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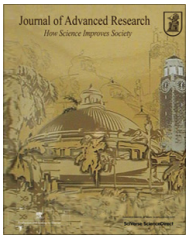

REVIEW

An overview on the potential of natural products as ureases inhibitors: A review☆

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ABSTRACT

Ureases, enzymes that catalyze urea hydrolysis, have received considerable attention for their impact on living organisms' health and life quality. On the one hand, the persistence of urease activity in human and animal cells can be the cause of some diseases and pathogen infections. On the other hand, food production can be negatively affected by ureases of soil microbiota that, in turn, lead to losses of nitrogenous nutrients in fields supplemented with urea as fertilizer. In this context, nature has proven to be a rich resource of natural products bearing a variety of scaffolds that decrease the ureolytic activity of ureases from different organisms. Therefore, this work compiles the state-of-the-art researches focused on the potential of plant natural products (present in extracts or as pure compounds) as urease inhibitors of clinical and/or agricultural interests. Emphasis is given to ureases of *Helicobacter pylori*, *Canavalia ensiformis* and soil microbiota although the active site of this class of hydrolases is conserved among living organisms.

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Introduction

Urease (EC 3.5.1.5) is a key enzyme for the global nitrogen cycle, occurring in plants, fungi and bacteria. This type of hydrolase speeds up by one-hundred-trillion-fold the urea hydrolysis rate to ammonia (NH_3) and carbon dioxide [1–3].

Since its discovery in plants [4], *Canavalia ensiformis* (Fabaceae) urease has been exhaustively investigated and became the milestone in Biochemistry science as the first enzyme to be crystallized [5] and also proven to be strictly dependent on nickel ions (Ni^{2+}) [6]. The dependence on nickel ions for catalytic activity is a unique feature of urease among hydrolytic enzymes [1,2]. The first three-dimensional structure of a urease was fully reported by Jabri and coworkers in 1995 from Crystallography studies performed with urease from *Klebsiella aerogenes* [7]. Later on, other structures were disclosed for ureases from *Bacillus pasteurii* [8], *Helicobacter pylori* [9] and most recently *C. ensiformis* [10]. Indeed, the elucidation of the urease structure from a legume was crucial to better understand the requirements for ureolytic activity of this class of enzymes in different organisms [10]. The great similarity of amino acid sequence among ureases from multiple origins [11] suggests a common ancestral for this enzyme. Ureases share a basic trimeric array with 1, 2 or 3 subunits that can fuse forming hexameric or dodecameric architecture. Each active site contains two Ni^{2+} ions apart from each other in 3.5–3.7 Å, bridged by oxygen atoms of a lysine carbamate residue and a hydroxide ion [3,12]. Plants and fungi ureases exhibit a single polypeptide chain while bacteria have two or three different subunits (α, β and γ) [1,13]. The incorporation of Ni^{2+} in protein structure is assisted by accessory proteins, believed to be urease-specific chaperones [11].

Ureases in the context of Helicobacter pylori

The increase of medium pH by the accumulation of NH_3 is a urease trait of tremendous medical importance [3]. Urine and/or gastrointestinal infections by ureolytic bacteria can cause health complications in humans and animals, which include kidney stone formation, pyelonephritis, hepatic encephalopathy and ultimately hepatic coma [3,12]. Therefore, major public health issues are related with *H. pylori*, gram-negative bacteria that are able to survive in an environment as acidic as that of the stomach (pH 2). As a consequence, *H. pylori* infection can induce gastric inflammation and increase the risk for the development of duodenal and gastric ulcers, gastric adenocarcinoma and gastric lymphoma [3,14]. About 50% of global population is committed by *H. pylori*. This bacteria species can persist in the stomach for the whole life of infected individuals without causing disease symptoms. The high prevalence of *H. pylori* in human population indicates that such microorganism has developed mechanisms for resistance against host defenses [14]. Urease enzyme in cytoplasm and/or bound to *H. pylori* surface is the main virulence factor of such human pathogen [15]. It is postulated that the lyses of some pathogen cells leads to the release of cytosolic ureases that bind to the surface of intact bacterial cells and cause the hydrolysis of urea present in human guts at a concentration of 3 mM. The NH_3 formed increases the medium pH, which creates a friendly environment for *H. pylori* survival [15,16].

During the past 20 years, the recommended first-line therapy for *H. pylori* eradication consisted of the combination of the antibiotics amoxicillin and clarithromycin with omeprazole, a proton pump cell inhibitor. However, the increase of *H. pylori* resistance to these antibiotics (particularly to clarithromycin) made this therapy a non-attractive option in recent years [2,17,18]. Indeed, other treatment strategies have emerged to fight *H. pylori* infection, which include the use of bismuth salts combined with a proton pump cell inhibitor or the combination of other classes of antibiotics (*e.g.* fluoroquinolones, aminopenicillins, tetracyclines, etc.) [2,18,19].