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ZINGIBER OFFICINALE EFFECT ON *HELICOBACTER PYLORI* INFECTION IN HUMAN; A SYSTEMATIC REVIEW

Vahid Mirzaee [1], Abdollah Jafarzadeh [2-5], Afshin Tahmasebi [1] and Shila Jalalpour [*2]

Department of Internal Medicine [1], Department of Immunology, School of Medicine [3] Rafsanjan University of Medical Sciences, Rafsanjan, Iran.
Molecular Medicine Research Center [2], Immunology of Infectious Diseases Research Center [5], Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.
Department of Immunology, School of Medicine [4], Kerman University of Medical Sciences, Kerman, Iran.

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Correspondence to Author:
Shila Jalalpour

Molecular Medicine Research Center, Research Institute of Basic Medical Sciences, Rafsanjan University of Medical Sciences, Rafsanjan, Iran.

E-mail: shilla.jalalpoor@yahoo.com

ABSTRACT: *Helicobacter pylori* (*HP*) as a non-invasive microbe, has been cloned in the stomach. The most important side effects of *HP* are inflammation, peptic ulcer (PU) and gastric cancer (GC). Control of inflammation, leads to preventing other *HP* side effects and antibiotic resistance, therefore it is important to use of natural anti-inflammatory compounds. In present study, review the effect of *Zingiber officinale* (*Z. officinale*) in controlling side effects of *HP* in human. Related articles were collected in Google Scholar, Pub Med, Science direct, Scientific Information Database and Scopus. For this purpose, using the terms pylori, *Zingiber officinale* and Ginger in the title of the all articles published to 2020. Based on search results, were absorbed 15 articles in Google Scholar, 10 articles in Pub Med, 1 articles in Science direct, 1 article in Scientific Information Database and 13 articles in Scopus. After removing the same articles, protocols and no English language articles, finally reviewed, 8 English-language articles and 1 Farsi language article. Regard to long-term treatment of *HP* and the multiple side effects of routine therapy and possible formation of antibiotic-resistant strains, it's necessary to use natural drugs with less side effects. The *Z. officinale* effects on *HP* such prevention, inhibitory proliferation and control of the side effects of *HP* colonization, and so economic efficiency and easy accessibility, have been identified as an appropriate candidate for treatment and prevention and of *HP* infection.

INTRODUCTION: *HP* has infected mankind in Africa continent since the early Stone Age [1]. Prior to the twentieth century, the majority of the world's population was infected with *HP* [2]. The history of *HP* dates back to 1875 when the German scientists first found spiral bacteria in the lining of the human stomach [3].

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Medical scientists know that *HP* was only cultured recently, in 20th century at Royal Perth Hospital in Western Australia, *HP* discovery by Prof. Robin Warren and Barry Marshall in 19th century [4, 5].

HP, is a Gram negative helix-shaped (not spirochaete), 0.5 µm diameter and about 3 µm long. It is microaerophilic; that is, it's an anaerobic; (low oxygen concentration, requires). *HP* contains a hydrogenase enzyme. *HP* produces 3 important enzyme include urease, oxidase and catalase. *HP* can to form biofilms and convert from helix to a possibly viable but non-cultural coccoid form [3, 6]. The coccoid form can adhere to gastric epithelial cells *in-vitro* condition, whose ecological niche is

the human stomach which is also linked to severe gastritis-associated diseases [7, 8]. *HP* infection is one of the prevalent bacterial infections involved about 50% of the population worldwide [9]. Recurrence of *HP* infection after successful eradication is rare in developed countries and more frequent in developing countries [10]. *HP* infection and prevalence in developed countries were reduced in younger patients (less than 20% but remaining still high (over 50%) in the elderly population. The incidence is stable in developing countries with a prevalence of 70-80%. The prevalence of *HP* in Iranians population is 54%, also observed that this prevalence was significantly different according to age and *HP* diagnostic method [9]. *HP* colonization usually does not lead to disease, since 85% of infected people remain asymptomatic throughout life, but this infection is more common in developing countries compare to developed communities [9].

Different studies have been done in many countries, reported the prevalence of *HP* infection from <20% in European countries to more than 80% in some Eastern Mediterranean countries [9]. *HP* prevalence is more than half in Africa, Asia Central/South America and East/South Europe and *HP* prevalence in countries with high GC is twofold higher than other country, in North America and Northern Europe, about 33% of adults population are infected [11]. In developed countries, *HP* has highly outbreak in the immigrants population. It became evident that the bacterium was present in all human races, on all continents, although it was more common in developing countries and less common in western countries or affluent communities within countries [11]. Side effects of *HP* colonization are classified at two groups of gastrointestinal and non-gastrointestinal: gastroduodenal diseases including chronic gastritis, PUs, gastric adenocarcinoma (Adenocarcinoma is the main type of gastric malignancy [12]) and gastric lymphoma [7, 8, 13, 14] **Fig. 1** and around 15%-20% of the infected individuals develop gastroduodenal diseases [15, 16, 17]. Non gastrointestinal symptoms following *HP* colonization include: respiratory disorders, vascular, autoimmune antibodies, middle ear disorders, cardiovascular disease and iron-deficiency anemia and adenovirus and Tansylar ischemic heart disease [18, 19, 20]. Persistent stomach infection with *HP* causes chronic mucosal inflammation (gastritis), which is widely recognized as an essential precursor to GC [21], Therefore preventing and controlling inflammation is important in controlling cancer [22, 23]. A standard triple therapy (STT), including the proton pump inhibitor (PPI)/amoxicillin and clarithromycin or metronidazole, as proposed at the first Maastricht conference, was globally accepted as first-line *HP* eradication therapy.

