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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].

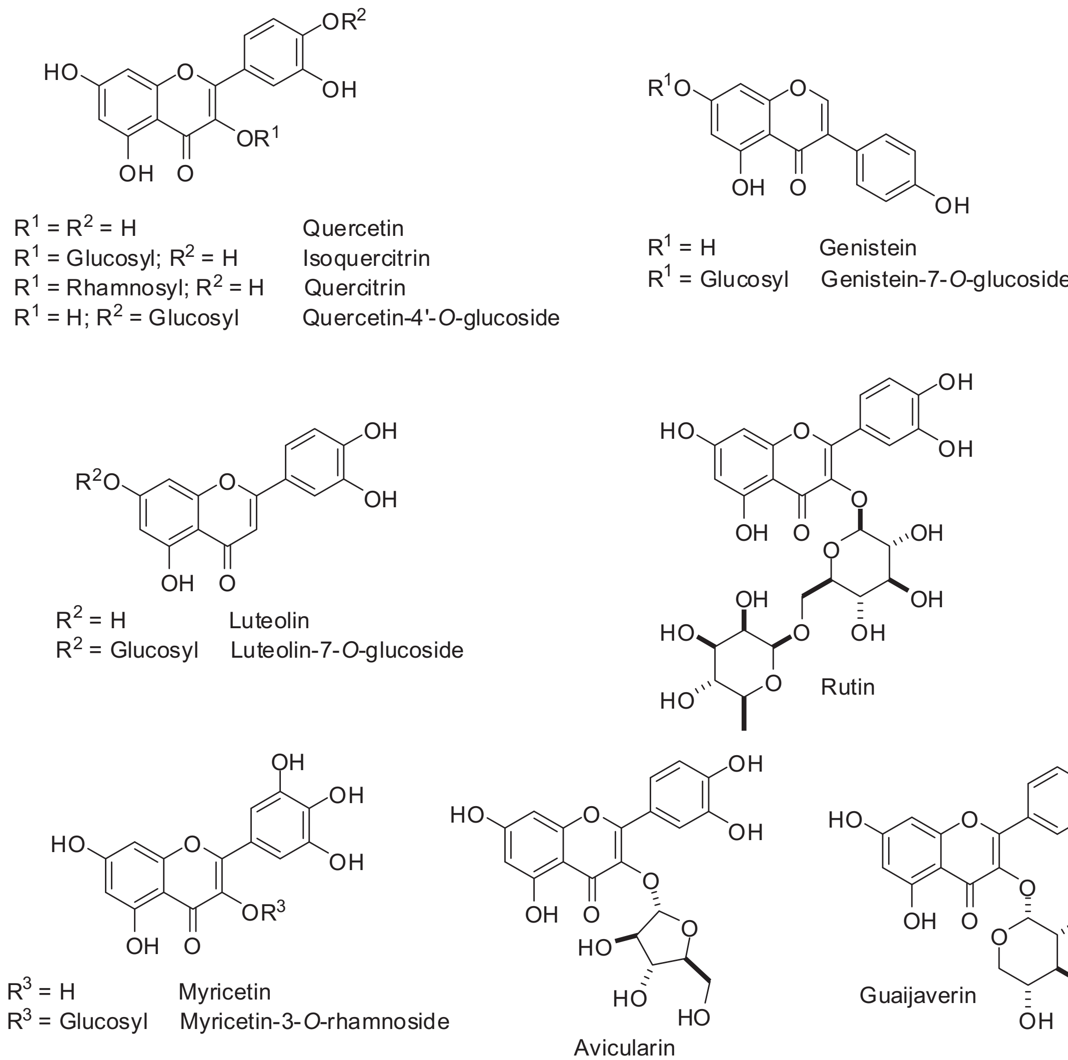


Fig. 1 Structure of flavonoids notable by the ability to inhibit ureases activity.

Additionally, urease inhibitors may be effective therapies for the treatment of diseases caused by urease-dependent pathogenic microorganisms. However, the commercially available urease inhibitors, such as phosphorodiamidates, hydroxamic acid derivatives and imidazoles are toxic and of low stability, features that prevent their clinical use [20,21]. Then, the search for novel urease inhibitors with improved stability and low toxicity is mandatory to improve life quality of human beings and animals.

