Bali Medical and Wellness Journal - *bmw-journal.com*

Original article

The Potential of Curcumin as Prevention and Alternative Treatment for Helicobacter Pylori Associated Diseases

Anak Agung Sagung Mirah Prabandari[1], Ni Nyoman Shinta Prasista Sari[2]

[1]Clinical Nutrition Department, Medical Faculty of Udayana University, Denpasar-Indonesia

[2]Medical Faculty of Udayana University, Denpasar-Indonesia

Corresponding author:

Anak Agung Sagung Mirah Prabandari

mirahpraban@gmail.com

ABSTRACT

Introduction: Helicobacter pylori (H. pylori) is a pathogenic bacterium found in half of the world's population, causing gastrointestinal problems ranging from gastritis and peptic ulcers to gastric cancer. Current triple therapy treatment for H. pylori faces issues of resistance, side effects, and high cost, necessitating alternative therapies. Studies suggest that curcumin, a compound found in turmeric, may have antibacterial effects against H. pylori.

Method: This literature review evaluated the potential of curcumin against H. pylori infection. Relevant articles were systematically searched in PubMed, Scopus, Web of Science, and Google Scholar databases using combinations of keywords including "curcumin," "turmeric," "Helicobacter pylori," "antibacterial," "anti-inflammatory," "antioxidant," and "bioavailability."

Results: Curcumin, a polyphenol compound extracted from turmeric, possesses antibacterial, anti-inflammatory, anti-carcinogenic, and antioxidant properties. Turmeric is a natural, inexpensive, and readily available plant in Indonesia. Curcumin prevents H. pylori-associated diseases by inhibiting bacterial adherence to gastric cells and exhibiting bactericidal effects through disruption of bacterial metabolic enzymes and inhibition of ammonia production. Additionally, curcumin treats H. pylori-induced inflammation by suppressing inflammatory pathways such as NF-κB, AP-1, JNK, and MAPK.

Conclusion: Curcumin shows potential as both a preventive and therapeutic agent for H. pylori-associated diseases. Further research should focus on improving curcumin's delivery system to enhance its efficacy in clinical applications.

Received: June, 17 2024
Accepted: July, 18 2024
Published online: July, 31 2024

BMWJ 2024;Vol (1), page (56) – (71)

Correspondence to:
Anak Agung Sagung Mirah Prabandari,
mirahpraban@gmail.com

DOI:
http://dx.doi.org/10.37689/bmwj/2024AO00028722

Keywords:
Chronic gastritis, curcumin
Gastric cancer, helicobacter pylori
Pptic ulcer

INTRODUCTION

Helicobacter pylori (H. pylori) are gram negative bacteria which present in about 50% of the global population (Shmuely et al., 2016). Even though most of H. pylori infections are asymptomatic, but 10-15% of the infected patients or about 500 million people suffer from this bacteria (Testerman and Morris, 2014). H. pylori infections are the most common cause of gastrointestinal problems such as dyspepsia, chronic gastritis and peptic ulcer diseases. H. pylori infection is also strongly related to duodenal ulcer, mucosa-associated lymphoid tissue lymphoma (MALT) and gastric cancer. World Health Organization classified H. pylori as carcinogen to human. Approximately 30 million people with H. pylori infection develop gastric cancer which has only 29% of 5-years survival rates and has killed 700,000 people each year. H. pylori could also induce serious complication such as internal bleeding, absorption impairment, stomach perforation, and peritonitis (Salih, 2009).

Beside gastrointestinal problem, H. pylori is increasingly being associated with extra gastric diseases such as autoimmune disease, iron deficiency anemia, pregnancy problem, insulin resistance, skin disease, chronic otitis, nasal polyp, chronic obstructive pulmonary disease, glaucoma, development of Alzheimer and Parkinson, hepatocellular carcinoma, and cardiovascular disease. Annual cost of H. pylori infection in USA is estimated to be $6 billion, with significant decrease in productivity and quality of life (Wong et al., 2014).

Several trials showed that eradicating H. pylori is more effective and less expensive than continuous therapy for chronic gastrointestinal problem (Sarkar et al., 2016). Unfortunately, current treatment of H. pylori by using triple therapy (TT) which is combination of two antibiotics and proton pump inhibitor often fail in clinical setting because of resistance issue, side effect that affecting patient compliance, and high price. Thus, it is essential to find alternative therapies against H. pylori infection (Testerman and Morris, 2014; Ayala et al., 2014).

Studies suggest that some active compounds derived from plant has antibacterial effect against H. pylori, those are resveratrol from red wine, catechins from green tea, allicin from garlic, and curcumin in turmeric (Shmuely et al., 2016; Ayala et al., 2014). From those active compounds, curcumin shows high antibacterial activity, with additional anti-cancer, anti-inflammatory, and anti-oxidant properties (Sarkar et al., 2016). Curcumin also could be found easily in almost every parts of Indonesia and is not hard to be cultivated, make curcumin to be affordable in term of price and availability (De et al., 2009). The aim of this study is to summarize the potential of curcumin against H. pylori infection.

METHODS

This is a literature review to evaluate the potential of curcumin against Helicobacter pylori infection. The following databases were systematically searched for relevant articles: PubMed, Scopus, Web of Science, and Google Scholar. The search was conducted using combinations of the following keywords: "curcumin", "turmeric", "Helicobacter pylori", "H. pylori", "antibacterial", "anti-inflammatory", "antioxidant", and "bioavailability". Inclusion criteria were original research articles and review papers; studies published in English; in vitro, in vivo, and clinical studies related to curcumin's effects on H. pylori; studies discussing curcumin's antibacterial, anti-inflammatory, and antioxidant properties; and research on curcumin's bioavailability and delivery systems. Exclusion criteria were rticles not available in full text and studies focusing solely on other applications of curcumin unrelated to H. pylori or gastrointestinal health.

