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Review Article

Holarrhena antidysenterica (Linn.) Wall. (Apocynaceae) – A Plant for Gastrointestinal Disorders

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Abstract

Because of lack of hygienic conditions of living and contaminated potable water system, the rural and urban slum people of Bangladesh suffer in large numbers from gastrointestinal disorders like diarrhea and dysentery (mostly caused by *Vibrio cholerae*, rotavirus, *Escherichia coli* and *Shigella*). More than a third of the 160 million people of the country earns below the poverty level income, defined as less than US$ 1 per day. Because of poverty, year round occurrences of gastrointestinal disorders cause the rural and urban poor to seek traditional medicinal help. *Holarrhena antidysenterica* (Linn.) Wall., belonging to the Apocynaceae family and known in English as bitter oleander, has been used for possibly thousands of years in the Indian sub-continent countries (like India and Bangladesh) as an effective plant against diarrhea and dysentery. The present review gives an account of ethnomedicinal uses of the plant and plant parts and attempts to justify the traditional use of the plant against diarrhea and dysentery based on scientific reports of the phytochemical constituents of the plant and reported pharmacological activities, as well as molecular docking studies between three constituents (conessine, holarrhenine, and kurchessine) of the plant and Capsid Protein VP6 of Group A rotavirus. The docking energies of the phytochemicals with Capsid Protein VP6 suggest that they can be effective inhibitors of rotavirus and therefore merit further studies as potential drugs against diarrhea and dysentery.

Keywords: *Diarrhea; Dysentery; Phytotherapy; Holarrhena antidysenterica; Bangladesh*

Abbreviations

FMP: Folk Medicinal Practitioner; FM: Folk Medicine; TMP: Tribal Medicinal Practitioner; TM: Tribal Medicine

Introduction

Bangladesh is yet to develop a proper system for supplying pathogen-free water for drinking and cooking even in urban areas. Virtually all rural people as well as the urban slum dwellers collect their cooking and drinking water from nearby water bodies like ponds, rivers and ditches. Unsafe disposal of feces is frequently followed [1], and the same water bodies may be used to defecate and to wash following defecation causing contamination of the water with pathogens. In turn, this unsafe disposal of feces gives rise to enteric diseases like diarrhea and dysentery.

Vibrio cholerae, rotavirus, *Escherichia coli* and *Shigella* (including ciprofloxacin-resistant) are among the various pathogens causing diarrhea and dysentery in Bangladesh [2-5]. Since the disorders are more among the rural and urban poor, there is a lack of treatment due to medical costs, which in turn can lead in particular to higher child mortality [6,7]. This factor causes the poorer segments of the population to seek remedies in traditional medicines, many of which are plant-based. Traditional medicines like as in Ayurvedic or Unani preparations have the advantage of being used for hundreds if not thousands of years. A number of Bangladeshi plants have been tested and found to be useful for treatment of enteric disorders [8-10]. Taken together, there is a strong case for more scientific studies on the indigenous plants, which may result in more affordable and efficacious medicines against enteric disorders like diarrhea and dysentery.

Holarrhena antidysenterica (Linn.) Wall., belonging to the Apocynaceae family and known in English as bitter oleander, has been used for possibly hundreds if not thousands of years in the Indian sub-continent countries (like India and Bangladesh) as an effective plant against diarrhea and dysentery. The plant is known locally as indrajol or kurchi. It is a small deciduous tree, which flowers from April to July and fruits from August to October. The plant is indigenous to India but is also grown in Bangladesh for medicinal uses. Besides the two established traditional medicinal systems in Bangladesh, namely Ayurveda and Unani, parts of the plant are used against enteric disorders in Bangladesh by folk medicinal practitioners (FMPs) in folk medicine (FM) and tribal medicinal practitioners (TMPs) in tribal medicine (TM) [11-13]. In Ayurveda, the plant is known as kutaja, and in the form of medications named Kutajarishta and Kutaj Ghanavati used against diarrhea and irritable bowel syndrome. The objective of this review will be to consider the ethnic uses of *H. antidysenterica* for enteric disorders along with relevant pharmacological reports and phytochemical constituents. For purposes of this review, several databases have been searched like PubMed, SCOPUS and Google Scholar.