Ureases in the context of agriculture

Urea is used as a nitrogen fertilizer in agriculture worldwide. This organic compound exhibits some advantages over other nitrogen fertilizer, namely, high N content (46%), low price, water solubility and easy management [22]. However, under field conditions, urea efficiency is markedly reduced due to nitrogen losses (over 50%) caused, among other factors, by NH_3 volatilization from the action of microorganisms ureases present in soil matrices [1,22,23].

The excessive emission of NH_3 to atmosphere gradually will cause an unbalance in nitrogen cycle, which can imply in disastrous long-term environmental consequences [24–27]. Most of the NH_3 generated from urea-based fertilizers may impact negatively natural ecosystems by inducing eutrophication processes and formation of nitrous oxide, a greenhouse gas [23]. On the other hand, once produced in the soil solution, NH_3 is converted to ammonium ion (NH_4^+) that, in turn, can undergo nitrification by the action of *Nitrosomona* and/or *Nitrobacter* species, yielding nitrate (NO_3^-). The NO_3^- uptaken by plant root cells will contribute to the production of amino acids, nucleic acids and some secondary metabolites, while the remainder still in soil can easily be leached to aquifers, rivers and lakes. Aquatic environments enriched with NO_3^- may go to eutrophication, resulting in algae blooms, reduction of fish and animal populations and threat to human health [23,28].

There are current some alternatives to minimize nitrogen losses from urea fertilizers and improve its uptake by crops. Slow-release nitrogen fertilizers comprise agricultural inputs that consist on the fertilizer surface covered by hydrophobic chemicals to provide a physical barrier against water. This promotes the gradual release of urea to soil solution [29]. Another strategy is the use of nitrification inhibitors that are able to delay NH_4^+ oxidation by nitrifying bacteria, preventing NO_3^-

formation and nitrogen leaching from the soil [29]. Urease inhibitors are some of the most used approaches to overcome nitrogen losses in field, as they delay urea hydrolysis, increasing the chances of urea incorporation in soil by rain, irrigation or mechanical operations [22].

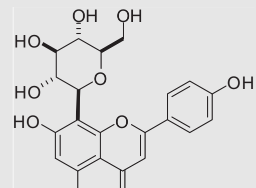
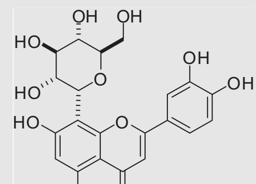
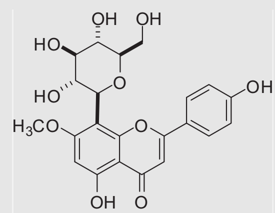
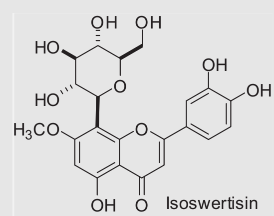
Among the known soil urease inhibitors, *N*-(butyl) thiophosphoric triamide (NBPT) is currently the most efficient compound. In the presence of soil microbiota, NBPT is converted to the respective *oxo*-analogue called *N*-(butyl) phosphoric triamide (*oxo*-NBPT) that exhibit high capacity of inhibiting urease [30]. Many other substances have been investigated with respect to the potential to inhibit urease activity in soil, but very few were found to be promising for further studies. In this sense, the great challenge is to find good candidates that are eco-friendly, nontoxic and of low toxicity to plants, chemically stable, efficient at low concentrations, compatible with urea and of competitive costs.

Where to start digging up for new urease inhibitors?

There is no doubt that nature is a vast source of natural products of that exhibit a plethora of biological activities. The diversity of chemical structure makes natural products very valuable to pharmaceutical industries and agricultural segments as well. Natural products from plants, in particular, have been a great source of inspiration for improving human and animal life quality as disease therapeutics and also for increasing food resources [31–36].

In this context, the investigation of the potential of plant-derived natural products as urease inhibitors can be valuable for the development of therapeutics for diseases associated with intense urease activity and improved nitrogen fertilizer formulations to increase food production. This work brings an overview on the state-of-the-art research performed with plant crude extracts and/or pure plant-derived natural products were used as ureases inhibitors of pharmacological and agricultural interest.