The selected articles were thoroughly reviewed, and relevant information was extracted and synthesized. The data were organized into several key themes: curcumin's antibacterial effects against H. pylori, its anti-inflammatory and antioxidant properties, safety profile, bioavailability issues, and novel delivery systems. Data from the selected studies were analyzed qualitatively The information was then synthesized to provide a comprehensive overview of curcumin's potential as a therapeutic agent against H. pylori infection.

RESULTS AND DISCUSSION

Helicobacter pylori

H. pylori is the most important species in the genus Helicobacter, genus which infect stomach and intestine. The outer membrane consists of lipopolysaccharide A that has low endotoxin activity, core oligosaccharide, and O side chain resembling the Lewis blood group antigens and thus allowing H. pylori to evade host immune response (Morgan and Crowe, 2016).

H. pylori infection pathogenesis occurs through colonization, inflammation, alteration of gastric acid production, and tissue destruction. H. pylori has strict tissue tropism in gastric mucosa or other sites with gastric metaplasia (Morgan and Crowe, 2016). Once ingested, H. pylori colonization could persist lifelong when the infection remains untreated. Colonization process is facilitated by inhibition of gastric acid production by H. pylori acid-inhibitory protein and neutralization of gastric acid by ammonia produced by urease activity (Marcus and Scott, 2016).

Adaptation of H. pylori to low pH is achieved by increasing the expression of genes encoding urease (Nakano et al., 2016) hence improving the urease activity. H. pylori is highly motile in a corkscrew manner using multiple polar flagella (Morgan and Crowe, 2016) and it adapts to the acidic environment by increasing expression of genes encoding proteins involved in the motility apparatus, allowing it to move rapidly through viscous mucus layer to reside in a neutral pH milieu (Morgan and Crowe, 2016). It has multiple surface adhesion proteins named adhesins

that aid in attachment to the epithelial cells and evasion of host immune detection and clearance mechanisms (Senda and Hatakeyama, 2016).

Local tissue damage is mediated by urease byproducts (mucinase, phospholipases) together with vacuolating cytotoxin A (VacA) (Morgan and Crowe, 2016), a virulence factor that produce vacuoles upon epithelial cells endocytosis, damaging the cell by escaping autophagy, inducing apoptosis, immunosuppression activity, and disrupt various signaling transduction pathways (Marcus and Scott, 2016).

Some strains of H. pylori are more virulent and are associated with more severe mucosal damage as they possess cytotoxin-associated gene pathogenicity island (cag PAI) in their genome which encodes a type IV secretion system (T4SS) and cytotoxin-associated gene A (CagA) (Senda and Hatakeyama, 2016). T4SS injects CagA protein into host epithelial cells, causing abnormal cytoskeletal structures of the epithelial cells (Morgan and Crowe, 2016) and potentiates oncogenic signaling (Senda and Hatakeyama, 2016).

Curcumin

Curcumin is a bright yellow polyphenol compound derived from turmeric (Curcuma longa), a rhizomatous perennial herb belonging to the family Zingiberaceae. Turmeric is widely distributed throughout tropical and subtropical regions around the world and is native to South-East Asia, especially Cochin, China, and East Indies. This plant has an underground rhizome that is deep yellow to orangish in color, measuring 2.5–7.0 cm in length and 2.5 cm in diameter. An individual plant can grow up to 1 m with a reduced stem with broad green leaves on top of the rhizome (Prasad and Aggarwal, 2011; Ravindran et al., 2007).

Turmeric in a standard form contains mostly carbohydrates (69.4%), protein (6.3%), fat (5.1%), minerals (3.5%), and moisture (13.1%) (Nasri et al., 2014). In its standard form, turmeric contains 5-6.6% curcumin and less than 3.5% volatile oils. Curcumin acts as a coloring agent, giving the yellow color to the rhizome while turmerone, arturmerone, and zingiberene are responsible for the aroma. Curcumin is more stable in acidic pH, thus it can survive in gastrointestinal tract (pH 1 to 6) (Prasad and Aggarwal, 2011).

Anti-bacterial Effect of Curcumin Against Helicobacter Pylori

Curcumin exerts its antimicrobial property against parasite, pathogenic fungi, and bacteria (Helicobacter pylori, Bacillus subtilis, Plasmodium falciparum) (Sarkar et al., 2016). The anti-H. pylori effects of curcumin are mainly by inhibition of bacterial enzymes which followed by bactericidal effect (Han et al., 2007). Beside that, curcumin also prevent the adherence of H. pylori to gastric cell (Pattiyathanee et al., 2009), and inhibit signaling of bacterial virulence factor which produce urease important to protect H. pylori from stomach acidic pH (Srivastava et al., 2015). Mechanism of anti-bacterial effect of curcumin against H. pylori can be seen in figure 1.

