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Effect of Non Antibiotic Antimicrobial *Curcuma Longa* on *Helicobacter Pylori* Infection

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Review Article

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Abstract

Helicobacter pylori [*H. pylori*] induced gastric infection and inflammation, which is potentially carcinogenic, is common in India. Despite the availability of triple drug therapy, its failure is quite common due to the high cost factor, adverse drug reactions and emerging resistance to antibiotics. This necessitates the need for discovering new drugs for treating *H. pylori* infection. Curcumin [diferuloylmethane], an active ingredient of turmeric [*curcumin longa*], has been extensively studied and proved to be effective in eradicating *H. pylori* infection, correcting gastric mucosal damage and to prevent or regress gastric carcinogenesis. Curcumin has strong free radical scavenging and anti oxidant property. It bears anti inflammatory and antimicrobial potential against *H. pylori*. Mechanisms of its antimicrobial actions are l) The inhibition of shikimate pathway by inhibiting enzyme shikimate dehydrogenase [SDH] resulting in to the failure of synthesizing aromatic amino acids [AAA]. folates and ubiquinone. 2) By inhibiting the assembly dynamics of bacterial profilament FtsZ. Curcumin has anti tumerogenesis potential through it's anti inflammatory, antioxidant and free radical scavenging actions. Thus curcumin provides potential alternative or an adjunct therapy to treat *H. pylori* infection and prevent it's complications.

Keywords: Anti Inflammatory; *Curcuma Longa*; Helicobacter Pylori; Shikimate Dehydrogenas

Introduction

Helicobacter pylori [H. Pylori] is a gram negative microaerophilic bacteria which produces gastric mucosal inflammation and damage. More than half of the population in the world gets infected by *H. pylori* and its prevalence in the developing countries like India even exceeds 90%.In India the strains of these bacteria genetically differ from those of East Asia and the Western countries [1,2]. This infection is responsible for peptic ulcer and considered to be group 1 carcinogen by the international agency for research for cancer [3,4]. Several

putative virulence related factors contribute to its pathogenesis and enhance the risk of gastric adenocarcinoma [5]. Hence eradication of this infection from the gastric lumen of the infected individual is necessary to prevent its complications.

Existing triple therapy which constitutes two antibiotics and one proton pump inhibitor [PPI] provides significant relief from the disease process [6]. But sometimes this triple therapy may not be adequate as *H. pylori* is showing resistance to metronidazole and clarithromycin to the tune of 10-90% and 0-15% respectively [6-9]. This triple therapy has many undesirable adverse effects which results in to non compliance. The cost of these drugs is also a discouraging factor to complete the desired pharmacotherapy. Hence this necessitates an urgent need to search for appropriate newer therapy.

Curcumin [diferuloylmethane] which is an active ingredient of turmeric [*Curcuma longa*] has medicinal properties. Many studies have revealed it's antimicrobial properties against *H. Pylori* infection [10-13]. Various clinical trials have shown that curcumin has therapeutic potential for diseases like inflammatory bowel diseases, ulcerative colitis, familial adenomatous polyposis, colonic cancer, pancreatic malignancy, pancreatitis, hyperlipidemia, atherosclerosis, psoriasis and gastritis [14]. It has action against immunodeficiency virus type I and II [15] and also has a potential role in the treatment of Alzheimer disease [16].

Antimicrobial Potential of Curcumin

Curcumin longa has been traditionally used since long as an antimicrobial agent and also as an insect repellant [17]. Curcumin was found to inhibit growth of various bacteria like *Staphylococcus aureus*, *S.epidermidis, Klebsiella pneumoniae, E. coli, Bacillus subtilis* and others [18-21]. The compounds of curcumin studied for antibacterial activity were indium curcumin, diacetyl curcumin and diacetyl indium curcumin. Out of these indium curcumin was proved to have better antibacterial activity. It also inhibited the growth of *H. pylori* [22]. It has antiviral activity against human immunodeficiency virus type I and II [15]. It bears antifungal potential against commonly observed pathogenic fungi like *Candida albicans, Cryptococcus neoformans* [19] and parasites like *P.malaria* [23].

Various studies have proved the mechanisms for anti *H. pylori* activity of curcumin. These are the 1) inhibition of activation of nuclear factor kappa B [Nf-kB] and decreased release of cytokines like interleukin [IL]-6 and 8 [10-13]. 2) Inhibition of enzyme shikimate dehydrogenase [SDH] in the shikimate pathway, required for the synthesis of aromatic amino acids [AAA] and folates [22]. 3) Inhibition of matrix metalloproteinases like MMP 3 and 9 [24]. 4) Through the non Shikimate pathways like inhibition of bacterial cell proliferation by inhibiting the assembly dynamics of bacterial profilament FtsZ [25]. 5) Inhibition of inflammatory mediators like cytokines, chemokines, Toll like receptors [TLR] and TLR adaptor molecule MyD88 [26] and 6) the inhibition of the production of inducible nitric oxide synthase [iNOS], cyloxygenase -2 [COX-2], pro inflammatory cytokines IL-1,6,8 and 12, tumor necrosis factor alpha [TNF alpha], interferon gama , monocyte chemo attractant protein [MCP], migration inhibitory protein [MIP] and down regulation of mitogen activated and Janus kinases [27].