Table 1 Concentration (μM) of *C*-glycosylflavonoids necessary to inhibit the activity of *Canavalia ensiformis* urease by 50%.

Compounds	IC_{50} (μM)
 Vitexin	35
 Orientin	28
 Isoswertiajaponin	38
 Isoswertisin	43

Potential of plant extracts as urease inhibitors

Studies with focus on urease of clinical interest

The ethnomedicinal use of plants to treat chronic gastritis, ulcers and related gastroduodenal disorders, diseases that can be caused by *H. pylori*, is widely reported [37–39]. Studies carried out with several plant extracts allowed for the identification of urease inhibitors that may be useful for the control of *H. pylori* strains growth [40–43].

Alk(en)yl thiosulfinates (TS) are the main constituents of many foodstuffs, for example diallyl thiosulfinate (allicin) corresponds to around 70% of TS content in fresh aqueous garlic extract [44,45]. Commonly used as a flavoring, garlic (*Allium sativum*; Liliaceae) is recognized as an antimicrobial and anti-urease food due to allicin levels [44,46,47]. The urease inhibition by garlic extract is an irreversible time- and TS-concentration dependent; 18-min incubation of urease with garlic extract is sufficient to cause total loss of enzyme activity [44]. The inhibitory effect of TS-enriched garlic extract was attributed to the ability of TS to oxidize the –SH group of a cysteine residue present in the enzyme active site [44].

Plant juices obtained from *A. sativum* (garlic), *Allium cepa* (yellow and white onions), *Allium porrum* (leek), *Brassica oleraceae* var. *capitata* (cabbage; Brassicaceae) and *Brassica oleraceae* var. *gemmifera* (Brussels sprouts) were also effective urease inhibitors [45]. It was found that the higher the TS content, the better the juice was concerning the inhibition of ureolytic activity of urease. Thus, the best inhibitory effects were achieved when garlic juice was used, followed by the employment of Brussels sprouts one. With exception of cabbage juice, all foodstuffs juice tested lost the effect after heating at 95 °C [45]. Therefore, authors recommend the ingestion of raw garlic, onion, cabbage and Brussels sprout so that the urease inhibitory properties can be preserved and still work in the treatment of *H. pylori* infection [45]. The *in vitro* anti-*H. pylori* activity of methanolic leaf extracts (50 mg/mL) of *Allium ascalonicum* (Liliaceae) was found to be due to the ability of