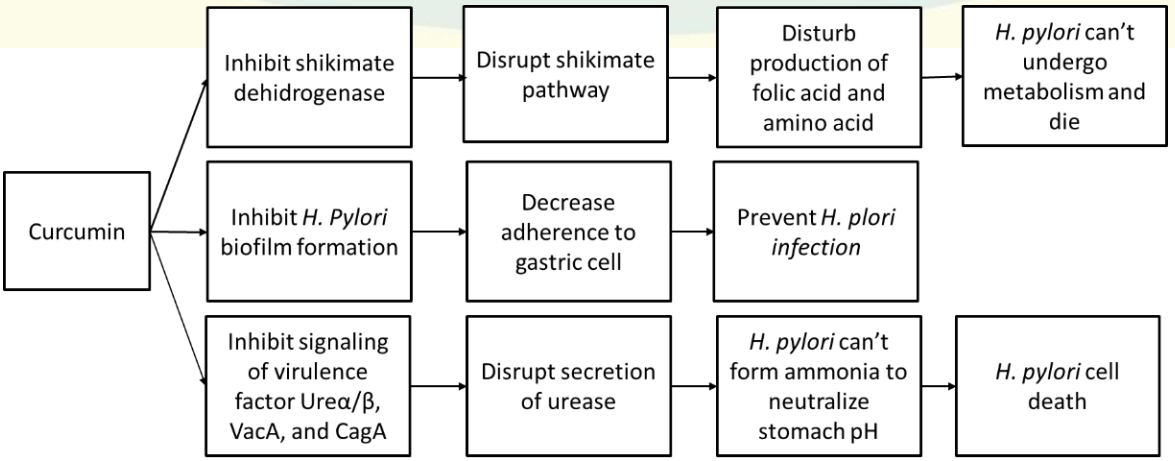

Figure 1. Mechanism of anti-bacterial effect of curcumin against H. pylori

One of the studies by Pattiyathanee et al. (2009) indicated that biofilm formation by Helicobacter pylori was reduced at sub-inhibitory concentrations of curcumin, thus significantly decreased the ability of H. pylori to adhere to the HEp-2 cells. This mechanism could explain that curcumin can prevent the recurrence of H. pylori by inhibit its adherence to gastric cell.

Mechanism upon non-toxic bactericidal effect of curcumin is due to inhibition of shikimate pathway which disrupt bacterial metabolism (Shmuely et al., 2016). Shikimate pathway is a seven-step metabolic route used by bacteria, fungi, algae, and some protozoan for the biosynthesis of folates, aromatic amino acids (phenylalanine, tyrosine, and tryptophan) and ubiquinone. Shikimate dehydrogenase (SDH) was involved in this pathway, make it as novel drug targets for developing non-toxic antimicrobial agent. Study by Han et al. (2007) showed curcumin to be a noncompetitive inhibitor of SDH, thus disrupt shikimate pathway which cause H. pylori can't produce compound essential for its life, lead to its death.

An in-silico study by Srivastava et al. (2015) revealed that curcumin bind, interacted, and inhibit the signaling of virulent factors (Ureα/β, VacA-p55, and CagA) in H. pylori. Ureα/β regulate urease enzyme which hydrolyses urea into ammonia for neutralization of acidic environment in human lumen and establishing the neutral microenvironment surrounding the bacteria. VacA secretes toxin that induces extensive vacuolation in the cytoplasm of mammalian cells. CagA has been established at time of cytotoxin expression, developing to gastric polyps and adenocarcinoma in transgenic mice. Inhibition role of curcumin toward those virulent factors may indicate antibacterial effect of curcumin towards H. pylori.

Several in vitro studies did from 2002-2009 consistently proved that curcumin has antibacterial effect against H. pylori. When pre-clinical trial was done, study in 2010 shows H. pylori eradication in only 5.9% patients but study in 2011 shows eradication in 77% patients. This was probably due to higher dose and longer duration in second study. Previous researches about Anti-bacterial Effect of Curcumin Against Helicobacter Pylori can be seen in table 1.

Table 1. Anti-bacterial Effect of Curcumin Against Helicobacter Pylori

Author	Study Design	Doses	Result
Mahady et al, 2002	In vitro to 19 strains *H. pylori*	0.78-100 µg/ml	Curcumin inhibit *H. pylori* with MIC 6.25-50 µg/ml (mostly 12.5 µg/ml)
Han et al, 2006	In vitro to *H. pylori* SS1 strain	16 µg/ml	Curcumin inhibit *H. pylori* with MIC 16 µg/ml
De et al, 2009	In vitro to 67 strains *H. pylori*	5-50 µg/ml	Curcumin inhibit *H. pylori* with MIC 5-50 µg/ml (mostly 15 µg/ml)
Pattiyathanee et al, 2009	In vitro co-culture	8 µg/ml	Curcumin inhibit 83.21% of *H. pylori* adherence to gastric cell
Koosirirat et al, 2010	Pre-clinical trial with 36 chronic gastritis and (+) *H. pylori* patients	700mg 3x daily, 4 weeks	*H. pylori* eradication rate in curcumin 5.9%, but relieved symptoms found
Aljamal, 2011	Pre-clinical trial with 55 peptic ulcer patient, 35 (+) *H. pylori*	500mg 4x daily, 8 weeks	27 of 35 patients (77%) had successful *H. pylori* eradication and 47 of 55 patients (85%) had their peptic ulcers absent

Anti-inflammation Effect of Curcumin

Main pathogenesis of symptomatic H. pylori infection is inflammation, where if untreated can lead to serious complication such as gastric cancer (Shmuely et al., 2016). An advantage ofcurcumin is instead of eradicating H. pylori as prevention of inflammation, it can also treat the inflammation which is already happening, thus alleviate inflammatory disease such as gastritis and peptic ulcer, and prevent gastric cancer (Sarkar et al., 2016). Evidence of curcumin effect in alleviating symptoms of gastrointestinal disease can be seen in table 2.

Curcumin anti-inflammatory mechanism is attributed through suppression of nuclear factor κB (NF-κB), activating protein (AP-1), mitogen activated protein kinase (MAPK), and Janus kinases pathway, thereby inhibit inducible nitric oxide synthase (iNOS), Cycloxygenase-2 (COX-2), Lypoxigenase (LOX), production of pro-inflammatory cytokines IL-1, IL-6, IL-8, IL-12, interferon γ (IFN-γ), tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein (MCP), and migration inhibitory protein (MIP) (Sarkar et al., 2016; De et al., 2009; Sintara et al., 2010; Kundu et al., 2011; Santos et al., 2015).

