceae*	Polyphenol	Tomczyk, Leszczyńska, and Jakoniuk (2008)
Punica granatum	*Lythraceae*	Ethanol, methanol, butanol	Voravuthikunchai, Limsuwan, and Mitchell (2006)

(Continues)

TABLE 2 (Continued)

Scientific names	Family	Extract fraction/compound	References
Rosa damascena	*Rosaceae*	Quercetin, camphor, geraniol	Kodouri and Tabaei (2007)
Salvia officinalis	*Lamiaceae*	Alfa-terpineol, Beta-pinene, cineole	Aleebrahim-Dehkordy et al. (2017); Hajimahmoodi et al. (2011); Moghaddam (2011)
Salvia mirzayanii	*Lamiaceae*	Methanol	Atapour et al. (2009)
Sanguinaria canadensis	*Papaveraceae*	Methanol	Mahady et al. (2003)
Scleria striatinux	*Cyperaceae*	Methanol	Ndip et al. (2007)
Stachy setifera	*Lamiaceae*	Methanol	Khanavi et al. (2008)
Silybum marianum	*Asteraceae*	Silymarins	Aleebrahim-Dehkordy et al. (2017)
Terminallia chebula	*Combretaceae*	Alkohol	Malekzadeh, Ehsanifar, Shahamat, Levin, and Colwell (2001)
Thymus kotschyanus	*Lamiaceae*	Thymol, carvacrol	Aleebrahim-Dehkordy et al. (2017)
Trachyspermum copticum	*Apiaceae*	Petroleum, benzene/diethyl methanol/diethyl	Nariman, Eftekhar, Habibi, and Falsafi (2004); Nariman et al. (2009)
Tribulus terrestris	*Zygophyllaceae*	Steroids, saponins, flavonoids, alkaloids, sterol, phenol compound	Ivanova et al. (2009)
Zataria multiflora	*Lamiaceae*	Oil	Hosseininejad et al. (2011)

Note. The HM compounds in Table 2 have exerted anti-*H. pylori*, anticancer, anti-inflammatory, and antioxidant properties. They act through induction of cancer cell apoptosis, inhibition of proinflammatory cytokines and related kinases expression and other mechanisms or cell circuits hindering cell growth in vitro and in vivo.

disruption of the respiratory chain by caspases (Mani, Taneja, Jain, & Singh, 2018; Mohammad, 2018), the release of apoptosis inducers, the inactivation of topoisomerase enzymes 1 and 2 (Mashhadi, Salimi, Forouzandeh, & Naghsh, 2016), fragmentation, and chromatin density by caspase 6 by breaking down of the structural nuclear protein and nuclear membrane lamina (3, DNA fragmentation and disturbance in the process of cell division by harmine, inhibition of the cell cycle via the G2 stage arrest through harmine-mediated P53 activation inhibiting tumorigenicity and reduction of membrane potential and mitochondrial ATP levels by harmalacidin (Rüben, Panstruga, & Becker, 2015). Furthermore, these compounds inhibit DNA synthesis/replication through DNA synthesis enzymes inactivation (topoisomerase by harmine) and cell division inhibition, inhibition of differentiation of malignant and myeloid immature cells into neutrophils and monocytes by ataxia telangiectasia and Rad3-related (ATR) proteins and vitamin D3. Notably, B-carboline-mediated inhibition of the DNA synthesis and DNA helix intercalate leading to inhibition of the DNAs topoisomerases-1 and 2 and the growth inhibition of cancer cells in mice was confirmed. In addition, the inhibitory effect on the DNA and RNA synthesis was exerted through the creatine phosphokinase (CPK) effect of topoisomerase enzyme inhibition in the G1 phase of cell division (Kadhim, Aziz, & Hadi, 2016; Shu et al., 2019).

Garlic compounds such as diallyl sulfide (NAG-1 proapoptotic gene induction), methyl allyl trisulphide (inhibition of benzo-pyrene and lipoxygenase in cancer cells), *S*-methyl-1-systein sulphoxide, and methiin (cell cycle arrest) are associated with epithelial cancer cell apoptosis and cell cycle arrest (Kaowinn et al., 2018; Moosavi et al., 2016; G. Wang, Liu, Ye, Fu, & Zhang, 2016).