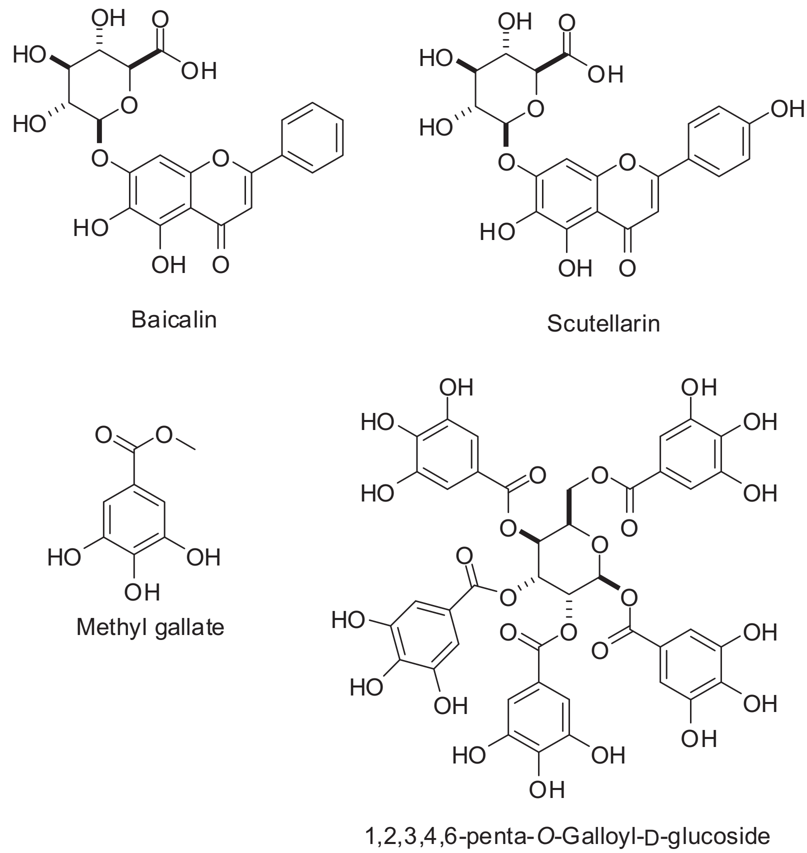


Fig. 2 Structures of polyphenols with remarkable inhibitory effect on ureases.

such extract to decrease urease activity [48]. The methanolic extracts were determined to contain alkaloids, cardiac glycosides, saponins and traces of flavonoids.

The antibacterial effect of alcoholic extract or essential oil of *Cuminum cyminum* (cumin; Apiaceae) on *Klebsiella pneumonia* (Gram-negative bacteria) was shown to be as result of the inhibition of urease activity [49]. Based on active site similarities shared by ureases, chemical constituents of cumin could also be effective against *H. pylori*, a hypothesis that should be further investigated.

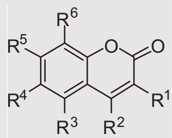
To investigate the scientific basis for the traditional use of plants for the treatment of ulcers, an *in vitro* study was conducted with shoot extracts of *Artemisia scoparia* (Asteraceae) [50]. The concentration of methanolic crude extract necessary to inhibit *C. ensiformis* urease activity by 50% (IC_{50}) was 4.1 mg/mL. Notably, the flavonoid fraction was shown to be even more effective as attested by the IC_{50} value of 2.1 mg/mL.

A screening performed with over one hundred traditional Iranian herbal medicines revealed that 37 extracts inhibited urease activity by at least 70% when employed at 10 mg/mL. Urease inhibition near to 100% was achieved using methanolic (50%) extracts of *Areca catechu* (Arecaceae; fruit extract), *Capsicum annuum* (Solanaceae; fruit extract), *Citrus aurantifolia* (Rutaceae; fruit extract), *Hibiscus gossypifolius* (Malvaceae; herb extract), *Hypericum perforatum* (Hypericaceae; herb extract), *Nymphea alba* (Nymphaeaceae; flower extract), *Papaver rhoeas* (Papaveraceae; flower extract), *Perlagonium graveolens* (Geraniaceae; flower extract), *Pistacia vera* (Anacardiaceae; rind extract), *Punica granatum* (Lythraceae; flower and rind extracts), *Quercus infectoria* (Fagaceae; rind extract), *Rheum ribes* (Polygonaceae; root extract), *Rosa centifolia* (Rosaceae; flower extract), *Sambucus ebulus* (Adoxaceae; fruit extract) and *Veratrum album* (Melanthiaceae; leaf extract). Among these plant species, *S. ebulus* and *R. ribes* were the most potent exhibiting IC_{50} values of 57 and 92 μg/mL, respectively [51]. Inhibition of urease activity was observed for methanolic (50%) extracts of *Camelia sinensis* (Theaceae; IC_{50} for leaf extract = 35 μg/mL), *C. aurantifolia* (Rutaceae; IC_{50} for fruit extract = 28 μg/mL), *Nasturtium officinale* (Brassicaceae; IC_{50} for leaf extract = 18 μg/mL), *P. granatum* (IC_{50} for flower extract = 30 μg/mL) and *Matricaria recutita* (Asteraceae; IC_{50} for flower extract = 37 μg/mL) [42]. Moreover, the methanolic (50%) extract of a commercial green tea containing 70.6% epigallocatechin derivatives, 9.9% gallocatechin derivatives, 4.1% (−)-epicatechin and 1.1% catechin exhibited an IC_{50} of 13 μM against *H. pylori* urease [40]. The ingestion of drinking water containing green tea extract in the range of 500–2000 ppm by *H. pylori*-challenged Mongolian gerbil animals for 6 weeks suppressed both gastritis and bacterial infection prevalence [40].