In order to investigate the anti-inflammatory effect of curcumin, Sintara et al. (2010) divided 25 rats into five groups: control rats (Control), control rats supplemented with 600 mg/kg curcumin (Cur), H. pylori-infected rats (Hp), H. pylori-infected rats supplemented with 200 mg/kg curcumin once daily (Hp + curI), and H. pylori-infected rats supplemented with 600 mg/kg curcumin once daily (Hp + curII). After seven day, NF-κB expression in gastric epithelial cells was examined by immunohistochemistry and macromolecular leakage in gastric mucosa was examined by intravital fluorescence microscopy. Result showed that curcumin can suppress both NF-κB and macromolecular leakage significantly.

Table 2. Effect of Curcumin in Reducing Symptoms of Helicobacter pylori Associated Disease

Author	Study Design	Doses	Result
Prucksunand ,2001	Clinical trial in 45 peptic ulcers subjects	600 mg 5x daily	Peptic ulcers were absent in 12 patients (48%) after 4 weeks, in 18 patients after 8 weeks, and in 19 patients (76%) after 12 weeks. Symptoms decreased in 1-2 weeks.
Holt, 2005	Pilot study in 5 Crohn disease and 5 ulcerative colitis (UC) patients	550 mg 2x daily for 1 month, then 3x daily for 2nd month	All patients have significant symptom's improvement, decrease of inflammatory marker to normal limit.
Hanai, 2006	Randomized double-blind, multicenter trial to 89 UC patients	1000 mg 2x daily	Of 43 patients (2 violated the protocol) who received curcumin, 2 relapsed during 6 months of therapy (4.65%), compared to 8 of 39 patients (20.51%) in the placebo group.
Jurenka, 2009	Pilot study in 207 IBS subjects	72 and 144 mg in 4 weeks	Reduced symptoms in 53% patients in 72 mg group and 60% patients in 144 mg groups
Sintara, 2010	Pre-clinical trial to 36 gastritis patients	700 mg 3x daily for 4 weeks	Reduced symptoms in all patients

The suppression of pro-inflammatory mediators may explain symptoms relieve in patients treated by curcumin which found consistently in previous literatures. Beside treating the symptoms, curcumin also found restoring the histological structure of gaster (Sintara et al., 2010). Another mechanism of curcumin anti-inflammation effect is by downregulating Matrix metalloproteinases (MMPs) MMP-3 and MMP-9. MMPs are enzymes secreted by gastric cell which cause extracellular matrix degradation and inflammation of gastric epithelium, thus contribute to the pathogenesis of gastric ulcer and gastric cancer. MMP was induced by H. pylori (Kundu et al., 2011). An in vitro study by Kundu et al. (2011) showed secretion of MMP-3 and -9 was inhibited 90% by 60µg curcumin, 50% by triple therapy (TT), 50% by antibiotic, and 0% by omeprazole in SS1 strain infected gastric cell.

Histologically, in vivo study by Santos et al. (2015) showed that three of seven (42.8%) H.pylori-infected mouse presented moderate inflammation at Week 6, and mild inflammation was also observed in three out of seven mice (42.8%) at 18 weeks, while no inflammation of gastric mucosa was observed in the curcumin-treated mice with 500mg/kg dose 2 weeks after infection, at either 6 or 18 weeks post-infection. This study was supported by De et al. (2009) which stated that curcumin can effectively restore inflammation in mouse's gastric pit cells. A group of H. pylori-infected mice were orally fed with 25 mg/kg curcumin for 7 days consecutively after 2 weeks being infected, then the histology being analyzed. Curcumin group shows similar histological appearance with healthy mice and different appearance with infected mice.

Anti-Carcinogenic Effect of Curcumin

Anti-inflammatory mechanisms implicated in the anti-carcinogenic potential of curcumin includes: (1) inhibition of NF-κB and COX-2 (increased COX-2 level is associated with many types of cancer); (2) inhibition of arachidonic acid metabolism via lipoxygenase and scavenging of free radicals generated in this pathway; (3) decreased expression of inflammatory cytokines e.g., IL-1β, IL-6, and TNF-α, resulting in inhibition cancer cells growth; and (4) down regulation of enzymes for instance protein kinase C that mediate inflammation and tumor-cell proliferation. Curcumin has the potential to decrease matrix metalo-protease activity which is thought to be a prognostic marker of neoplasm (Kumar et al., 2012).Curcumin also block cancer promotion by phorbol esters and other experimental agents in animals, and can interfere with angiogenesis and metastasis (Kidd, 2009).Curcumin's induction of apoptosis in cancer cells by a variety of mechanisms, as well as its inhibition of DNA topoisomerase II at micromolar concentrations, hints at its potential for chemotherapeutic activity in the treatment of cancer (Martin-Cordero et al., 2003).

Anti-Oxidant Effect of Curcumin

Curcumin is characterized by its high antioxidant activity, which is comparable to vitamin C and ten times higher than the activity of the vitamin E. Study shows the antioxidant action of curcumin results in an increase of cellular resistance to oxidative damage for at least 18 hours. Curcumin is one of the few antioxidants that possess both a phenolic group and one diketonic in the same molecule. This explains why curcumin possesses the ability to interrupt the chain that transmits the oxidation of biological structures until the oxidant energy is sufficient (Sharma et al., 2005; Irving et al., 2011). Besides its direct anti-oxidant property, curcumin may function indirectly as anti-oxidant by inhibiting the activity of inflammatory enzymes (Weber et al., 2005).