It has been highlighted that silymarin compounds have cancer regression or anticancer effects. In particular, silybum has inhibitory effects in epidermal and prostate cells and also mouse and animals breast cancer in vitro and in vivo (Padma et al., 2019). Silymarin has conferred cytoprotective effect on human prostate and breast cells exposed to carcinogens (Chandrasekar, Sivagami, & Babu, 2018). It has shown synergistic effects with adriamycin on preventing cancer cell growth. In the case of breast and lung cancer cells in humans, silybum exacerbated the cytotoxic effects of cisplatin and doxorubicin. In addition, it is promising that the stimulatory effects of silymarin were exerted on liver normal cells DNA but not on cancer cells in rats with hepatoma and did not stimulate tumor growth. In human studies with hepatocellular carcinoma, after healing with silymarin, the disease was improved daily. Nanoformulation of silymarin eliminated tumors via increasing SOD, CAT, and GSH concomitant with decreasing MDA (El-Far, Salah, Essam, Abd El-Azim, & El-Sherbiny, 2018). The anticancer and anti-inflammatory effects of common HM fractions have been demonstrated in Figures 1-3.

As outlined in Tables 2 and 3, major anti-*H.pylori* HM compounds exert anti-inflammatory traits, which are pivotal for gastroprotection. These effects are conferred mostly through the phosphorylation of Akt and endothelial nitric oxide synthase, nitrous oxide (NO), and HO-1 induction through NF-E2-related factor 2 signaling pathways, apoptosis induction through c-Jun *N*-terminal kinase pathway, activation, and mitochondrial Bax translocation, decrease of TNF-α, IL-1β, IL-6, MCP-1, and IL-12 and increase of IL-10 and TGF-β1.

HM are mainly used to stimulate mucosal cells, inhibit acid secretion, antioxidant production, and also through HK-ATPase.

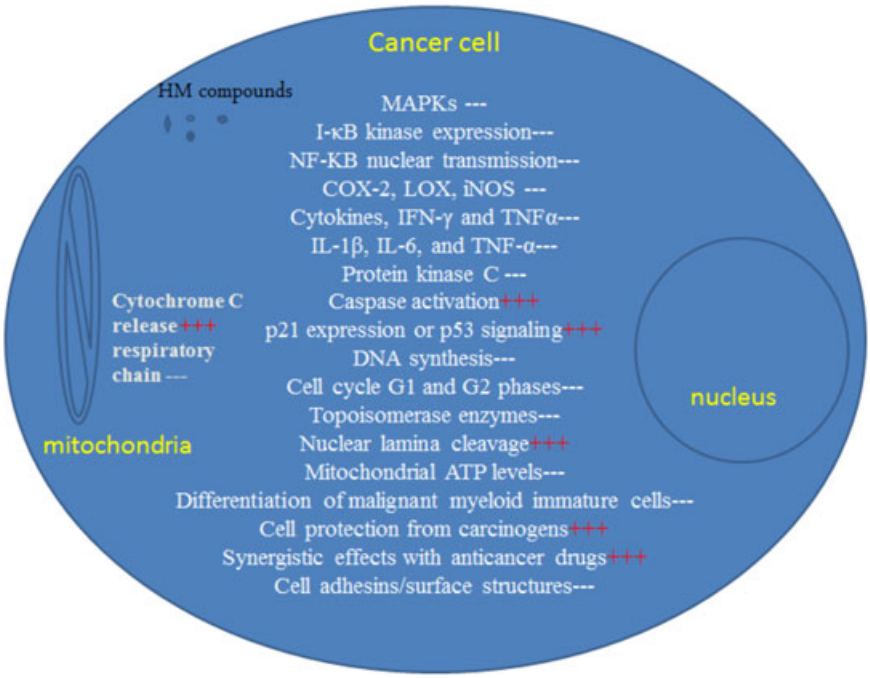
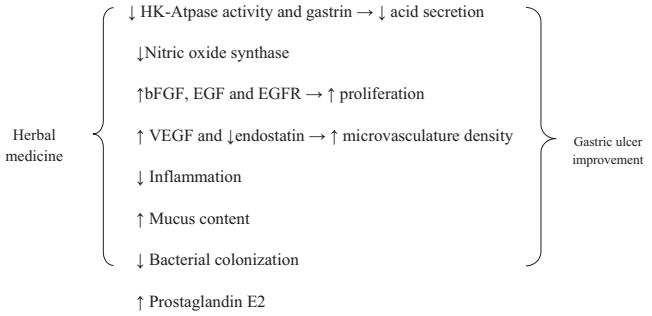