Glycyrrhiza glabra (Leguminosae; licorice) is a common Mediterranean herb known by the antioxidant properties and ability to inhibit urease activity. The ethyl acetate root extract (2.5 mg/mL) of such plant species inhibited *C. ensiformis* urease by 72% while methanolic root extract negatively affected urease activity by 64% [52].

Whole-plant acetone extracts of the traditional Pakistan herb *Fagonia arabica* (Zygophyllaceae), were reported to be more potent than the metronidazole (reference drug) against *H. pylori* [43].

Table 2 Concentration (μM) of some coumarins necessary to inhibit the activity of *Helicobacter pylori* urease by 50%.



Coumarin scaffold

Compound	R^1	R^2	R^3	R^4	R^5	R^6	IC_{50} (μM)
1	H	OH	H	H	H	H	58.9
2	H	CH_3	H	H	OH	OH	54.6
3	H	H	H	CH_3	OH	H	68.9
4	H	CH_3	H	H	OH	H	72.6
5	H	OH	H	CH_3	H	H	70.7
6	H	CH_3	H	OH	H	H	61.9
7	H	C_6H_5	H	H	OH	H	48.9
8	H	C_6H_5	OH	H	OH	H	53.9
9	H	C_6H_5	H	H	OH	OH	55.3
10	C_6H_5	OH	OH	H	OH	H	47.8

Aqueous extract of commercial powder of *Origanum vulgare* (oregano; Lamiaceae) and *Vaccinium macrocarpon* (cranberry; Ericaceae) were very efficient in controlling the growth and urease activity of *H. pylori* [41]. Such effect was attributed to the phenolic contents in both plant extracts. Methanolic (50%) extracts of *Eucalyptus grandis* (Myrtaceae) stem bark inhibited the activity of clinical isolated strains of *H. pylori* (UCH97001, UCH97009 and UCH98026) in a concentration-dependent manner (6.5–50.0 mg/mL) [53]. The authors attributed the anti-*H. pylori* effect of *E. grandis* extracts to the presence of tannins and triterpene saponins, based on other works published elsewhere [53 and cited Refs.]. The use of *Paeonia emodi* (Paeoniaceae) roots in Asia for medicinal purposes is ancient due to the inhibition of urease and α-chymotrypsin activities [54]. Ethanolic crude extracts of *P. emodi* shoots (12.5 μg/mL) inhibited *C. ensiformis* and *B. pasteurii* ureases by over 70% [54].

Two commercial samples of red wine with different resveratrol contents (1.3 or 10.5 μg/mL) were shown to inhibit ureases of *H. pylori* 26695, 1692/05 and 553A/02 strains [38]. Samples containing higher amounts of resveratrol were more potent although the effect of other constituents in the red wine studied cannot be ruled out.