Table 3. Anti-Carcinogenic Effect of Curcumin

Author	Study Design	Doses	Result
Martin-Corder, 2003	In vitro to the antineoplastic agent etoposide	50 microM	Curcumin inhibition of DNA topoisomerase II at micromolar concentrations
Cheng et al, 2001	Phase I clinical trial with 25 subjects premalignant lesions	500 mg capsules, 3 months	Histological improvements independent of dosage were observed in precancerous lesion in 7 of the 25 subjects.
Cruz-Correa, 2006	Phase I clinical trial: 5 patients with familial adenomatous polyps	480 mg 3x daily, 6 months	All five patients (100%) had a decrease in number and size of polyps from their baseline
Miris, 2010	In vitro in the acute promyelocytic human leukemia (HL-60) cells	10, 15, 20, and 40 μM	Apoptotic rates were determined as 1.2, 81.1, 84.5, and 88.6%, respectively. On the incubations with the concentrations of curcumin, caspase-3 expressions (+) were found to be elevated by 8.5, 18.6, 91.2, and 92.4%, respectively. It was shown that curcumin had significant cytotoxic and apoptotic effects on HL-60 cells.

Safety of Curcumin

Turmeric and its active component curcumin is approved as GRAS (generally regarded as safe) by the U.S. Food and Drug Administration (FDA) (Dadhaniya et al., 2011). Around the globe, turmeric is a well-known spice and have been used for centuries in Indian populations (Pandey and Rangarajan, 2012).

Early studies in both animals and humans have not found any toxic effects of turmeric (Lao et al., 2006). Oral doses up to 5g/kg body weight (BW) in rat model did not result in any significant toxicity and no side effects is reported in pre-clinical study by National Cancer Institute in rat, dogs, or monkeys with doses up to 3.5 g/kg BW for 3 months (Sarkar et al., 2016).

Several phase I clinical trials also found that curcumin is safe and well tolerated even at higher doses (12 g/d) (Anand et al., 2007). In a phase IIA clinical trial of curcumin in human for colorectal neoplasia at the dose 2 and 4 g once daily per oral, 59% and 63% of patients experienced gastrointestinal disturbances (diarrhea, distension, and gastroesophageal reflux disease), no subclinical liver toxicity detected by liver function tests and none requiring drug discontinuation (Carroll et al., 2011).

One study by Hsieh et al. (2014) found that curcumin induced activation on CYP3A4, thereby concluded it is not recommended for chronic patients using medications regularly, especially the drugs that are metabolized by CYP3A4: proton pump inhibitors (esomeprazole, omeprazole), antihyperlipidemic (atorvastatin, simvastatin), anti-HIV agents (indinavir, ritonavir), anti-infection agents (erythromycin, ketoconazole), immunosuppressants (cyclosporine, tacrolimus), anti-hypertensive agents (amlodipine, felodipine), anticonvulsants (carbamazepine),

anti-depressants (quetiapine, sertraline) and anti-cancer agents (paclitaxel, vinblastine) (Zhou, 2008). Patients with biliary tract obstruction should not take curcumin as it enhances biliary flow from the liver and high dose curcumin should not be taken on empty stomach to prevent gastric irritation (Gossard et al., 2013).

Weakness of Curcumin and Effort to Manage

Even with its promising safety profile and potentials, the major problem affecting curcumin efficacy is its bioavailability. Curcumin undergoes poor absorption, rapid and extensive metabolism, and rapid clearance from the body, resulting in poor bioavailability. Recent studies proposed novel approaches in improving bioavailability by using adjuvants and improving delivery systems (phospholipid complexes, liposomes, PLGA, nanoparticle).

Adjuvants is a compound that, when taken together with a certain drug, can increase or aid its effect. Piperine inhibits hepatic and intestinal glucoronidation and prevent cessation of curcumin effects. Curcumin (2 g/kg orally) and piperine (20 mg/kg orally) concomitant administration increases curcumin bioavailability by 20-fold more (Sharma et al., 2010). Other study reported that piperine also enhances intestinal absorption and prolong transit time in body tissues (Suresh and Srinivasan, 2010).

Curcumin phospholipid complexes administration in rats increase the half-life by 1.5 fold over free curcumin (Liu et al., 2006) and increase aqueous solubility by 3 fold with better efficacy (Maiti et al., 2007). Several researchers found that curcumin phospholipid complexes enhances curcumin bioavailability, pharmacokinetics, and hepato-protective property (Gupta et al., 2011).

Liposomes serve as an effective delivery system as they are able to solubilize hydrophobic compounds (Prasad et al., 2014). Liposome formulations as curcumin-loaded silica-coated flexible liposomes (CUR-SLs) and curcumin-loaded flexible liposomes (CUR-FLs) without silica-coatings showed 7.76- and 2.35-fold higher bioavailability, respectively. Higher bioavailability in CUR-SLs is due to its silica coating that improved flexible liposomes stability (Li et al., 2012).

Polylactic-co-glycolic acid (PLGA) and other formulation encapsulation of curcumin can increase its bioavailability and thereby improve its pharmacokinetics properties. Formulation of PLGA and PLGA-polyethylene glycol (PEG) (PLGA-PEG) nanoparticles containing curcumin showed increased mean half-life by 4 and 6 hours, C(max) by 2.9- and 7.4-fold, and bioavailability by 15.6- and 55.4-fold, respectively (Khalil et al., 2013). The molecular weight of PLGA has an impact on curcumin oral bioavailability. Higher molecular weight PLGA conjugated curcumin had 1.67- and 40-fold higher bioavailability than that of low molecular weight PLGA conjugated curcumin and conventional curcumin, respectively (Tsai et al., 2012).