The widespread use of antibiotics the success percent of *HP* eradication treatment can be reduced [24]. Treatment of *HP* is hard today because of its high resistance to tronidazole and clarithromycin resistance rates are alarming although they vary among populations [25]. Due to the spread of antibiotic resistance microorganisms in worldwide, anti-*HP* treatment is continuing to be a high challenge for physicians in clinical practice. The Real-world Practice & Expectation of Asia-Pacific Physicians and Patients in *HP* Eradication (REAP-*HP*) Survey demonstrated that the accepted minimal eradication rate of anti-*HP* regimen in *HP*-infected patients was 91% [26]. Anti *HP* induced inflammation activity by natural products, usually relevant to mitogen-activate protein kinase pathway activation, suppression of nuclear factor-κB and inhibition of oxidative stress. Anti *HP* gastritis effects of herbal products, including apple peel polyphenol, carotenoids-rich algae, quercetin, tea product, apigenin, garlic and finger-root extract, have been documented [27].

Those herbal products have demonstrated high potential as pharmaceutical candidates for *HP* eradication and *HP* induced related gastric disorders prevention [27]. The word “nutraceuticals” means the bioactive compounds that are found in foods, herbal products and dietary supplements. Therefore, nutraceuticals are those molecules/ plants which have health-promoting, disease-preventing medicinal properties [28]. Since, *Z. officinale* has been introduced in Iranian traditional medicine as a herbal anti-inflammatory and according to the traditional treatment of gastrointestinal diseases, *Z. officinale* have potential effects in control of *HP* side effect [29]. *Z. officinale* have anti-inflammatory, anti-oxidants and the anti-cancer effects and protection of the gastrointestinal tract and anti-ulcer on *HP*.

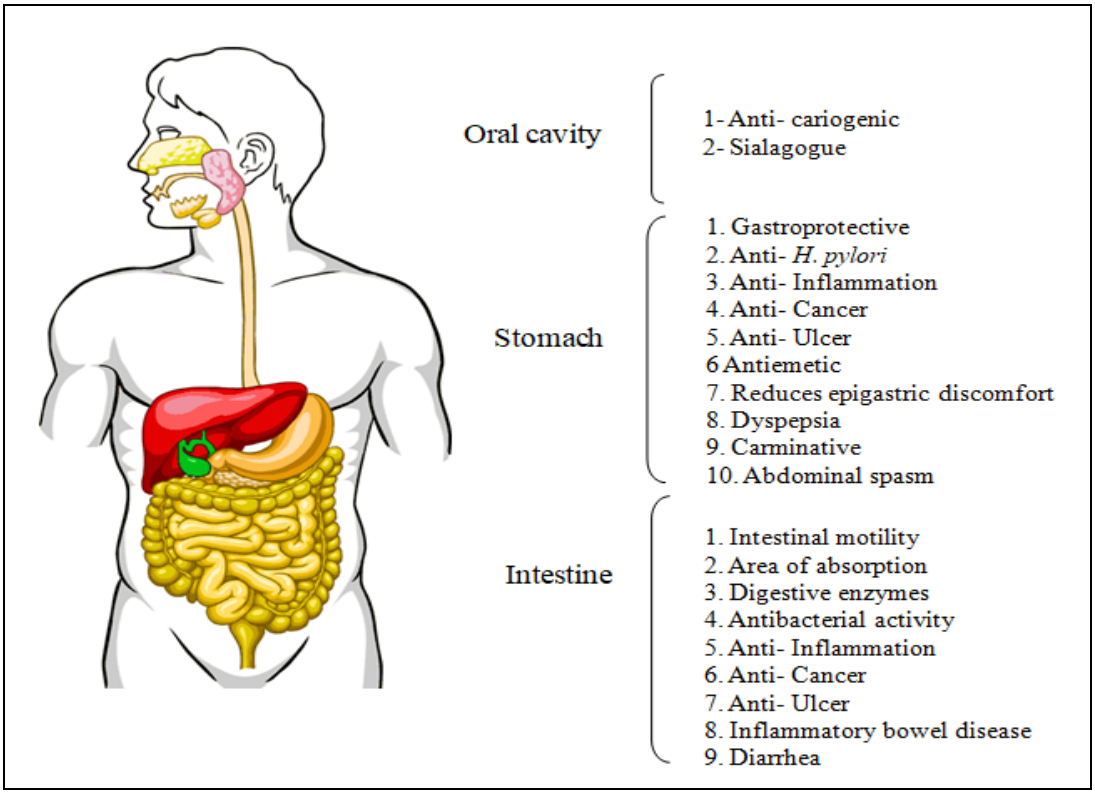

FIG. 1: EFFECT OF *ZINGIBER OFFICINALE* (GINGER) ON THE HUMAN GASTROINTESTINAL TRACS

The *Z. officinale* have been used to therapy of arthritis, asthma, catarrh, cramps, dementia, diabetes, gingivitis, hypertension, infectious diseases, nervous diseases, muscular aches, pains, rheumatism, sprains, sore throats, stroke, toothache, treat vomiting, nausea, dyspepsia, inflammation, indigestion, asthma, cough, palpitation, loss of appetite, constipation, common cold, stomachache, fever and influenza [30].