Ethnomedicinal uses of the plant or plant parts

Although reported ethnomedicinal uses of the plant includes uses for treatment of diabetes and malaria [14,15], most reported ethnic uses of the plant or plant parts are against various enteric disorders. The bark of the plant is used against intestinal amoebiasis by various tribal people of Khammam district of Andhra Pradesh, India [16]. The Kurichia tribe of Wayanad district, Kerala, India, use stem and bark powder to treat stomach problems [17]. The bark is used by tribals of Hoshangabad, Madhya Pradesh, India, to treat dysentery [18]. The Pao tribals from Majhgawan Block of District Satna, Madhya Pradesh, India, use decoction of stem bark, which is orally administered twice a day to treat diarrhea [19].

The bark is used to treat dysentery by the inhabitants of the Garhwal Himalaya Region, India [20]. Bark extract is given during diarrhea and bark powder given as treatment for piles by tribals of Alirajpur District, Madhya Pradesh, India [21]. The Malayali tribals in Yelagiri Hills of Eastern Ghats, Tamilnadu, India, use decoction of root bark to get relief from dysentery [22]. The ethnic people of Kalahandi District, Odisha, India, uses pounded stem bark in water along with pounded stem bark in water of *Careya arborea* Roxb. to treat dysentery [23]. Thus ethnomedicinally, the plant appears to be in general use in various regions of Bangladesh and India against enteric disorders.

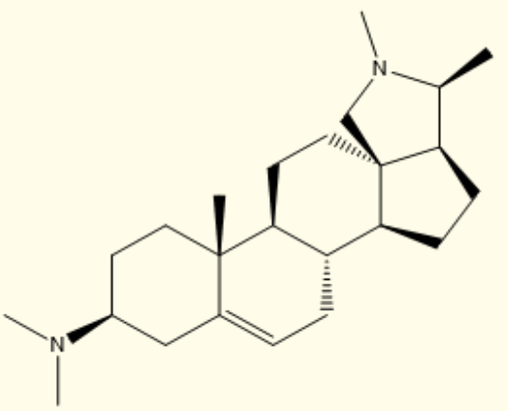
Pharmacological studies against enteric disorders

Hydro-ethanolic crude extract of seeds of the plant has been reported to give pyrilamine-sensitive spasmogenic effect. It was concluded that further gut stimulant and relaxant effects observed in the same study in different experiments were compatible with the traditional use of the plant in gut motility disorders like constipation, colic, and possibly diarrhea [24]. Aqueous extract of seeds has been reported to inhibit a number of diarrhea-causing microorganisms like *Escherichia coli*, *Salmonella*, and *Staphylococcus* species [25]. Antidiarrheal effect has been observed with ethanol extract of seeds in castor oil and *Escherichia coli*-induced diarrhea in Wistar albino rats [26]. Petroleum ether extract of the bark reportedly was effective against *E. coli*-induced diarrhea [27]. Water and ethanol extract of stem bark reportedly has been found to be active against *Staphylococcus aureus* [28].

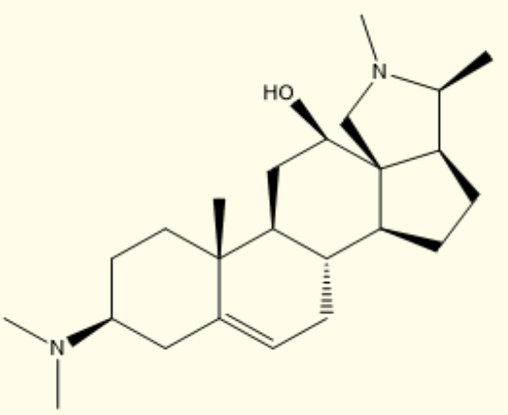
Phytochemicals

A total of 68 alkaloids have been reported from various parts of the plant [29]. Some of these alkaloids include conessine, isoconessine and conarrhimine from both stem bark and seeds; conessine, holarrhenine, kurchessine, holarrifine, kurchamide, kurcholessine, holarrhi-

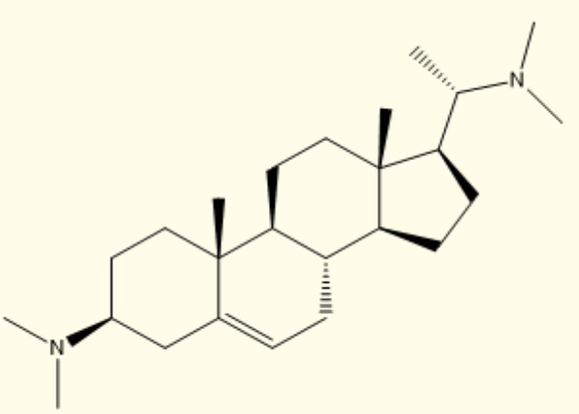
dine, kurchenine, conessidine, holadysenterine, lettocine, kurchimine, holacine, holafrine, conamine, conkurchine, pubadysone, puboestrene, holadiene, kurchinidine, kurchinine, pubescine, norholadiene, pubescimine, holonamine, and regholarrhenine A-F from stem bark; holantosine A-F, holarosine A, B, holarricine, kurchiphyllamine, kurchaline, and kurchiphylline from leaves; conimine and antidysentericine from seeds. The structures of conessine, holarrhenine, and kurchessine are shown in figure 1. They can be obtained from methanol extract of stem bark. There does not appear to be any reports on isolation of these three alkaloids from seeds.