FIGURE 1 The anticancer and anti-inflammatory properties of HM contributing to the healing of *H. pylori*-induced cell carcinoma and cancer progression of a cell. HM: herbal medicine; IFN-γ: interferon-γ; IL-6: interleukin 6; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor-κB; TNF-α: tumor necrosis factor α [Color figure can be viewed at wileyonlinelibrary.com]



According to the studies, herbal-based therapies both in animal models and in human models have been shown to be equally effective with drugs such as omeprazole and cimetidine but the Western Medical System still treats antibiotic-based regimens for the treatment of gastrointestinal disturbances caused by *H. pylori* (Bi, Man, & Man, 2014).

The statistics have demonstrated that out of every 10 people with cancer, about six people use HM along with traditional therapies for cancer. Currently, there is almost no solid medical reason for the use of HM in treating or preventing cancers. However, there is still a widespread study of effective HM for preventing cancer, reducing its symptoms and/or side effects and even treating it (Bi et al., 2014).

According to a review evaluating studies on the impact of Chinese HM on reducing the side effects of chemotherapy in people with intestinal cancer, it was suggested that a herbal remedy known as "Huang Qi" contains compounds that reduce the side effects of chemotherapy. In addition, there are reasons to suggest that HM stimulate the immune system cells but do not affect the level of antibodies in the blood (Safavi, Shams-Ardakani, & Foroumadi, 2015).

Researchers continue to believe that extensive clinical trials are needed to confirm the usefulness of HM in the treatment or prevention of cancer, and to unravel HM with the potential of application along with conventional therapies for cancer elimination. Moreover, some herbs or herbal extracts tested in laboratories indicate that they have anticancer effects, so they become anticancer drugs but there is no scientific evidence from human experiments on the effect of HM on cancer treatment. At the same time, Carctol and Chaparral can be mentioned in the variety of herbal remedies that some claim to be effective in treating cancer. On the other hand, it is important to note that some herbal remedies can interfere with the common therapies that are prescribed by physicians for treating cancer, such as chemotherapy, radiotherapy, biological therapy, or hormone replacement therapy. Several adverse effects of these compounds have been observed such as severe kidney failure, increased prothrombin times, intracranial hemorrhages, fatal case of interstitial pneumonia, etc., (Safavi et al., 2015). Assessing previous in vitro and in vivo studies, those predominant anti-*H. pylori* HM fractions with specific cellular mechanisms (anti-inflammatory and anticancerous pathways) have been depicted in Table 3 (Al-Sayed, Gad, El-Shazly, Abdel-Daim, & Nasser Singab, 2018; Arreola et al., 2015; W. Chen et al., 2014; Chowchaikong, Nilwarangkoon, Laphookhieo, Tanunyutthawongse, & Watanapokasin, 2018; Han, Zhang, Deng, Lei, & Tan, 2016; Herrera-Aco et al., 2019; Jamuna et al., 2015; Jin, 2016; Salehi et al., 2018; Schäfer & Kaschula, 2014; Shin et al., 2013; Taher et al., 2016; Q. Wang et al., 2017; Zou et al., 2017). The formulation of these fractions will open new venues toward efficient therapies.

3.1 | Future perspectives

It seems that the combination of HM compounds with antimicrobials and even with anti-inflammatory medicines is promising, opening new insights in vitro and in vivo studies and clinical trials toward achieving