Considering the importance and prevalence of *HP* in higher than 50% of the population and the need for a natural drug with the ability to induce proper immune system to prevent the onset of *HP*, and also the need for therapy to inhibit bacterial proliferation and in particular inhibit the inflammation caused by the host to bacteria. The aim of present study was systematic review the effect of *Z. officinale* on controlling and preventing complications following colonization of *HP* in human.

METHODS: The current review was conducted in 2020 by reviewing all full-text articles published in English/Persian language on the effect of *Zingiber officinale* on *HP*. Articles were collected from international and national search websites of Google Scholar, Pub Med, Science Direct, Scientific Information Database, and Scopus. For this purpose, using the 3 terms "pylori", *Zingiber officinale* and "ginger" in the title of the articles.

RESULTS: Based on search results, 40 articles were identifier. 15 articles in Google Scholar, 10 articles in Pub Med, 1 article in Science direct, 1 article in Scientific Information Database and 13 articles in Scopus. After removing the same articles, protocols and no English language articles, finally reviewed, 9 articles such 8 English-language articles and 1 Farsi language article **Fig. 2**.

Z. officinale Roscoe (Zingiberaceae family) that known as ginger, is indigenous to tropical southern China or India and Asia. The rhizomes of *Z. officinale* have a powerful aroma [31]. Over 4000 years *Z. officinale* was used as a spice in food usage and as a home-remedy for digestive problem and during pregnancy [32].

Compositional analysis has revealed the presence of carbohydrates, fats, vitamins, minerals, and extractable oleoresins [33]. *Z. officinale* has been fractionated into at least 14 bioactive compounds, including [4]-gingerol, [6]-gingerol, [8]-gingerol, [10]-gingerol, [6]-paradol, [14]-shogaol, [6]-shogaol, 1-dehydro-[10]-gingerdione, [10]-ginger-

dione, hexahydrocurcumin, tetrahydrocurcumin, gingerenone A, 1,7-bis-(4′ hydroxyl-3′ methoxy-phenyl)-5-methoxyhepthan-3-one, and methoxy-[10]- gingerol [34]. The myriad pharmacological effects are supposed to be due to the presence of volatile compounds like zingiberene, curcumene, farnesene, bisabolene, b-sesquiphellandrene, 1, 8-cineole, linalool, borneol, neral, and geraniol and the nonvolatile ones like shogaol, gingerols, zingerone and paradols. The other constituents include capsaicin, diarylheptanoids, ginger pro-tease, gingediol, galanolactone, gingesulfonic acid, galactosyl glycerols, gingerglycolipids, neral, and phytosterols [1].