Conessine



Holarrhenine



Kurchessine

Figure 1: *Structures of conessine, holarrhenine and kurchessine.*

Molecular docking studies

Molecular docking studies were carried out between three randomly chosen phytochemicals of the plant, namely conessine, holarrhenine, and kurchessine with Capsid Protein VP6 of Group A rotavirus. Group A rotavirus is the major pathogen causing gastroenteritis in animals and thus plays an important role in the epidemiology of diarrheal diseases [30]. Molecular docking study of Capsid Protein VP6 with conessine, holarrhenine, kurchessine was conducted with AutoDockVina software [31]. Before starting docking the phytochemicals against VP6, the grid box was positioned at the center of the protein structure. The best grid box, which covered the full protein structure (box size: 78.76 × 87.13 × 50.88 and box center: 29 × 12.13 × 14.12) was designed in which all the binding modes could be generated for the most suitable bindings. Finally after docking, the binding pose with the lowest binding energy was analyzed by PyMOL (PyMOL Molecular Graphics System version 1.7.4).

The comparative molecular docking profile of the three phytochemicals against Capsid Protein VP6 is presented in table 1. The VP6 of rotavirus, a major Capsid protein, plays an important role in the organization of the virion and acts as a physical adaptor between cell entry and genomic RNA packaging [32,33]. The lowest docking energy was found in kurchessine and that was -10.5 kcal/mol. An ideal ligand must have a low docking score [34]. Hence, our analyzed molecules can act as possible drug candidates, since through binding it can prevent entry of rotavirus into human cells and so mitigate diarrhea or dysentery caused by rotavirus. Graphic depictions of molecular docking of Capsid Protein VP6 with conessine, holarrhenine, and kurchessine are, respectively, shown in figures 2-4.

Phytochemical name	Docking Energy (kcal/mol)
Conessine	-10.3
Holarrhenine	-10.2
Kurchessine	-10.5

Table 1: *Comparative Molecular Docking Study between Structure of the Capsid Protein VP6 of Group A Rotavirus (PDB ID: 1qhd) and phytochemicals present in Holarrhena antidysenterica.*

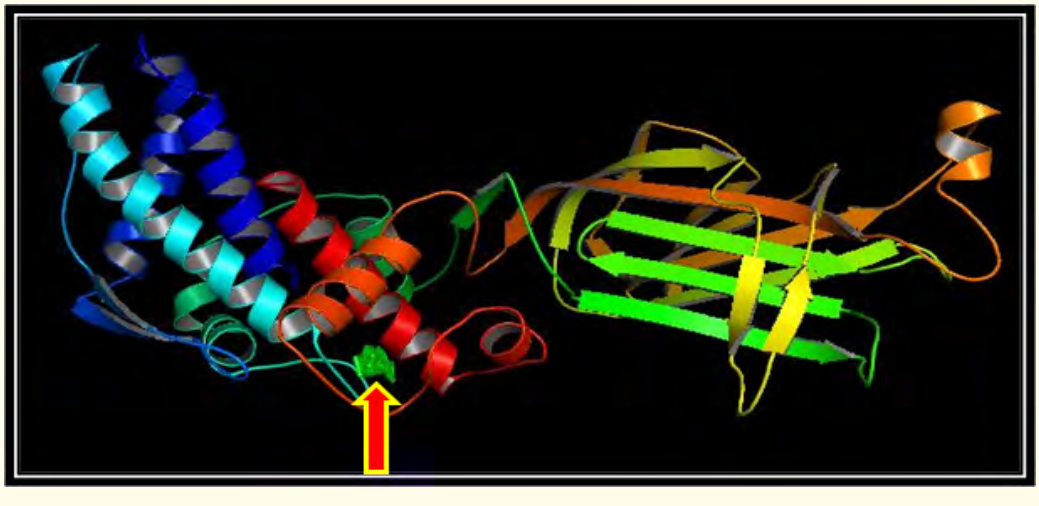


Figure 2: *Graphical Representation of Molecular Docking Study between Capsid Protein VP6 of Group A Rotavirus and conessine (pointed out with arrow).*