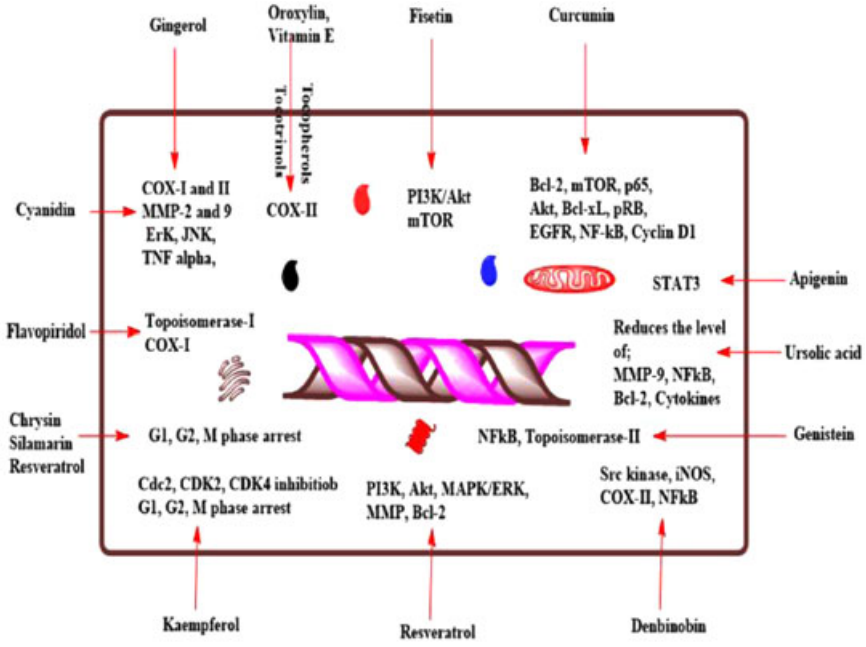


FIGURE 2 The anticancer exertion mechanisms of HM fractions. Akt: protein kinase B; ERK: extracellular signal-regulated kinase; HM: herbal medicine; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor-κB; PI3K: phosphoinositide-3-kinase [Color figure can be viewed at wileyonlinelibrary.com]

proper therapeutic approaches without side effects. In addition, pharmacological qualities and safety of HM need to be clarified. The World Health Organization has not introduced an exact amount of HM and conditions/mechanisms of resistance to them, thus future studies are helpful to achieve a standard amount unraveling their pharmacokinetics and pharmacodynamics. Furthermore, mechanisms of resistance to these compounds are yet to be elucidated. For example, curcumin had MIC (Osato, et al., 2001) value of between 5 and 50 μg/ml against 65 clinical isolates of *H. pylori* (the antimicrobial activity of curcumin against *H. pylori* isolates from India and during infections in mice). However, some studies have poor effectiveness of curcumin and its combination with pantoprazole, *N*-acetylcysteine, and lactoferrin for the eradication of *H. pylori*. In vivo studies have demonstrated the significant effect of this compound against inflammation and *H. pylori* infection. Furthermore, gastroprotective HM is helpful, which can be prescribed combined with 7probiotics. It

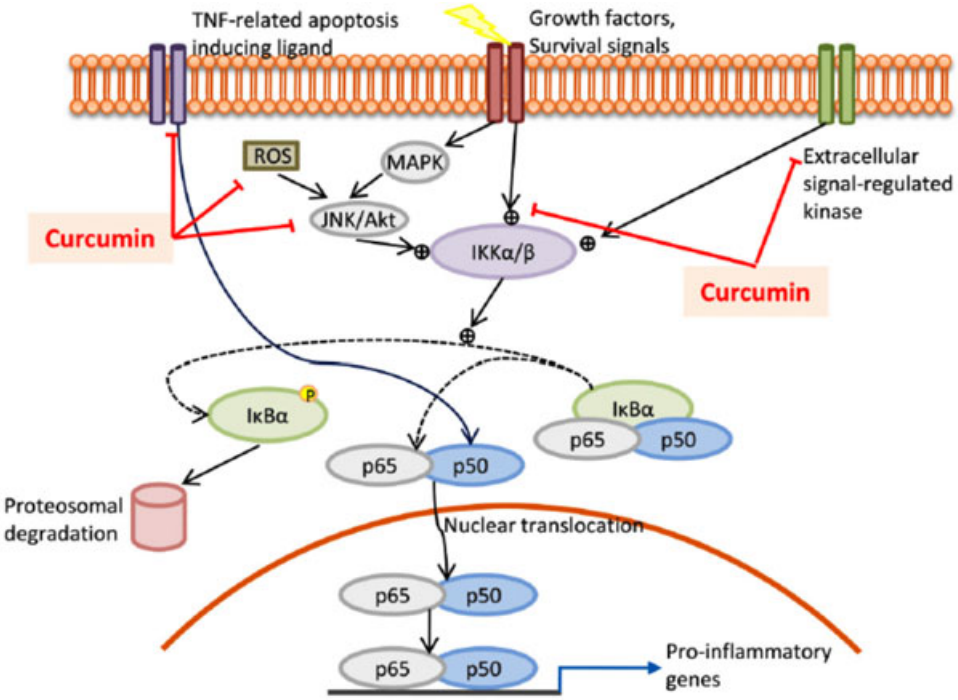


FIGURE 3 The anticancer and anti-inflammatory mechanisms of curcumin on cellular circuits (Boyanapalli et al., 2018; Lin & Lin, 2008). Akt: protein kinase B; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Anti-inflammatory and anticancer cellular mechanisms of major anti-*H. pylori* HM fractions