Nanoparticle is used mainly to deliver substances with poor aqueous solubility such as curcumin, aiming for better dispersion and availability of curcumin (Basniwal et al., 2014; Shehzad et al., 2014). Nano-delivery system increased oral bioavailability by 9-fold compared to piperine adjuvant administration (Tsai et al., 2011). Administration of nanoemulsion curcumin (NEC) in mice, containing up to 20% curcumin (w/w) increase the area under the blood concentration-time curve (AUC) 24 hours and the C(max) by 10 and 40-fold, respectively, compared to curcumin (Zhongfa et al., 2012). Another nanoparticle called 'theracurmin' had 27-fold higher AUC than that

of curcumin powder when administrated via oral in healthy human volunteers at the dose 30 mg (Sasaki et al., 2011).

CONCLUSION

Curcumin is able to eradicate H. pylori in in-vitro study, prevent recurrence by inhibit H. pylori adherence to gastric cell, relieved symptoms of chronic gastritis and peptic ulcer by anti-inflammation effect, and prevent gastric cancer by anti-carcinogenic effect. Curcumin have potential as prevention and treatment of H. pylori associated disease and improvement is needed in delivery system. Since curcumin have anti-H. pylori effect, cheap, and easily available in developing countries like Indonesia, more studies with larger number of subjects are necessary. In addition, further study upon best way of curcumin preparation to increase its bioavailability is also needed.

REFERENCES

Ak, T., & Gülçin, I. (2008). Antioxidant and radical scavenging properties of curcumin. Chemico-Biological Interactions, 174(1), 27-37.

Aljamal, A. (2011). Effects of Turmeric in Peptic Ulcer and Helicobacter pylori. Plant Sciences Research, 3(3), 25-28.

Anand, P., Kunnumakkara, A. B., Newman, R. A., & Aggarwal, B. B. (2007). Bioavailability of curcumin: Problems and promises. Molecular Pharmaceutics, 4(6), 807-818.

Ayala, G., Escobedo-Hinojosa, W. I., de la Cruz-Herrera, C. F., & Romero, I. (2014). Exploring alternative treatments for Helicobacter pylori infection. World Journal of Gastroenterol, 20(6), 1450-1469.

Basniwal, R. K., Khosla, R., & Jain, N. (2014). Improving the anticancer activity of curcumin using nanocurcumin dispersion in water. Nutrition and Cancer, 66(6), 1015-1022.

Carroll, R. E., Benya, R. V., Turgeon, D. K., Vareed, S., Neuman, M., Rodriguez, L., Kakarala, M., Carpenter, P. M., McLaren, C., Meyskens, F. L., Jr, & Brenner, D. E. (2011). Phase IIA clinical trial of curcumin for the prevention of colorectal neoplasia. Cancer Prevention Research, 4(3), 354-364.

Cheng, A. L., Hsu, C. H., Lin, J. K., Hsu, M. M., Ho, Y. F., Shen, T. S., Ko, J. Y., Lin, J. T., Lin, B. R., Ming-Shiang, W., Yu, H. S., Jee, S. H., Chen, G. S., Chen, T. M., Chen, C. A., Lai, M. K., Pu, Y. S., Pan, M. H., Wang, Y. J., ... Hsieh, C. Y. (2001). Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Research, 21(4B), 2895-2900.

Cruz-Correa, M., Shoskes, D. A., Sanchez, P., Zhao, R., Hylind, L. M., Wexner, S. D., & Giardiello, F. M. (2006). Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. Clinical Gastroenterology and Hepatology, 4(8), 1035-1038.

Dadhaniya, P., Patel, C., Muchhara, J., Bhadja, N., Mathuria, N., Vachhani, K., & Soni, M. G. (2011). Safety assessment of a solid lipid curcumin particle preparation: Acute and subchronic toxicity studies. Food and Chemical Toxicology, 49(8), 1834-1842.

De, R., Kundu, P., & Swarnakar, S. (2009). Antimicrobial Activity of Curcumin against Helicobacter pylori Isolates from India and during Infections in Mice. Antimicrobial Agents and Chemotherapy, 53(4), 1592-1597.

Dikmen, M., Canturk, Z., Ozturk, Y., & Tunali, Y. (2010). Investigation of the apoptotic effect of curcumin in human leukemia HL-60 cells by using flow cytometry. Cancer Biotherapy and Radiopharmaceuticals, 25(6), 749-755.

Gossard, B., Fieldman, L., & Schmid, K. (2013). Life Extension Disease Prevention and Treatment (5th ed.). LE Publications.

Gupta, S. C., Prasad, S., Kim, J. H., Patchva, S., Webb, L. J., Priyadarsini, I. K., & Aggarwal, B. B. (2011). Multitargeting by curcumin as revealed by molecular interaction studies. Natural Product Reports, 28(12), 1937-1955.

Han, C., Zhang, J., Chen, L., Chen, K., Shen, X., & Jiang, H. (2007). Discovery of Helicobacter pylori shikimate kinase inhibitors: bioassay and molecular modeling. Bioorganic & Medicinal Chemistry, 15(2), 656-662.

Hanai, H., Iida, T., Takeuchi, K., Watanabe, F., Maruyama, Y., Andoh, A., Tsujikawa, T., et al. (2006). Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. Clinical Gastroenterology and Hepatology, 4(12), 1502-1506.

Holt, P. R., Katz, S., & Kirshoff, R. (2005). Curcumin therapy in inflammatory bowel disease: a pilot study. Digestive Diseases and Sciences, 50(11), 2191-2193.

Hsieh, Y. W., Huang, C. Y., Yang, S. Y., Peng, Y. H., Yu, C. P., Chao, P. D., & Hou, Y. C. (2014). Oral intake of curcumin markedly activated CYP 3A4: In vivo and ex vivo studies. Scientific Reports, 4, 6587.