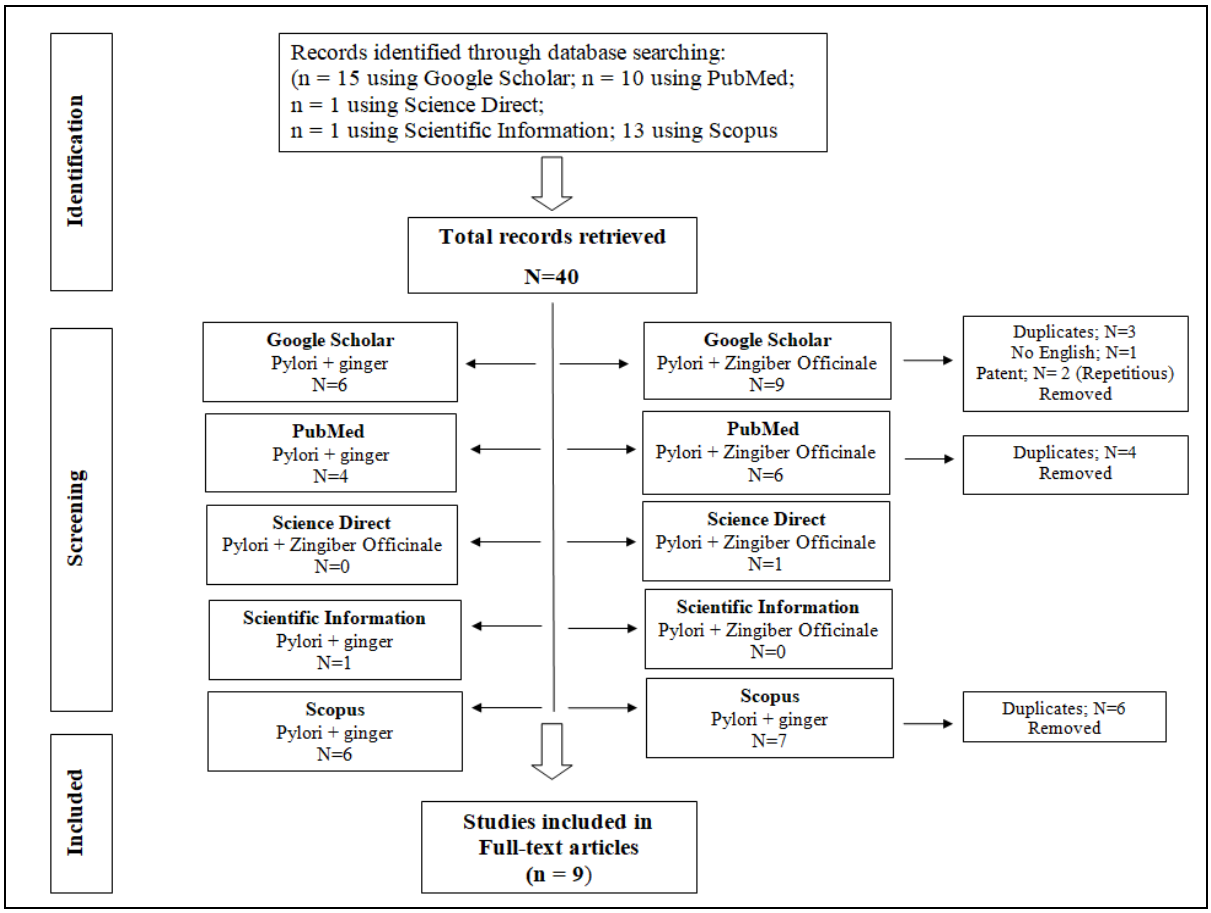

FIG. 2: PRISMA FLOW DIAGRAM FOR GINGER EFFECT ON *HELICOBACTER PYLORI* INFECTION IN HUMANS

At least 115 component in fresh and powder *Z. officinale* have been identified the methanolic extracts of fresh *Z. officinale* rhizome has at least 31 gingerol related compounds [28]. In fresh *Z. officinale* the amount of 6-shogaol, is very low but much higher after the steaming process. With significantly higher anticancer activities, 6-shogaol can serve as an agent for drug discovery. The compound structure modification can be performed based on its three key functional and reactive groups [35]. Gingerols (GNs) (a volatile phenolic compound) have response to pungent taste of fresh Z. officinale rhizome, 6-gingerol is the main compound of the *Z. officinale*, and other gingerols such as 4, 8, 10 and 12-gingerol, are present in lower concentrations. These compounds are thermally labile and are transformed at high temperatures to shogaols (SGs), which impart a pungent and spicy-sweet fragrance 6-gingerol ((5S)- 5- hydroxy-1-(4-hydroxy- 3-methoxyphenyl) decan-3-one), 8-gingerol ((5S)-5-hydroxy-1-(4-hydroxy- 3- methoxyphenyl)dodecan-3-one), 10-gingerol((5S)-5-hydroxy-1-(4-hydroxy-3-methoxy-phenyl)tetradecan-3-one), 6-shogaol ((E)- 1- (4-hydroxy- 3 -methoxyphenyl)dec- 4- en-3-one), 8-shogaol ((E)- 1- (4-hydroxy- 3- methoxyphenyl) dodec-4-en-3-one) and 10-shogaol ((E)- 1- (4-hydroxy-3-methoxyphenyl) tetradec- 4- en-3-one) gingerol analogues are sensitive to temperature but shogaols which spicy taste is found in dried *Z. officinale*. Both shogaols and gingerols have biological activities, ranging from anti-microbial, anti-cancer, anti-oxidant, anti-inflammatory and anti-allergic [31].

Consumption of *Z. officinale* regularly leads to decreased pain levels in patients with rheumatoid arthritis or osteoarthritis along with improvements in their mobility [28], also usage *Z. officinale* has effective role in, gastritis, nausea, vomiting, dyspepsia, belching, bloating, epigastric discomfort, gastric ulcerations, indigestion, and scientific studies have validated the ethno medicinal uses [36].

1. Ani-inflammatory Effect of *Z. officinale* on *H. pylori*: *Z. officinale* has ancient of use as an anti-inflammatory and many of its component have been demonstrated as having anti-inflammatory effect [37]. *Z. officinale* can inhibit prostaglandin biosynthesis [38]. *Z. officinale* has same pharmacological effect with non-steroidal anti-inflammatory drugs (NSAIDs) because *Z. officinale* suppresses prostaglandin synthesis by the limitation of cyclooxygenase and cyclooxygenase-1 [39]. Identification of the molecular targets of individual *Z. officinale* constituents creates an chance to optimize and standardize *Z. officinale* products with respect to their property on special biomarkers of inflammation [40]. The anti-inflammatory effect of gingerols is thought to have importance in these problems. *Z. officinale* could be related to inhibition of leukotriene and prostaglandin synthesis [28]. Previous studies carried out in the recent past indicate that inflammation plays a cardinal role in various pathophysiological processes and that it is mediated by TNF-a, NF-kb, i-NOS and COX-2, and increased generation of proinflammatory eisonaoids [41]. *Z. officinale* and its compounds have been studied in detail for its anti-infammatory effects and studies have shown it to suppress synthesis of prostaglandin by inhibiting COX-1,-2 and inhibiting 5- LOX [42, 43]. The 8-shogaol and 8-paradol have high avibility inhibitory effects on COX-2 activity *in-vitro* condition [44]. *Z. officinale* and 8-shogaol and 8-paradol are also shown to decrease the levels of pro-infammatory cytokines and to reduce the elevated expression of NFkB [45].