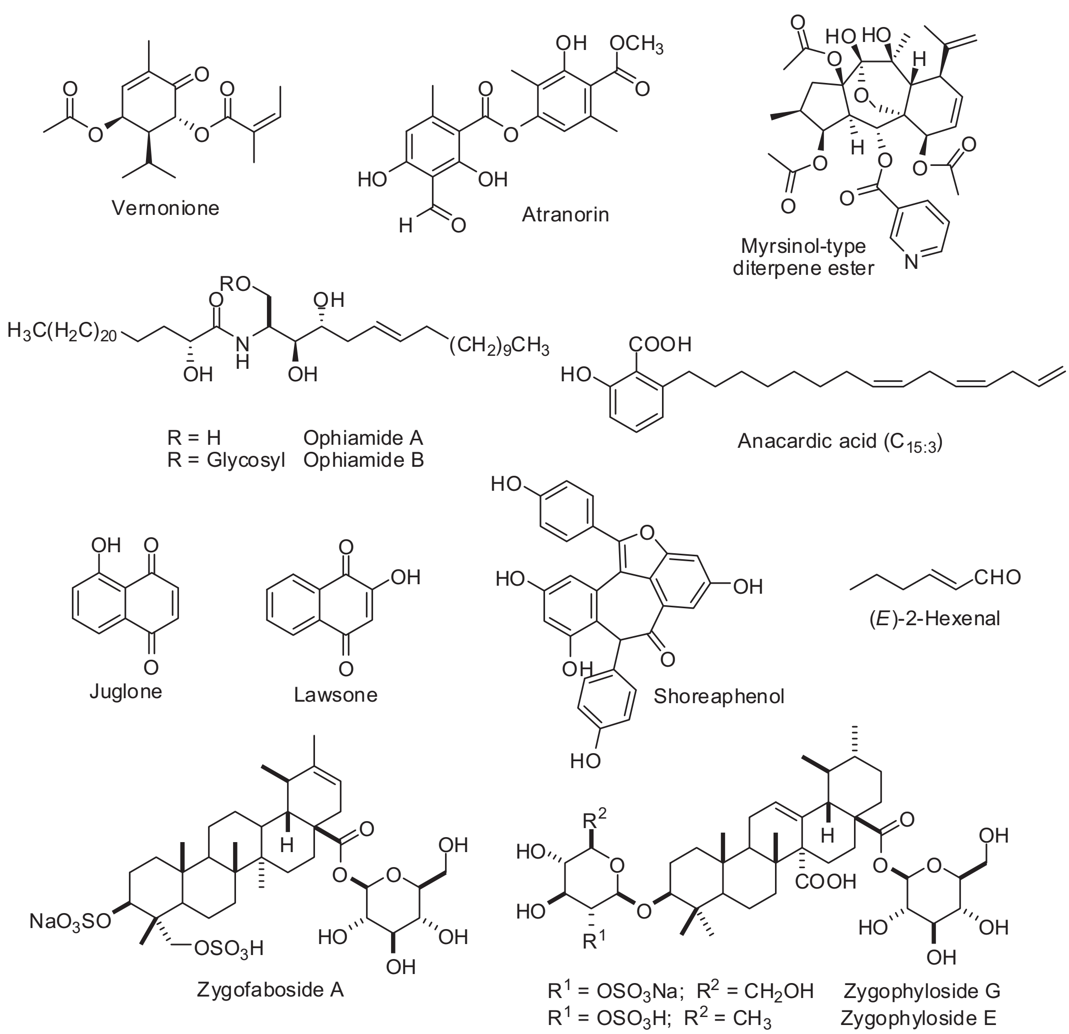


Fig. 3 Structure of natural products from different classes that exhibit activity against ureases.

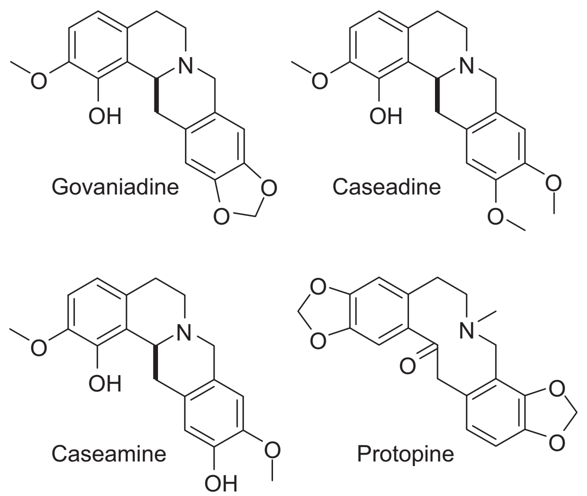


Fig. 4 Structure of plant alkaloids that exhibit activity against ureases.

Studies with focus on urease of agricultural interest

Polyphenolics-containing extracts obtained from the bark of *Acacia decurrens* (green wattle; Fabaceae) or seed coat of *Terminalia chebula* (inknut; Combretaceae) inhibited both pure urease (urease tablets-BDH) and soil ureases to the same extent that did mercuric chloride and catechol, known urease inhibitors [55]. Indeed, NH_3 volatilization from soil surface was decreased upon soil fertilization with urea–polyphenol mixtures. These results highlight the potential of tannin-like polyphenols from green wattle and inknut as potent urease inhibitors [55]. Interestingly, addition of *C. sinensis* (black tea) waste to soil surface (50 g/kg soil) right before urease activity tests substantially affected enzyme activity [55].