HM fraction	Study	Cellular mechanisms	Anti-inflammatory	Anticancerous[b]
Allicin (garlic powder)[a]	In vivo	Increasing the phosphorylation of Akt and endothelial nitric oxide synthase (eNOS), NO, and HO-1 induction through NF-E2-related factor 2 (Nrf2) signaling pathways. Apoptosis induction through JNK pathway activation and mitochondrial Bax translocation. The decrease of TNF-α, IL-1β, IL-6, MCP-1, and IL-12. An increase of IL-10 and TGF-β1	Yes	Yes
Allicin	In vivo		Yes	Yes
Diallyl disulfide	In vivo	Reduction in PGs, NO, IL-1β, IL-6, MCP-1, IL-12, and TNF-α levels; increase in IL-10 levels; inhibition of COX-2, iNOS, and NF-κB activity.	Yes	Yes
Diallyl tetrasulfide[a]	In vivo	Reduction in IL-1β, IL-6, TNF-α, NO, and PGs levels; inhibition of COX-2 and iNOS activity.	Yes	Yes
Scopoletin	In vitro	iNOS, IL-1β, IL-6, and COX-2 downregulatory effects	Yes	ND
Haemanthamine and haemanthidine	In vivo	Inhibition of cytokines production and apoptosis.	Yes	Yes
Alkaloids	In vivo	Significant reduction in IL-1β, IL-6, TNF-α, NO, and PGs levels; significant inhibition of COX-2, iNOS, and NFκB activity.	Yes	Yes
Scopolin	In vivo	TNF-α, IL-1β, and IL-6 reduction; modulation of COX or PGE_2 actions.	Yes	Yes
Licoricidin	In vivo	IL-6, IL-1β, IL-12, iNOS, and COX-2 downregulatory effects.	Yes	Yes
Licoisoflavone	In vivo	iNOS and COX-2 downregulatory effects.	Yes	Yes
Fuscaxanthone I	In vivo	ND	ND	ND
Beta-mangostin	In vivo	TLR4-mediated NF-κB and MAPK signaling pathway.	Yes	Yes
Fuscaxanthone A	–	ND	ND	ND
Cowanin	In vivo	PCs regulation.	Yes	ND
Cowaxanthone	In vivo	phosphorylation and activation of Akt.	Yes	ND
Alpha-mangostin	In vivo	Decreases the activation state of dendritic cells and its production of Th1-type cytokines diminishes the IL-6 production apoptosis in Th1 and Th17-polarized lymphocytes.	Yes	Yes
Cowanol	–	ND	ND	ND
Isojacareubin	In vivo	PCs regulation	Yes	ND
Fuscaxanthone G	In vivo	ND	ND	ND
Nigrolineabiphenyl B	In vivo	PCs regulation	Yes	
1,3,5,6-Tetrahydroxyxanthone	–	ND	ND	ND
Vokensiflavone	In vivo	PCs regulation	Yes	ND
Morelloflavone	In vivo	NO decrease by MQs reducing IL-6, TNF-α, and IL-1β.	Yes	Yes
Berberine	In vivo	AMPK activation, NFB inhibition, AP-1 pathway inhibition leading to inhibition of PCs expression.	Yes	ND
-Hydrastine	–	ND	ND	ND
Sanguinarine	In vitro	Reducing the TNF-α, IL-6, IL-18, IL-12, and AMPK/Smad1 signaling pathway.	Yes	Yes
Chelerythrine	In vivo	Through the NF-κB signaling pathway mediated by Nrf2 and MAO inhibition.	Yes	Yes
Protopine	In vivo	IL-6, IL-1β, IL-12, iNOS, and COX-2 downregulatory effects.	Yes	ND
Palmatine[a]	In vivo	IL-6, IL-1α, IL-1β, IL-8, IL-12, and iNOS decrease granulocyte-colony stimulating factor and granulocyte macrophage colony-stimulating factor TRIF-dependent NF-κB pathway M2-macrophagic polarization and STAT6 activation	Yes	Yes