Z. officinale extract inhibited the activity of COX-2, NF-kB and to inhibit the release of IL-1b, IL-6, IL-8, and TNF-a from LPS-stimulated human PBMCs in combating HP infection [36]. Several experiments have been carried out to survey the anti-inflammatory effects of *Z. officinale* on animal models and cell cultures, and all have been able to confirm the anti-inflammatory property of *Z. officinale* [46, 47]. Red *Z. officinale* (*Z. officinale* var. Rubra) was used an analgesic for arthritis pain. Color of the *Z. officinale* var. Rubra is purple because it contains anthocyanidins. Shimoda and *et al*., study anti-inflammatory activity of 40% ethanolic extract of red ginger extract. In an acetic acid-induced animal model, 10–100 mg/kg red ginger extract can inhibited the frequency of writhing and the enhancement in permeability of abdominal capillaries. Consumption with red ginger extract (10 mg/kg) significantly reduced footpad inflammation in animal model adjuvant arthritis model. Red ginger extract (3 and 10 mg/mL) significantly reduced PGE2 production and limited NO production at 100 mg/ml. 6-shogaol and gingerdiols inhibits NO production. Red dye fractions presumed to be proanthocyanidins also inhibited production of NO at 100 mg/ml. suppressive property of red ginger extract on inflammation, be involved inhibition activation of macrophage, [6]- Shogaol, gingerdiols and proanthocyanidins were identified as constituents that inhibited NO production [47]. Gaus and *et al*., study effects of the *Z. officinale* extract on prevention and eradication of infection in an animal model. Animals consume daily 100 mg/kg dose of *Z. officinale* extract for 3 weeks before being infected or 6 weeks being infected. Consume of *Z. officinale* extract significantly reduced HP load and lowered acute and chronic mucosal and sub-mucosal inflammation. So *Z. officinale* suppressed the activity of cyclooxygenase-2 and nuclear factor-kappaB transcriptional response in kBZ Jurkat cells, and significantly inhibited the release of tumor necrosis factor-alpha and IL-1 beta, -6, -8 from lipopolysaccharide-stimulated PBMCs with IC_{50} values of 3.89, 7.7, 8.5, and 8.37 mug/mL, respectively. These results suggest *Z. officinale* extracts may be helpful for development as compound to reduce HP-induced inflammation and as for GC chemoprevention [48].

In human and animals Cisplatin treatment causes vomiting and nausea 37 25, 50, 100 and 200 mg/kg oral doses of acetone/ ethanolic extracts of *Z. officinale* exhibited significantly protection, but aqueous extract has not ineffective against cisplatin emesis in and animals such rats [49] and dogs [50].

2. Anticancer effect of *Z. officinale* on *H. pylori*: GC is the fourth common cancer in men and the fifth common cancer in women [51] and is the third most common cause of death from cancer in the world [52, 53]. From the first reports based on the role of HP with adenocarcinoma [54, 55], to recent studies, all confirmed the association between *HP* and adenocarcinoma [56, 57]. Finally in 1994, the International Agency for Research on Cancer classified HP as a type I carcinogen bacterium [52].

Z. officinale are applied by various compounds, including vanilloids, 6-paradol, 6-gingerol, Shogaols, zingerone, Galanals A and Galanals B [58, 59] Galanals A and Galanals B are strong induction of apoptosis in Jurkat cells human T [58]. Anticarcinogenic properties of Z. officinale to be mediated by various pathways [60]. *Z. officinale* reported to has anti colon cancer activity [61]. Gingerols, kill ovarian cancer cells by inducing autophagocytosis and apoptosis [62]. In ovarian cancer, pro-inflammatory state has been important contributing factor. *Z. officinale*, reduced inflammatory mediator such IL-8, vascular endothelial growth factor and prostaglandin E2 in the ovarian cancer cells [62]. Mixed treatment with TNF and 6-shogaol-related to induces apoptosis in type of cancer cells such breast carcinoma MDA-MB-231 cells, renal carcinoma Caki cells and glioma U118MG cells, but not in normal mesangial cells and normal mouse kidney cells. 6-Shogaol also can reduce cytochrome c and mitochondrial membrane potential released from mitochondria to cytosol *via* Bax activation. 6-Shogaol also resulted down-regulation of c-FLIP(L) expression at the posttranslational levels [63]. Gingerol inhibited human colorectal cancer [61].

The effects of aquatic extract of *Z. officinale* on Brest cancer in mice shown, cancer significantly inhibited [62]. Tumor development are multistep processes contains metabolic changes and genetic [63]. A cytostatic/ cytotoxic effect, mediated by apoptosis, was found for 6-paradol and 6-gingerol in promyelocytic leukemia HL-60 cells [64] and also for 4 diarylheptanoids and 2 shogaols [28]. 6-gingerol, 6-shogaol, 6-paradol, have potential effect for treatment and prevention of non-small cell lung carcinoma, among this compounds, 6-gingerols has most effective in inhibition the proliferation of non-small cell lung carcinoma [60]. *Z. officinale* and its constituents are also helpful against pancreatic cancer [65]. Whole *Z. officinale* extract or its constituents, inhibited induced death of pancreatic cancer [66]. *Z. officinale* limitation of leukotriene A4 hydrolase activity and this properties resulted to prevention of colorectal cancer. In human colorectal cancer cells treatment with *Z. officinale* reduction of cell viability and induce apoptosis by the increased ATF3 expression via activating ATF3 promoter [67]. *In-vitro* condition studies revealed that *Z. officinale* components are efficient against liver cancer. 6-shogaol induce apoptotic of Mahlavu hepatoma cells by an oxidative stress-mediated caspasedependent mechanism [68].