Seed kernel powder of *Azadirachta indica* (neem; Meliaceae) was demonstrated to decrease the rate of urea hydrolysis in acidic soils, contributing to urea incorporation into soil to be hydrolyzed in the rhizosphere and then provide nitrogen for uptake by plant roots [56].

Another study has used several extracts from four plant species native to Mediterranean zone of Chile [57]. Ethanolic extracts from the bark of *Acacia caven* (Fabaceae) and *Pinus radiate* (Pinaceae) inhibited urease activity in soil as a result of phenolic contents in a concentration dependent manner. No direct correlation could be made with respect to the condensed tannins present in both plant species extracts [57].

Overall, the bodies of evidence about the inhibitory action of various plant extracts on urease of clinical and agricultural interest provide subsidies to further investigate which constituents mostly contribute for their biological profiles.

Isolated plant natural products as urease inhibitors

Polyphenols, specially flavonoids, have been pointed out as notable *H. pylori* urease inhibitors [58–60]. Therefore, genistein, an isoflavone widely produced by plants of Fabaceae family, was found to inhibit *H. pylori* urease by 50% when used at 430 μg/mL while its 7-*O*-glucoside derivative exhibited no effect on the enzyme activity (Fig. 1) [58].

The therapeutic potential of *Lonicera japonica* (Caprifoliaceae) against *H. pylori* is well known [61]. A pool of flavonoids extracted from flowers of this plant exhibited an IC_{50} value of 946 μM on *H. pylori* urease [62]. By testing pure compounds, the flavonols quercetin, rutin, myricetin and myricitrin and the flavones luteolin and luteolin 7-*O*-glucoside were found the most potent against *H. pylori* urease, presenting IC_{50} values of 11.2 μM, 67.6 μM, 77.2 μM, 98.7 μM, 35.5 μM, and 55.8 μM, respectively [62]. Quercetin-4′-*O*-D-glucoside (Fig. 1) isolated from *A. cepa* (Liliaceae) showed an IC_{50} of 190 μM against *C. ensiformis* urease [63]. Other, quercetin glucoderivatives (Fig. 1) isolated from *Psidium guajava* fruits (guava; Myrtaceae) negatively affected the activity of *C. ensiformis* urease, such as isoquercitrin (IC_{50} = 160 μM), quercitrin (IC_{50} = 200 μM), avicularin (IC_{50} = 140 μM) and guaijaverin (IC_{50} = 120 μM). The IC_{50} for quercetin aglycone toward *C. ensiformis* urease was determined to be 80 μM [63].

A study carried out with seven natural products isolated from a butanolic subfraction of the ethanolic extract of *Celtis africana* (Celtidaceae) revealed the remarkable antiureolitic property of four flavone *C*-glucosides with IC_{50} lower than 50 μM (Table 1) [64].

Baicalin (Fig. 2), a flavone glucuronide and main constituent of dried roots of *Scutellariae baicalensis* (Lamiaceae), was able to inhibit *C. ensiformis* urease (IC_{50} = 2.7 mM), exhibiting an inhibition constant (K_i) of 3.89×10^{-3} mM [65]. Another flavone *C*-glucuronide (scutellarin; Fig. 2) isolated from *Erigeron breviscapus* (Asteraceae) was shown to be twice as potent (IC_{50} = 1.4 mM) as baicalin with respect to the inhibition of *C. ensiformis* urease [66]. The inhibitory effect o scutellarin was attributed to its ability to bind the sulfhydryl group of L-cysteine residue present in the enzyme active site [66].

Methyl gallate and 1,2,3,4,6-penta-*O*-galloyl-D-glucoside (PGG) (Fig. 2), widely produced by *Paeonia lactiflora* (Paeoniaceae) roots, were tested as pure compounds against *H. pylori* urease [67]. It was observed that PGG (IC_{50} = 72 μM) is roughly as potent as the reference inhibitor acetohydroxamic acid. Methyl gallate presented an IC_{50} of 1.3 mM [67].

Coumarins are phenylpropanoid compounds produced by various plant families. Ten pure coumarins out of 24 tested by Jadhav and coworkers [68] against *H. pylori* urease were shown to be very promising enzyme inhibitors. The IC_{50} for such natural products were lower than 75 μM (Table 2).