Irving, G. R., Karmokar, A., Berry, D. P., Brown, K., & Steward, W. P. (2011). Curcumin: The potential for efficacy in gastrointestinal diseases. Best Practice & Research Clinical Gastroenterology, 25(4-5), 519-534.

Jurenka, J. S. (2009). Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Alternative Medicine Review, 14, 141–153.

Khalil, N. M., do Nascimento, T. C., Casa, D. M., Dalmolin, L. F., de Mattos, A. C., Hoss, I., Romano, M. A., & Mainardes, R. M. (2013). Pharmacokinetics of curcumin-loaded PLGA and PLGA-PEG blend nanoparticles after oral administration in rats. Colloids and Surfaces B: Biointerfaces, 101, 353-360.

Kidd, P. M. (2009). Bioavailability and activity of phytosome complexes from botanical polyphenols: the silymarin, curcumin, green tea, and grape seed extracts. Alternative Medicine Review, 14, 226–246.

Kidd, P. M. (2009). Bioavailability and activity of phytosome complexes from botanical polyphenols: The silymarin, curcumin, green tea, and grape seed extracts. Alternative Medicine Review, 14(3), 226-246.

Koosirirat, C., Linpisarn, S., Changsom, D., Chawansuntati, K., & Wipasa, J. (2010). Investigation of the anti-inflammatory effect of Curcuma longa in Helicobacter pylori-infected patients. International Immunopharmacology, 10(7), 815-820.

Kumar, D., Kumar, M., Saravanan, C., & Singh, S. K. (2012). Curcumin: a potential candidate for matrix metalloproteinase inhibitors. Expert Opinion on Therapeutic Targets, 16, 959–972.

Kumar, D., Kumar, M., Saravanan, C., & Singh, S. K. (2012). Curcumin: A potential candidate for matrix metalloproteinase inhibitors. Expert Opinion on Therapeutic Targets, 16(10), 959-972.

Kundu, P., De, R., Pal, I., Mukhopadhyay, A. K., Saha, D. R., & Swarnakar, S. (2011). Curcumin alleviates matrix metalloproteinase-3 and -9 activities during eradication of Helicobacter pylori infection in cultured cells and mice. PLoS One, 6, e16306.

Lao, C. D., Ruffin, M. T., 4th, Normolle, D., Heath, D. D., Murray, S. I., Bailey, J. M., Boggs, M. E., Crowell, J., Rock, C. L., & Brenner, D. E. (2006). Dose escalation of a curcuminoid formulation. BMC Complementary and Alternative Medicine, 6, 10.

Li, C., Zhang, Y., Su, T., Feng, L., Long, Y., & Chen, Z. (2012). Silica-coated flexible liposomes as a nanohybrid delivery system for enhanced oral bioavailability of curcumin. International Journal of Nanomedicine, 7, 5995-6002.

Liu, A., Lou, H., Zhao, L., & Fan, P. (2006). Validated LC/MS/MS assay for curcumin and tetrahydrocurcumin in rat plasma and application to pharmacokinetic study of phospholipid complex of curcumin. Journal of Pharmaceutical and Biomedical Analysis, 40(3), 720-727.

Mahady, G. B., Pendland, S. L., Yun, G., & Lu, Z. Z. (2002). Turmeric (Curcuma longa) and curcumin inhibit the growth of Helicobacter pylori, a group 1 carcinogen. Anticancer Research, 22(6C), 4179-4181.

Maiti, K., Mukherjee, K., Gantait, A., Saha, B. P., & Mukherjee, P. K. (2007). Curcumin-phospholipid complex: Preparation, therapeutic evaluation and pharmacokinetic study in rats. International Journal of Pharmaceutics, 330(1-2), 155-163.

Marcus, E. A., & Scott, D. R. (2016). Gastric Colonization by H. pylori. In N. Kim (Ed.), Helicobacter pylori (1st ed., pp. 23-31). Singapore: Springer.

Martin-Cordero, C., Lopez-Lazaro, M., Galvez, M., Ayuso, M. J., Toro, M. V., & Alarcon de la Lastra, C. (2003). Curcumin as a DNA topoisomerase II poison. Journal of Enzyme Inhibition and Medicinal Chemistry, 18(6), 505-509.

Morgan, D. R., & Crowe, S. E. (2016). Helicobacter pylori Infection. In Sleisenger and Fordtran's Gastrointestinal and Liver Disease (10th ed., pp. 857-861). Philadelphia, PA: Elsevier.

Nakano, M., Hirayama, T., Moss, J., & Yahiro, K. (2016). Helicobacter pylori VacA Exhibits Pleiotropic Actions in Host Cells. In H. Suzuki, R. Warren, & B. Marshall (Eds.), Helicobacter pylori (pp. 49-66). Springer Japan.

Nasri, H., Sahinfard, N., Rafieian, M., Rafieian, S., Shirzad, M., & Rafieian-Kopaei, M. (2014). Turmeric: A spice with multifunctional medicinal properties. Journal of HerbMed Pharmacology, 3, 5–8.

Pandey, M. K., & Rangarajan, S. (2012). PEGylated Curcumin: A Potent Drug Candidate. In J. Sasaki & M. Kichida (Eds.), Curcumin: Biosynthesis, Medicinal Uses and Health Benefits (pp. 155-175). Nova Science Publishers.

Pattiyathanee, P., et al. (2009). Effect of curcumin on Helicobacter pylori biofilm formation. African Journal of Biotechnology, 8(19), 5106-511.

