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Punica granatum is More Effective to Prevent Gastric Disorders Induced by Helicobacter Pylori or any Other Stimulator in Humans

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Abstract: *Helicobacter pylori* (*H. pylori*) is the bacterium responsible for many gastric disorders such as gastritis, gastric ulcer and gastric cancer. Half of the world's population is infected with *H. pylori*. Interestingly, the use of medical plants such as *Punica granatum (P. granatum)*, commonly known as pomegranate, are being increasingly used throughout the world because of their efficacy and low toxicity. Studies have reported the antibacterial, anti-inflammatory and anticancer activities of *P. granatum* by various mechanisms including anti-adhesive, regulation of proliferation, cell survival, motility, invasion, apoptosis and cell-cycle pathways, increase in JNK phosphorylation and caspase-3 enzyme activity, decrease Akt and mTOR activation as well as inhibitory effects on IL-1β and NF-kB. Therefore, it can be suggested that *P. granatum* may reduce gastric diseases by eradication of *H. pylori* and also, it may reduce gastric disease symptoms and inhibit the progression of these diseases by its valuable properties. Our hypothesis will be confirmed in the future by experimental investigations such as using *P. granatums* alone or in combination with other drugs to create an herbal medicine for the prevention of gastric disease development which is induced by *H. pylori*.

Key words: *Helicobacter pylori*, gastric disorders, *Punica granatum,* anti-adhesive, antibacterial, anti-inflammatory, anticancer

INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram-negative and spiral shaped bacterium which is present in half of the world's population (Kivi *et al*., 2005; Brown, 2000; Czinn, 2005). The incidence of *H. pylori* infection has been estimated to be approximately 80% in less developed countries and 20% in Western countries (Czinn, 2005). Even though 80% of those infected with the bacterium are asymptomatic, individuals who show symptoms, include inflammation of the stomach lining (gastritis) that may cause mild or serious reactions to the stomach's contents including stomachache, acid reflux, regurgitation, vomiting, belching, flatulence and nausea. If left untreated for a long time, *H. pylori* infections may result in several serious illnesses including, gastric ulcers and cancers of the esophagus and stomach (Gashi *et al*., 2011; Matysiak-Budnik and Megraud, 2006; Yeomans, 2011). Studies have shown the relationship between *H. pylori* virulence factors (such as vacA and cagA) and strength of gastric diseases (Shin *et al*., 2011; Angelini *et al*., 2004). Vacuolating cytotoxin encoded by vacA and cytotoxin-associated toxin encoded by the cagA gene play an important role among the various virulence factors of *H. pylori* (Karaman *et al*., 2011). Furthermore, antibiotic resistance of *H. pylori* is prevalent in the world (Chang *et al*., 2009; De Francesco *et al*., 2010). However the use of herbal medicines such as *P. granatum* because of its potential antibacterial effect and low adverse chemical drug reactions may be increased in many countries (Duman *et al*., 2009).

P. granatum can be divided into several parts including juice, seed, leaf, peal (pericarp), bark and flower which have potential pharmacologic properties such as anticancer and anti-inflammatory activities as well as interfering with cell proliferation, cell cycle, angiogenesis and invasion (Lansky and Newman, 2007).

P. granatum has been shown to have antibacterial effects (Duman *et al*., 2009) and can minimize the problem of antibiotic resistance of *H. pylori* by increasing the cell surface hydrophobicity of *H. pylori* strains (Voravuthikunchai *et al*., 2006).

Because of these beneficial points we hypothesize the role of *P. granatum* as a potential preventive herbal drug for gastric disease which may be caused by *H. pylori*.