The role of shikimate pathway has been highlighted in the plants and microorganisms which play an important role in the synthesis of metabolites like AAA, folate and ubiquinone [28]. Enzyme SDH plays a crucial role in this pathway and forms a novel drug target for developing antimicrobial agent [29]. Curcumin is found to be noncompetitive inhibitor of SDH which prevents the synthesis of AAA and folate. The enzyme SDH encoded by aroE gene of *H. pylori* provides the vital information to treat *H. pylori* associated infection. Shikimate pathway does not exist in humans and animals. Hence the drug which targets SDH does not affect their metabolism [30].

Results of study done by Ronita De, et al. showed that all the selected 65 strains of *H. pylori* were potentially inhibited by curcumin. These strains were isolated from the patients who had gastric infection. Majority of these strains were resistant to metronidazole. Hence it can be concluded that curcumin acts through a different mechanism than that of metronidazole for the inhibition of *H. pylori*. This study revealed that there was complete eradication of *H. pylori* from the infected mouse stomach by curcumin. This eradication was irrespective of bacterial genotype. Histological studies concluded that curcumin effectively repaired the gastric tissue damage which suggests the anti inflammatory potential of curcumin [22].

Han et al demonstrated that curcumin inhibited the growth of *H. pylori* by acting on shikimate pathway which is essential for the synthesis of bacterial AAA. The nucleotide sequences of aroE genes encoding SDH form the target for the action of curcumin. Curcumin acts as a non competitive inhibitor of enzyme SDH [30].

All organisms require ubiquinone, Vit K and AAA like L-tyrosine, L-phenyl alanine and L-tryptophan for their physiological functions and survival. Micro organisms produce AAA by de novo synthesis through shikimate

pathway [31,32]. In bacteria this pathway exists in cytosol and is essential for the viability of the microorganisms. Deletion or mutation of any shikimate pathway genes resulted in to attenuated bacterial strains threatening their survival [33,34]. Shikimate pathway is necessary for the biosynthesis of AAA which involves seven enzymatic steps and converts primary metabolite Phosphoenol pyruvate and Erythrose 4-phosphate to chorismate. Chorismate synthase is the last enzyme of the AAA biosynthesis pathway. This enzyme catalyses the conversion of 5-Enolpyruvoyl shikimate 3- phosphate to chorismate. Chorismate acts as common precursor for the synthesis of AAA, Vit K, coenzyme Q and folate [30]. Various strains of *H. pylori* with genetic variations and polymorphism were uniformly inhibited by curcumin at different MICs. Strain to strain variations in the MIC of curcumin may be due to the differential uptake or efflux of curcumin by these bacteria [25].

Other possibility for the antimicrobial action of curcumin appears to be due to some additional mechanism than the shikimate pathway for the inhibition of growth of *H. pylori*. Study done by Rai, et al. suggested that the bacterial proliferation may be inhibited by curcumin through the inhibition of assembly dynamic of bacterial protofilament FtsZ and the prevention of it's polymerization to form Z ring at the mid cell which governs bacterial cell division. Assembly and the stability of protofilaments FtsZ have an important role in the bacterial cytokinesis and it forms an important antibacterial drug target. Curcumin has shown potent antibacterial activity against pathogenic bacteria like *S. aureus, S. epidermidis* and Enterococcus. Curcumin inhibited bacterial cytokinesis and induced filamentation in Bacillus subtilis. It also inhibited the formation of cytokinetic Z ring. Dynamics of FtsZ play an important role in the formation and functioning of Z ring. Curcumin inhibited the assembly of FtsZ and increased it's GTPase activity. Disturbances in GTPase activity of FtsZ assembly prove to be lethal for the bacteria. Thus curcumin inhibits the proliferation of bacteria by inhibiting assembly dynamics of FtsZ ring. This study results also showed that curcumin inhibited the growth of *H. pylori* irrespective of genetic makeup of the strain but in it's high MIC, which was attributed to it's poor bioavailability [25].