Prasad, S., & Aggarwal, B. B. (2011). Turmeric, the Golden Spice: From Traditional Medicine to Modern Medicine. In I. F. F. Benzie & S. Wachtel-Galor (Eds.), Herbal Medicine: Biomolecular and Clinical Aspects (2nd ed., Chapter 13). Boca Raton (FL): CRC Press/Taylor & Francis. Available from: https://www.ncbi.nlm.nih.gov/books/NBK92752/

Prasad, S., Tyagi, A. K., & Aggarwal, B. B. (2014). Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: The golden pigment from golden spice. Cancer Research and Treatment, 46(1), 2-18.

Prucksunand, C., Indrasukhsri, B., Leethochawalit, M., & Hungspreugs, K. X. (2001). Phase II clinical trial on effect of the long turmeric (Curcuma longa Linn) on healing of peptic ulcer. Southeast Asian Journal of Tropical Medicine and Public Health, 32(1), 208-215.

Ravindran, P. N., Nirmal Babu, K., & Sivaraman, K. (2007). Turmeric. The golden spice of life. In Turmeric. The Genus Curcuma (pp. 1-14). Boca Raton, FL, USA: CRC Press.

Salih, B. A. (2009). Helicobacter pylori Infection in Developing Countries: The Burden for How Long? Saudi Journal of Gastroenterol, 15(3), 201-207.

Santos, A. M., Lopes, T., Oleastro, M., et al. (2015). Curcumin Inhibits Gastric Inflammation Induced by Helicobacter Pylori Infection in a Mouse Model. Nutrients, 7(1), 306-320.

Sarkar, A., De, R., & Mukhopadhyay, A. K. (2016). Curcumin as a potential therapeutic candidate for Helicobacter pylori associated diseases. World Journal of Gastroenterol, 22(9), 2736-2748.

Sarkar, A., De, R., & Mukhopadhyay, A. K. (2016). Curcumin as a potential therapeutic candidate for Helicobacter pylori associated diseases. World Journal of Gastroenterology, 22(9), 2736-2748.

Sasaki, H., Sunagawa, Y., Takahashi, K., Imaizumi, A., Fukuda, H., Hashimoto, T., Wada, H., Katanasaka, Y., Kakeya, H., Fujita, M., Hasegawa, K., & Morimoto, T. (2011). Innovative preparation of curcumin for improved oral bioavailability. Biological and Pharmaceutical Bulletin, 34(5), 660-665.

Senda, Y., & Hatakeyama, M. (2016). CagA. In H. Suzuki, R. Warren, & B. Marshall (Eds.), Helicobacter pylori (pp. 33-44). Springer Japan.

Sharma, R. A., Gescher, A. J., & Steward, W. P. (2005). Curcumin: The story so far. European Journal of Cancer, 41(13), 1955-1968.

Sharma, V., Nehru, B., Munshi, A., & Jyothy, A. (2010). Antioxidant potential of curcumin against oxidative insult induced by pentylenetetrazol in epileptic rats. Methods and Findings in Experimental and Clinical Pharmacology, 32(4), 227-232.

Shehzad, A., Ul-Islam, M., Wahid, F., & Lee, Y. S. (2014). Multifunctional polymeric nanocurcumin for cancer therapy. Journal of Nanoscience and Nanotechnology, 14(1), 803-814.

Shmuely, H., Domniz, N., & Yahav, J. (2016). Non-pharmacological treatment of Helicobacter pylori. World Journal of Gastroenterol Pharmacol Ther, 7(2), 171-178.

Sintara, K., Thong-Ngam, D., Patumraj, S., Klaikeaw, N., & Chatsuwan, T. (2010). Curcumin suppresses gastric NF-κB activation and macromolecular leakage in Helicobacter pylori-infected rats. World Journal of Gastroenterology, 16(32), 4039-4046.

Srivastava, A. K., Kumar, V., & Roy, B. K. (2015). Insights from the molecular docking of curcumin to the virulent factors of Helicobacter pylori. Bioinformation, 11(10), 447-453.

Suresh, D., & Srinivasan, K. (2010). Tissue distribution & elimination of capsaicin, piperine & curcumin following oral intake in rats. Indian Journal of Medical Research, 131, 682-691.

Testerman, T. L., & Morris, J. (2014). Beyond the stomach: An updated view of Helicobacter pylori pathogenesis, diagnosis, and treatment. World Journal of Gastroenterol, 20(36), 12781-12808.

Tsai, Y. M., Chang-Liao, W. L., Chien, C. F., Lin, L. C., & Tsai, T. H. (2012). Effects of polymer molecular weight on relative oral bioavailability of curcumin. International Journal of Nanomedicine, 7, 2957-2966.

Tsai, Y. M., Jan, W. C., Chien, C. F., Lee, W. C., Lin, L. C., & Tsai, T. H. (2011). Optimised nano-formulation on the bioavailability of hydrophobic polyphenol, curcumin, in freely-moving rats. Food Chemistry, 127(3), 918-925.

Weber, W. M., Hunsaker, L. A., Abcouwer, S. F., Deck, L. M., & Vander Jagt, D. L. (2005). Anti-oxidant activities of curcumin and related enones. Bioorganic & Medicinal Chemistry, 13(11), 3811-3820.

Wong, F., Rayner-Hartley, E., & Byrne, M. F. (2014). Extraintestinal manifestations of Helicobacter pylori: A concise review. World Journal of Gastroenterol, 20(34), 11950-11961.

Zhongfa, L., Chiu, M., Wang, J., Chen, W., Yen, W., Fan-Havard, P., Yee, L. D., & Chan, K. K. (2012). Enhancement of curcumin oral absorption and pharmacokinetics of curcuminoids and curcumin metabolites in mice. Cancer Chemotherapy and Pharmacology, 69(3), 679-689.

Zhou, S. F. (2008). Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. Current Drug Metabolism, 9(4), 310-322.