The major components of *Z. officinale*, 6-gingerol and 6-shogaol, have anti-invasive property against hepatoma cells. In animal model, *Z. officinale* by reducing lipid peroxidation and scavenging the free radical formation, inhibited hepatocarcinogenesis [69]. An ethanol *Z. officinale* extract significantly protected effect against the development of skin tumors in mouse. Inhibition of 12-O-tetradecanoylphorbol-13-acetate-caused induction of cyclooxygenase (COX), epidermal ornithine decarboxylase and lipoxygenase activities [28, 70].

3. Antimicrobial Effect of *Z. officinale* on *H. pylori*: Antibiotic resistance is developing worldwide and consider as an important offender in the failure of antibiotic treatment. Consumption of antibiotics against microbes is effective treatment method but also causes side effects. *Z. officinale* having broad range of antimicrobial activity against both Gram+ and Gram- bacteria and fungi [71, 72]. Continuous consumption of *Z. officinale* reduced multiplication of colon bacteria. These micro-organisms fermented of undigested carbohydrates causing flatulence which can be counteract with *Z. officinale* [73]. *Z. officinale* and its constituents have a vital play in the limited of microorganisms growth or act as antimicrobial agents [74]. *Z. officinale* rhizome contains constituents which have antibacterial / antifungal effects. The shogaol and gingerol are identified as high active antimicrobial agents [75]. 10-Gingerol from *Z. officinale* has antimicrobial activity against a pathogenic microorganisms including Gram+ and Gram- bacteria and the *Candida albicans* [76]. Various studies demonstrated time-dependent anthelmintic activity of crude aqueous extract of dried *Z.*

officinale and crude powder (1–3 g/kg) in animal models infected with mixed species of gastrointestinal nematodes are reported [77]. *Z. officinale* inhibits Aspergillus sp., a carcinogenic organism [78]. 6-, 8-, and 10-gingerol have antimicrobial activity [78]. 10-gingerol and 8-gingerol were active (MIC 25–50 μg/ml) exhibiting toward *Mycobacterium avium* and *Mycobacterium tuberculosis* H37Rv. Besides 12-gingerol and 6-gingerol have antimicrobial activity against periodontal bacteria [79]. Thus, *Z. officinale* can provide protection effect against fungal and bacterial pathogens [28].

Z. officinale possesses anthelmintic effects against human pathogens [1]. Multiple studies demonstrated that *Z. officinale* and several of its phytochemical components possess antibacterial effects on both drug-resistant and sensitive bacteria [80, 81, 82]. Effect of *Z. officinale* and its constituents on the growth of oral microbial associated with periodontitis. It was observed that the ethanol and n-hexane extracts of *Z. officinale* exhibited antibacterial activities activity-guided fractionated studies were also performed and it was observed that 10-gingerol and 12-gingerol effectively limited the growth of these oral pathogens at a MIC range of 6–30 mg/ml and a MBC range of 4–20 mg/ml [1].

Today, there is a requirement for an antimicrobial agents with charactristics safe effective and economical. *Z. officinale* has inhibitory effect on several of the oral microbes. Giriraju and Yunus demonstrated antimicrobial effect of 10% *Z. officinale* extract against *C. albicans, S. mutans* and *E. faecalis* by using MIC (serial broth dilution) and Agar disk diffusion test. 10% ethanolic *Z. officinale* extract showed: (a) highest inhibition zone against *C. albicans, E. faecalis* and *S. mutans* were 14, 11 and 8 mm respectively. (b) MIC again *S. mutans, E. faecalis* and *C. albicans* were 1.25%, 2.5%, and 2.5% respectively. 10% ethanolic *Z. officinale* extract has antimicrobial effect against this pathogens microbe [83]. Ewnetu *et al*., estimated antimicrobial effects of *Z. officinale* rhizome powder and Ethiopian honeys extracts on *Staphylococcus aureus, Klebsiella pneumoniae* (R), *Escherichia coli* (R) and *Escherichia coli* (ATCC 25922). Broth and agar diffusion and media method were done to determine susceptibility of resistant clinical strains and standard strains isolates using honey/ *Z. officinale* mixtures. Honey- *Z. officinale* powder extract mixtures produced the highest inhibitory zone (25.62 mm ± 2.55) in comparison to the consumption of honeys (21.63 mm ± 3.30) or *Z. officinale* extracts (19.23 mm ± 3.42) individually. The ranges of inhibitions produced by honey- *Z. officinale* extract mixtures on susceptible test organisms (26–30 mm) and resistant strains (range: 19–27 mm) were higher compared to 7–22mm and 0–14mm by standard antibiotic discs. MIC of mixture of honeys- *Z. officinale* extracts were 6.25% (0.625 v/mL) on the susceptible bacteria compared to 75% for resistant clinical isolates. MBC of honey- *Z. officinale* extracts was 12.5% for all the test organisms. According their result honey- *Z. officinale* powder extract have antibacterial effect agents the drug resistant bacteria [30].

