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Urease: The Ultimate Therapeutic Target for Helicobacter *Pylori*

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Abstract

Gastric ulcer and carcinoma is quite frequent throughout the globe. The most prevalent causative agent of gastric ulcer and carcinoma is a gram-negative bacterium, *Helicobacter pylori* (*H. pylori*). The ineffectiveness and side effects of approved drugs as well as antibiotic resistance is a major problem in the treatment of H. pylori. *H. pylori* possess uncommon urease enzyme which catalyzes the hydrolysis of urea. Urease is necessary for colonization of *H. Pylori* in the gastric mucosa and is a potent immunogen that elicits a vigorous immune response. As urease acts as both colonization and virulence factor, new inhibitor of urease from plant sources with no/less adverse effect is vital to efface *H. pylori*.

Keywords: Helicobacter pylori; Urease; Virulence; Inhibitor; Antibiotic resistance

Introduction

H. pylori infection is common all over the world. Surviving in stringent conditions of low pH in human stomach is not feasible for most of the microorganisms. However, unlike other organisms' gram–negative (*H. pylori*) can "customize" its surrounding to make it comfortable for survival. And this survival tactic of the bacterium leads to chronic gastritis and plays important role in peptic ulcer disease, gastric carcinoma, and gastric lymphoma [1,2].

Consequences of *H. pylori* infection

Gastric cancer had been marked as a prominent cause of cancer related death with above 95% relation with infection by *H. Pylori* [1]. 70 to 90% of the residents of developing countries act as host of *H. pylori* on the other hand as in advanced countries, the predominance of infection is less [3]. Among infected individuals, approximately 10% develop severe gastric lesions such as peptic ulcer disease, 1%-3% progresses to Gastric carcinoma. Gastric carcinoma represents the second most frequent cancer in the world [4,5]. Gastric carcinogenesis is a multifactorial process and it results from interaction of the several factors that are related to diet, environment, genetic susceptibility, and *Helicobacter pylori* infection. Substantial epidemiological evidence exists for an increased risk of gastric carcinoma with *H. pylori* infection [6]. This carcinogenesis by *H. pylori* consists of two pathways. The direct pathway effects on gastric epithelial cells, by alteration of DNA and cellular proteins. And the indirect pathway works by initiating inflammation by innate and adaptive immunity [1]. Action of the bacterial associated protein cagA, its peptidoglycan, VacA toxin, sialic acid-binding adhesion (SabA), outer inflammatory protein (OipA), duodenal ulcer promoting gene (dupA) and the flagella altogether plays eminent roles in development of carcinogenesis [2]. Apart from these, a crucial role of gastritis is played by the unique feature of *H. pylori*; the urease enzyme [2].

Unique *H. Pylori* Urease in Action

Urea aminohydrolase also known as urease is a nickel-containing hexameric molecule. It catalyzes the hydrolysis of urea into ammonia and carbamic acid (Figure 1). Simultaneously carbamic acid decomposes into carbonic acid and a second ammonia molecule. Ammonium molecule being a weak base elevates the pH, hence making the surrounding for *H. pylori* comfortable to colonize in harsh acidic condition [7,8]. Significant amount of ammonium also promote cytotoxic chemical such as monochloramine which causes tissue damage. Moreover, the carbonic acid which is another product of the catalytic process diminishes the antimicrobial activity of peroxynitrite, a metabolite of nitric oxide. Therefore protecting the bacteria in every way possible [9]. All these features of the bacteria become evident due to the presence of its exclusive urease enzyme. This enzyme is composed of only two protein subunits UreA and UreB with ratio of 1: 1, unlike other ureolytic bacteria which consists of another UreC subunit. It is to be noted that bacterial ureases are activated by supplementary proteins UreD, UreE, UreF, UreG,

and UreH through a complex process [7,8]. Targeting these proteins as well as their respective genes can lead to an ideal formulation of drug aimed towards deregulation in colonization of *H. pylori* (Figure 1).