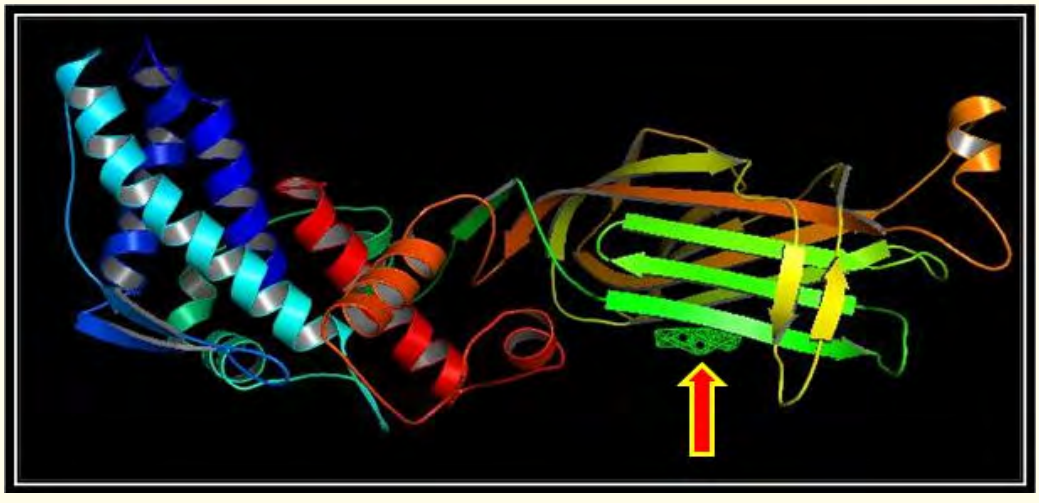


Figure 3: *Graphical Representation of Molecular Docking Study between Capsid Protein VP6 of Group A Rotavirus and holarrhenine (pointed out with arrow).*

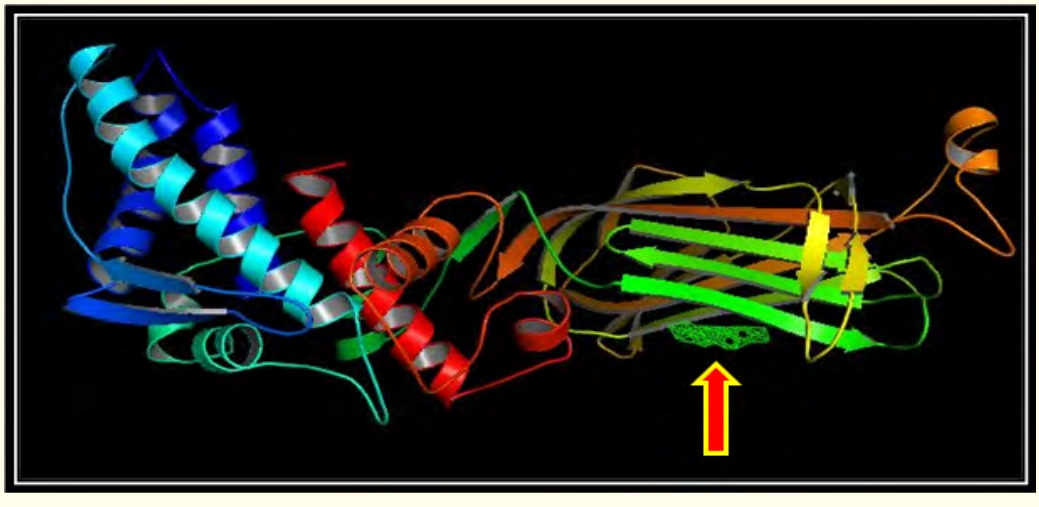


Figure 4: *Graphical Representation of Molecular Docking Study between Capsid Protein VP6 of Group A Rotavirus and kurchessine (pointed out with arrow).*

Conclusion

Ethnographic and pharmacological studies indicate that the plant *Holarrhena antidysenterica* may be an effective plant for treatment of diarrhea and dysentery and other enteric disorders. Molecular docking studies with three phytochemicals of the plant, namely conessine, holarrhenine, and kurchessine, show that they can bind to VP6 Capsid Protein of rotavirus and so possibly inhibiting its entry into human cells. It is to be noted that rotavirus is a major causative agent of diarrhea in Bangladesh [3]. The plant thus merits further scientific attention towards discovery of new drugs against enteric disorders.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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