Antioxidant and Free Radical Scavenging Property of Curcumin

Curcumin is less stable in alkaline pH and the acidic pH enhances its stability there by it remains more stable in gastric pH which favors its action [35,36]. Antioxidant and free radical scavenging potential of curcumin can be attributed to its polyphenolic contents. It donates hydrogen ions and bears the potential to neutralize reactive oxygen species [ROS]. In the studies done by Sai Krishna Bora, curcumin exhibited the potential of scavenging of 1,1-diphenyl-2-picryl-hydrazil [DPPH], superoxide [O2], nitric oxide [NO] and hydrogen peroxide radicals in dose dependent manner. Curcumin inhibited erythrocyte membrane lipid peroxidation and scavenged the peroxy radicals which are known to induce hemolysis of RBCs [37].

Anti Inflammatory Potential of Curcumin

Curcumin longa has been used in ayurvedic medical practice since long for various inflammatory conditions. Curcumin is a highly pleiotropic molecule having the potential to interact with various targets and stages of the inflammation. It bears anti inflammatory property comparable to steroidal and non steroidal anti inflammatory drugs without having their adverse effects [38].

Anti inflammatory mechanism of curcumin is attributed to the inhibition of enzymes COX- 2 and lipooxygenase [LOX]. It also inhibits the production of pro inflammatory cytokines like IL-1,6,8 and 12,TNF alpha, interferon gama and migration inhibitory protein [MIP] and monocyte chemoattractant protein [MCP]. Inhibition of iNOS, COX- 2 and inflammatory cytokines is mediated through the suppression of activation of transcription factors like NF-kB and activating protein-1 [AP-1]. The production of cytokines was also inhibited by curcumin through down regulation of intercellular signaling proteins such as protein kinase- C which mediates inflammation and tumor cell proliferation. Supression of NF-kB activation and down regulation of iNOS and COX- 2 expression results in to the inhibition of inflammation and tumerogenesis [27].

Effect of Curcumin on *H.Pylori* Induced Tumerogenesis

Curcumin by its strong antioxidant, free radical scavenging and anti inflammatory effects prevents or regresses *H. pylori* induced tumerogenesis [11].

The anti inflammatory mechanisms of curcumin which contribute to its potential of anti carcinogenesis are –1) inhibition of NF-kB, decreased expression of inflammatory cytokines like TNF alpha, inhibition of AP- 1, IL-1,6 and 8 2) down regulation of COX- 2 and LOX pathway and enzyme protein kinase-C which has a role in the mediation of inflammation and proliferation of tumor cells. 3) Scavenging of free radicals and anti oxidant action[27]. 4) Decreased secretion of MMP- 3 and 9 which play an important role in gastric extracellular matrix [ECM]

degradation and carcinogenesis [39]. 5) NF-kB induces the expression of activation induced cytidine deaminase [AICD], associated with the carcinogenesis, by *H. pylori* infected gastric cells, which is suppressed by curcumin. 6) Curcumin along with NF-kB and MMPs, inhibits vascular endothelial growth factor [VEGF] and intra-cellular adhesion molecule-1 [ICAM-1] which are related to proliferation, adhesion and metastasis of the tumor [35]. 7) As observed in vivo and vitro studies curcumin has direct anti angiogenic activity, through the inhibition of growth factor receptors, growth factor and inflammatory mediators responsible for neo vascularisation [40].

In vitro and in vivo experimental studies in mouse and rat have showed good activity of curcumin against *H. pylori*. In clinical trials curcumin is found to be extremely safe and well tolerated even in high dose of 12 gms/day [41]. But Di Mario et al when used curcumin along with PPI in human infected with *H. pylori*, found that though eradication was not significant, gastric inflammation was considerably decreased [42]. Another study had similar results when curcumin was compared with the effect of triple therapy. Curcumin was found to be very effective in animal studies than in human. This observed low efficacy could be due to it's less solubility and bioavailability in human [43]. Hence attempts have been made to enhance the bioavailabilty of curcumin by various techniques like heat, pH and complexations with metal ions, polymers or serum. It was found that by the use of heat, solubility of curcumin was raised up to 12 fold [44]. Some new approaches to overcome low bioavailability of curcumin are, the use of adjuvants which can block it's metabolic pathways like glucorunidation [45], adopting effective delivery systems e.g. the use of phopholipid complexes [46], liposomes [47]. Micelles [48] and nano particles [49-51]. Nano curcumin has 22 fold increase in oral bioavailability than free curcumin in rat model [52].

It can be concluded that with the use of appropriate pharmaceutical preparations of curcumin one can achieve better results to eradicate *H. pylori* due to its antimicrobial, anti inflammatory, free radical scavenging and antioxidant properties. All these properties of curcumin contribute to prevent or regress gastric tumerogenesis. More and more clinical trials are needed to encourage the use of curcumin in the treatment of *H. pylori* which is safe even in high dosages.

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