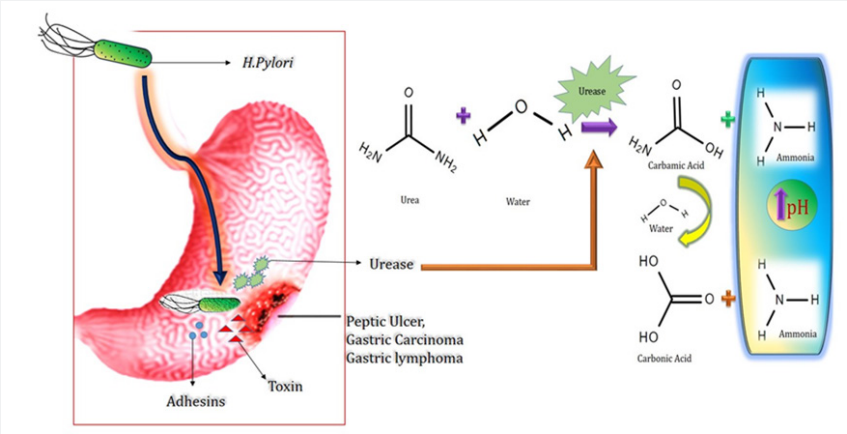

Figure 1: Pathogenesis of *H. pylori* and disease outcomes are mediated by a complex interplay between bacterial virulence factors and host interaction. After *H. pylori* enters the host stomach, four steps are critical for bacteria to establish successful colonization, persistent infection, and disease pathogenesis: Survival in the acidic stomach; movement toward epithelium cells by flagella-mediated motility; attachment to host cells by adhesins/receptors interaction; causing tissue damage, peptic ulcer, gastric carcinoma by toxin release. Urease and motility using flagella are essential factors for its colonization. Urease mediated pH changes through hydrolysis of urea promote *H. pylori* to colonize in the acidic stomach.

Current Therapeutics against *H. Pylori*

H. pylori is usually treated with triple therapy consisting of clarithromycin, amoxicillin and a proton pump inhibitor. Due to hike in antimicrobial resistance sequential, quadruple regimes had been introduced recently. However, newer quadruple combinations still result in a high frequency of side-effects and some studies report low cure rates [10]. The antibiotics administered, usually act on the bacterium, on the other hand inactivation of urease enzyme is not yet totally exploited. At present Palmatine, Bis (N-methylaminomethyl) phosphinic acid, and some derivatives of 3-Arylpropionylhydroxamic acid, pyrogallol and catechol were observed to suppress urease by acting on active site [11-14]. Acetohydroxamic acid (AHA), which is used to treating *H. pylori* by inhibiting urease enzyme, also exhibits severe side effects [15].

Urease: The Ultimate Target for *H. Pylori*

It is the enzyme 'urease' and its activity by which *H. pylori* colonize in the host. Therefore if the urease can be arrested, the bacteria would not have the advantage of inhibiting the acidic condition of the stomach. Though the available drugs work on various factors of urease as a whole, attention on its proteins UreA and UreB as well as UreD, UreE, UreF, UreG, and UreH, hence their respective genes could be focused on. Poor patient compliance with the available eradication therapy due to the development of side-effects may be associated with higher treatment failure rates and may favor the development of antibiotic-resistant strains of *H. pylori*. Therefore, *H. pylori* treatment still remains a challenge due to antibiotics resistance, side-effect and cost, mainly in developing countries [16-18].

Thus, developing alternative therapeutics with higher efficacy and lower side effects is a burning necessity. In this scenario, phytochemicals could be an effective alternative [19-22]. Till date, very few studies have been conducted on plant derived compounds for the identification of novel therapeutics against *H. pylori* [11,14]. If urease is widely explored to inhibit/ deactivate/ distort the enzyme through bioactive compounds from plant source(s), it can lead to a new hope to "un-root" *H. pylori* and prevent further infection.

Conflict of Interest

Authors declare no conflict of interest.

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