Note. Akt: protein kinase B; AMPK: 5′ AMP-activated protein kinase; HO-1: heme oxygenase-1; IL-1β: interleukin 1β; JNK: c-Jun *N*-terminal kinase; MAO: monoamine oxidase; MAPK: mitogen-activated protein kinase; MQs: macrophages; ND, not determined; NF-κB: nuclear factor-κB; NO: nitrous oxide; PCs: proinflammatory cytokines; PG: prostaglandin; TGF-β1: transforming growth factor-β1; TNF-α: tumor necrosis factor α.

[a]MIC was 3–6 μg/ml, thus being most effective anti-*H. pylori* bioactive compounds.

[b]If yes, both in vitro and in vivo studies have unraveled the anticancer effects of these fractions.

was elucidated that phenol metabolites act as prebiotics. Noticeably, the oral bioavailability, solubility, absorption, and lower metabolism of compounds should also be evaluated in vivo, where nanocarriers are promising insights for this purpose (Aleebrahim-Dehkordy et al., 2017). Future investigations for designation of efficient vaccines against bacterial virulence factors (vacA and cagA) can be a suitable approach for contamination inhibition. It is worth considering that some microRNAs (miRNAs) increase during chronic gastritis and gastric cancer induced by *H. pylori* such as miR-328, miR-223, miR-21, mir-30d, miR-222, miR-9, miR-96, miR-146a and miR-650, miR-34c and miR-223-3p. However, some exert reverse or suggested anti-inflammatory or anticancer effects such as mir-328, miR-155 and miR-146b, miR-223, miR-212-3p and miR-361-3p, miR-27b, miR-141, miR-3178, miR-34b/c and miR-133a, miR-375, miR-203, miR-30a and miR-204. Recent advent of knowledge of miRNAs participating in various cellular circuits has made it possible to target and downregulate inflammatory miRNAs and upregulate those anti-inflammatory miRNAs to protect the gastric mucosa.

4 | CONCLUSION

Induction of proinflammatory pathways plays a crucial role in the chronic inflammation and gastric carcinoma and *H. pylori* pathogenesis. HM and their bioactive compounds are nontoxic, inexpensive, and mostly anti-inflammatory, reminding meticulous emphasis on the elimination of *H. pylori* and gastric cancer. Several HM has exerted paramount anti-*H. pylori* traits. In addition, they exert anti-inflammatory effects through several cellular circuits such as inhibition of 5′-adenosine monophosphate-activated protein kinase, NF-κB, and activator protein-1 pathway activation leading to the inhibition of proinflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8, IL-12, INF-γ, and TNF-α) expression. Furthermore, they inhibit NO release and COX-2 and iNOS activity. The apoptosis induction in Th1 and Th17-polarized lymphocytes and M2-macrophagic polarization and STAT6 activation has also been exhibited. Although the effectiveness of HM has been exhibited in vitro and in vivo, the combination of these compounds with antimicrobials and even with anti-inflammatory drugs can be helpful in terms of prevention of side effects and antimicrobial resistance. Future clinical trials are also necessary to be investigated for revealing their pharmacokinetics. In the aspect of bioavailability, solubility, absorption, and metabolism of herbal compounds nanocarriers such as loading on poly lactideco-glycolide and nanoparticle formulations are helpful. Those gastro-protective and anti-inflammatory compounds such as curcumin, ginger, garlic acid, and cranberries have demonstrated appropriate anti-*H. pylori* properties. Application and employment of combined therapies composed of probiotics and drugs can also be examined for better clearance of gastric mucosa. In addition, downregulation of inflammatory miRNAs and upregulation of those anti-inflammatory miRNAs using HM is proposed to protect the gastric mucosa.

AUTHOR CONTRIBUTIONS

GA and FA were involved in manuscript preparation and data collection; SMS and MM were involved manuscript editing and also helped in data collection; AHA, OBB, AJC-B, HMY, and NSSM performed data collection and management; and AMA and MS advised, supported, and were also involved in manuscript editing.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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