Vernonione (Fig. 3), a terpene isolated from methanolic extracts of *Vernonia cinerascens* (Asteraceae) roots, is another example of plant natural product capable of inhibiting *C. ensiformis* urease (IC_{50} = 227.6 μM) [69]. Sulforaphane [$CH_3S(O)(CH_2)_4NCS$], an isothiocyanate derivative abundant in cruciferous vegetables, were proven to inactivate *H. pylori* urease by covalently binding to thiol group of one or more L-cysteine residues to form dithiocarbamates [70]. Atranorin (Fig. 3) was the most effective urease inhibitor out of the 21 natural products isolated from stem bark of *Stereospermum acuminatissimum* (Bignoniaceae) [71]. Atranorin (IC_{50} of 18.2 μM) was as potent as thiourea (IC_{50} = 21.0 μM), a known urease inhibitor [71]. A myrsinol-type diterpene ester purified from *Euphorbia decipiens* (Euphorbiaceae; whole plant) exhibited an IC_{50} of 81.4 μM toward *C. ensiformis* urease [72]. The novel sphingolipids named ophiamide A and ophiamide B (Fig. 3), isolated from methanolic extracts of *Heliotropium ophioglossum* (Boraginaceae), inhibited *C. ensiformis* urease activity with IC_{50} values of 23.1 μM and 12.6 μM, respectively [73].

Pure juglone and lawsone (Fig. 3), constitutional plant naphthoquinone isomers, were tested against *C. ensiformis* urease, in which it was found that only the former is active, exhibiting an IC_{50} value of 4.8 μM in 40-min reactions [74].

Six congeners of shoreaphenol purified from stem bark of *Hopea exalata* (Dipterocapaceae) were tested against *C. ensiformis* urease revealing that shoreaphenol (Fig. 3) was the only oligostilbenoid capable of inhibiting the enzyme activity (IC_{50} = 126.8 μM) [75].

The anti-*H. pylori* properties of anacardic acid ($C_{15:3}$) and (*E*)-2-hexenal (Fig. 3), both isolated from *Anacardium occidentale* (Anacardiaceae), was confirmed to be a result of urease inhibition [76]. Anacardic acid (IC_{50} = 125 μg/mL) and (*E*)-2-hexenal (IC_{50} = 50 μg/mL) were identified as competitive and non-competitive urease inhibitors, respectively [76].

The inhibitory effect on *C. ensiformis* urease of ursane-type sulfated saponin glycoderivatives was reported with zygofaboside A, zygophyloside E and zygophyloside G (Fig. 3) being able to inhibit in the range of 40–87% when used at 500 μM [77]. Such natural products were isolated from shoots of the plant species *Zygophyllum fabago* (Zygophyllaceae).

Example of alkaloids with expressive inhibitory effect on the ureolytic activity of *C. ensiformis* urease is also reported in the literature. Govaniadine, caseadine, caseamine and protopine (Fig. 4), all isolated from whole plant powder of *Corydalis govaniana* (Fumariaceae), presented IC_{50} values of 20.2 μM, 38.9 μM, 66.7 μM and 54.1 μM, respectively, thus having the potential to urease-associated physiological complications [78].

Concluding remarks

The body of evidence presented in this overview clearly demonstrates the great potential of plant secondary metabolites of different classes to negatively affect the activity of ureases. The use of this knowledge can contribute for the design of novel, safe and less costing urease inhibitors with the aim to improve human and animals life quality either by fighting urease-related diseases or by increasing the quality and food production. Although the environmental aspects were not the primary scope of this review, the use of urease inhibitors in agricultural practices can surely be valuable for the reduction of greenhouse gas emissions. Scientists engaged in the search for natural sources of urease inhibitors have some challenges to overcome, namely (i) plant-family-guided expansion of the number of explored extracts, (ii) identification and isolation of the major constituents of promising plant extracts, (iii) stablishment of structure–activity relationships accompanied by *in silico* (docking) studies, (iv) evaluation of the mechanism of action of the pure natural compounds and (v) production of the promising compounds in large scale when the availability is limited in nature.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with ethics requirements

This article does not contain any studies with human or animal subjects.

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