Dehghan and *et al*., studied the effect of ethanol, ether and water some herbal extracts on *HP* strains isolated from the patients, by the agar diffusion. Considered water extracts for their antibacterial effects, turmeric had the most anti *HP* efficacy (mean of inhibitory growth zone diameter 21.5 mm). *Z. officinale*, clove and cardamom were respectively placed thereafter. Among ethanol extracts, *Z. officinale* with diameter mean of 19.7 mm showed the most effective as compare with turmeric and clove. Ether extracts of the mentioned plants had anti *HP* effects (Mean of inhibitory growth zone diameter were 19, 13, 11.1 and 10.5 mm respectively [84].

HP is the primary agent associated with dyspepsia, gastric, PU and colon cancer, Mahady and *et al*., study alcoholic extract of *Z. officinale* and, 6-,8-, 10-gingerol and 6-shogoal, against 19 *HP* strains including 5 *HP* CagA+ strains. Their result show the antimicrobial effect of methanol extract of *Z. officinale* against all HP strains with a MIC range of 6.25–50 μg/ml. the gingerols fraction was active and limited the growth of all HP strains with an MIC range of 0.78-12.5 μg/ml and has significant activity against the HP CagA+ strains. Gingerols of *Z. officinale* extract, inhibit the growth of HP CagA+ [85]. Kahald and *et al*., studied the antimicrobial activity of *Z. officinale* syrup against HP on fifty volunteers (2 gr *Z. officinale*/ 3 months) they demonstrated level of antibody against HP were decreased to be nearly up normal values [86].

Nanjundaiah and *et al*., studied the ulcer-preventive effect of aqueous extract of *Z. officinale* (AEZ). AEZ at 200 mg/kg b.w. protected 77% and 86% for the ethanol stress and swim stress induced ulcers with an ulcer index of 50 ± 4.0 ± 4.0/46 respectively. Gastric mucin damaged rat was recovered up to 77% and 74% in swim stress and ethanol stress, respectively after AEZ treatment. AEZ also limited the growth of *HP* with MIC of 300 ± 38 μg and also possessed reducing power, free radical scavenging ability with an IC50 of 6.8 ± 0.4 μgmL−1 gallic acid equivalent (GAE). DNA protection was observed up to 90% at 0.4 μg.

Toxicity studies indicated there was no lethal effects of *Z. officinale* in rats fed until 5g/k b.w. study on ulcer-preventive of cinnamic and gallic phenolic acids, cinnamic acid appear to contribute to better H+, K+-ATPase and *HP* inhibitory activity, while gallic acid contributes significantly to anti-oxidant activity [87]. Attari and *et al*., studied gastro- protective effect of Z. officinale in HP+ patients, they studied 15 HP+ patients. Patients consume 3 gr/daily *Z. officinale* powder as three 1-gr tablets for 4-weeks. They demonstrated *Z. officinale* consumption accompanied by significant HP eradication rate of 53.3% (P = 0.019) [88]. Azadia, and *et al*., studied inhibitory effects of the mixture of cinnamon and *Z. officinale* on cagA expression of *HP*. They demonstrated the synergetic effect of cinnamon/ *Z. officinale* as anti HP compared to the Tetracycline 30 μg and shown there are significant decrease in the expression of the cagA after exposure to the extract mixture in comparison of the ureC reference gene ($p < 0.05$) [89].

Some *in-vitro* condition studies have shown the effectiveness of *Z. officinale* and cinnamon extracts against *HP*. Ahmed and *et al*., demonstrated the efficacy of *Z. officinale* and cinnamon preparations as components of dual or triple omeprazole-based *HP* eradication regimens in patients with *HP*-associated functional dyspepsia. *HP* status was tested using the non-invasive stool antigen test before and 4 weeks after eradication therapy. Following 14-day therapy, significantly higher eradication rates were obtained with dual *Z. officinale*/omeprazole and triple cinnamon/*Z. officinale*/omeprazole regimens compared to dual cinnamon/omeprazole regimen (70% and 80% versus 50%, $p \leq 0.05$). All eradication regimens lowered dyspeptic symptoms [90].

4. Gastrointestinal Effects of *Z. officinale* on *H. pylori*: PU is a major health problem worldwide in both males and females having several factors triggering its effect including food ingredients, stress, *HP*, and drugs. In traditional system of medicine, herbal has anti-ulcer effect in various ways, but usually their mechanism is not understood [91]. *Z. officinale* and its constituents increasing mucin secretion and with this mechanism prevent the PU findings demonstrated anti-ulcerative effects of *Z. officinale* in experimental GU models [92]. 6-gingerol and 6-shogaol suppressed gastric contraction in situ, with 6-shogaol having more intensive [93]. It was shown that acetone, 50% ethanolic extracts of *Z. officinale* (100–500 mg/kg) and *Z. officinale* juice (2–4 ml/kg) reversed cisplatin induced delay in gastric emptying in animal model when given orally [49]. *Z. officinale* has gastric motility effect. In animal model *Z. officinale* can stimulate bile secretion, trypsin, intestinal lipase, chymotrypsin, amylase, maltase and sucrase activities, 6 gingerol and 10 gingerol are responsible for this activity [66]. Recently findings explain the traditional use of *Z. officinale* as a digestive supplementary. *Z. officinale* utilized in alleviating symptoms of vomiting and nausea [94]. But its mechanism remains unknown. However, there are several proposed mechanisms. The antiemetic effect components in *Z. officinale*, are contains shogaols, gingerols and galanolactone [95].