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HYPOTHESIS

Potential clinical significance of *H. pylori* in gastric diseases such as gastritis, gastric ulcer and gastric cancer has been described in several studies (Gashi *et al*., 2011; Matysiak-Budnik and Megraud, 2006; Yeomans, 2011). Furthermore, antibacterial, anti-inflammatory and anticancer properties of *P. granatum* have also been shown in other studies (Duman *et al*., 2009; Lansky and Newman, 2007; Adams *et al*., 2006). The mechanism of anti-cancer and anti-inflammatory effects of *P. granatum* including suppression of inflammatory cell signaling (Adams *et al*., 2006) has been demonstrated in studies which have been touched upon earlier. Based on such information we hypothesize that *P. granatum* extract or its active components may be used clinically to eradicate *H. pylori* infection by their antibacterial and anti-adhesive activities which inhibit the attachment of *H. pylori* to gastric mucosa. In addition, the anti-inflammatory activity of *P. granatum* may be effective for modulating gastritis and gastric ulcer disorder. Gastritis may progress to gastric ulcer and gastric cancer. It also has anticancer effects as described previously and may have the potential to inhibit gastric cancer. Some clinical trials may be carried out to confirm our hypothesis in the future.

CONCLUSION

H. pylori is an important cause of gastritis, gastric ulcer and gastric cancer worldwide (Kivi *et al*., 2005; Brown, 2000; Czinn, 2005). Interestingly, *P. granatum* has been shown to have antibacterial, anti-inflammatory and anticancer activity by different mechanisms (Lansky and Newman, 2007; Adams *et al*., 2006; Khan, 2009; Khan *et al*., 2009). According to these properties *P. granatum* or its active components may has a protective role on gastritis, gastric ulcer and gastric cancer diseases which is induced by *H. pylori*. Aril isolated from *P. granatum* has been shown to have antibacterial properties against *Bacillus megaterium* DSM 32, *Pseudomonas aeruginosa* DSM 9027, *Staphylococcus aureus* Cowan 1, *Corynebacterium xerosis* UC 9165, *Escherichia coli* DM, *Enterococcus faecalis* A10, *Micrococcus luteus* LA 2971 and three fungi (*Kluvyeromyces marxianus* A230, *Rhodotorula rubra* MC12, *Candida albicans* ATCC 1023) (Duman *et al*., 2009). It has been shown that *P. granatum* has antiadhesive activity against *H. pylori* and can inhibit attachment of the *H. pylori* to gastric mucosa by altering the cell surface hydrophobicity of this bacterium, so it will possibly inhibit *H. pylori* infection by this mechanism (Voravuthikunchai *et al*., 2006).

P. granatum dose-dependently inhibits NF-kB-dependent reporter gene expression which regulates proliferation, inflammation, cell survival, invasion and motility in aggressive breast cancer therefore suggesting an anti-metastatic role for *P. granatum* aqueous extracts in lowering aggressive breast cancer species (Khan *et al*., 2009). It has also been shown to have inhibitory effects on interleukin-1β-induced activation of MKK-3, p38α-MAPK which is an important inflammatory pathway (Rasheed *et al*., 2010).

The methanol and ethyl acetate extracts at a concentration of 300 μg mL^{-1} have been shown to have significant anti-inflammatory activity in comparison with diclofenac which may be due to the presence of high phenolic content in these two extracts (Yoganandam *et al*., 2010).

Anticancer activities of *P. granatum* on colon (Khan, 2009), breast (Khan *et al*., 2009) and prostate (Lansky *et al*., 2005) cancer has been reported in literatures.

P. granatum inhibited the proliferation of mouse mammary cancer cell line (WA4) in a time and concentration-dependent manner via an arrest of cell cycle progression in the G0/G1 phase and induced apoptosis by increasing caspase-3 enzyme activity (Dai *et al*., 2010).

Highly potent pomegranate extract prepared from its skin and arils, minus seeds has been shown to have inhibitory activity on cell proliferation and induction of apoptosis by increasing JNK phosphorylation and by decreasing Akt and mTOR activation which are present in apoptosis pathways (Koyama *et al*., 2010).

Taken together, this evidence strongly suggests that *P. granatum* has a potential preventative effect on *H. pylori* induced gastric disease by eradicating *H. pylori* as well as showing anti-inflammatory and anticancer activity. It also reduces the progression of gastritis to gastric ulcer and gastric cancer. Furthermore, it may be used to reduce the remission period of gastric diseases. Our hypotheses will be supported with clinical trials in the future.

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