Based on *in-vitro* and animal models studies, demonstrated that Z. officinale extract has anti-serotoninergic and 5-HT3 receptor antagonism effects, this compound have an important role in vomiting and postoperative nausea [96]. The role of *Z. officinale* as an antiemetic component attributed to its carminative effect, which led to break up and exit intestinal gas. This idea was improved by the results of a trial study in which healthy people demonstrated *Z. officinale* stimulated antral contractions accelerated gastric emptying [97].

Contrary to these results, in one randomized crossover trial study of 16 healthy person, that consume *Z. officinale* (1 gr/orally), they had no effect on gastric emptying [98]. However, it's clear

that nausea and vomiting during pregnancy reduced in most pregnant women [99]. Overall consumption of dietary supplements in pregnant women appears to be low, but *Z. officinale* is usually recommended to prevent nausea [100]. Several clinical trials study demonstrated that *Z. officinale* consumption is safe and effective manner to control vomiting and nausea pregnancy women [101]. *Z. officinale* may also increase the conversion of cholesterol into bile acids by increasing the activity of hepatic cholesterol-7-α-hydroxylase, the rate limiting enzyme of bile acid biosynthesis [102]. *Z. officinale* increases the production of stomach acid thereby interfering with antacids, H_2 antagonists or proton pump inhibitors and sucralfate. Interestingly, shogaol, specially (6)-gingerol, has demonstrated inhibitory intestinal motility in intravenous preparations and facilitatory gastrointestinal motility in oral preparations. A number of animal models studies have shown hypo-cholesterolemic action of *Z. officinale* and *Z. officinale* extracts by reduce lipid peroxidation and increased fibrinolytic activity. *Z. officinale* decreased levels of triglycerides, total cholesterol, LDL-cholesterol, very low-density-lipoprotein-cholesterol and increased levels in high-density-lipoprotein-cholesterol [103]. According recent study, air-dried *Z. officinale* powder (100 mg/kg oral in daily) fed to rabbits with experimentally induced atherosclerosis for 75/days, inhibited atherosclerotic changes in the aorta and coronary arteries by a proximally 50% [104].

DISCUSSION AND CONCLUSION: Herbal in traditional medicinal system since ancient time have been used as a source of medicine therapy [105]. The WHO has described traditional medicine therapy as inexpensive way to achieve total people and has encouraged the rational use of herbal based traditional medicines by member states [106]. The WHO estimates that about 80% of the population are user of herbal medicine to treat various illnesses as means of primary healthcare [107]. The therapeutic application of herbs has been considered for their bioactive effects since ancient times [108, 109], the WHO has called on Member States to make rational use of herbs [30]. Unsuitable consumption of antimicrobial drug resulted in the development of resistant pathogenic microorganism's like anti-microbial resistant bacteria. The increasing antibiotic resistance in bacteria scientific focus on plants derived antimicrobial agents Traditional medicine therapy has become a type of supplementary natural therapy for multiple antibiotic resistant bacterial.

HP treatment is based on the consume of antibiotics and proton pump inhibitors that may due to the problems surrounding the consume of antibiotics and the side effects of anti-inflammatory agents [110]. Antibiotic therapy failure may arise upon of other factors *i.e.* the drug sensitivity to diet, such pH (tetracycline has high activity at a low pH and amoxicillin has high activity at a neutral pH) [27]. Herbal medicine supplementary therapy is still the mainstay of nearly 75% to 80% of the whole world population, commonly in developing countries, for primary treatment because of better cultural acceptability, better compatibility with the human body and fewer side effects. However, the last few years have seen a major increase in their use in the developed world [111]. The failed treatment and eradication success for *HP* infection are, largely due to the rapid emergence of antibiotic resistant strains [112]. Antibiotic resistance is a constantly changing phenomenon, according to prevalence studies, the prevalence of antibiotic resistance in HP strains varies considerably across countries, and this difference even across regions of one country [112] HP. Antimicrobial resistance is assessed by *HP* culture and antimicrobial susceptibility testing. Molecular method such resistance-associated mutations HP strains and genetic identification of HP and is an efficient way to replace of HP culture. Surveillance of antibiotic resistance by laboratory methods is necessary to inform physicians in their choice of therapy method for management of HP infection [112].

Z. officinale has been used to treat various gastrointestinal ailments. Due to its abundance, safety and low cost, *Z. officinale* remains a species with tremendous potential and countless possibilities for further investigation. The pharmacological activities of *Z. officinale* depended to the various phytochemicals. With regard to certain pharmacological effects (antibacterial and antiemetic effects against motion sickness and chemotherapy-induced nausea in humans), contradictory results are seen and this may be possibly due to the variation in the phytochemicals in the *Z. officinale* used.

The eating of *Z. officinale* in human health has been demonstrated since ancient times and they provide a useful natural source of new therapeutics.

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