

Cytoprotective and Anti-secretory Effects of Azadiradione Isolated from the Seeds of *Azadirachta indica* (neem) on Gastric Ulcers in Rat Models

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Azadirachta indica is well known medicinal plant mentioned in ancient herbal texts. It has been extensively used in Ayurvedic, Unani and Homoeopathic medicine and has become a luminary of modern medicine. As part of our drug discovery program we isolated azadiradione from the ethanolic extract of seeds of *A. indica* and evaluated for *in-vivo* antiulcer activity in cold restraint induced gastric ulcer model, aspirin induced gastric ulcer model, alcohol induced gastric ulcers model and pyloric ligation induced ulcer model. Azadiradione exhibited potent antiulcer activity through the inhibition of H⁺ K⁺-ATPase (proton pump) activity via its cytoprotective effect and also via its antisecretory effect. This combined effect has valuable potential in the future treatment of peptic ulceration. Copyright © 2015 John Wiley & Sons, Ltd.

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INTRODUCTION

Peptic ulcer disease (encompassing gastric ulcer and duodenal ulcer) affects a large portion of the world population. *Helicobacter pylori* infection is recognized as the leading cause of ulcer in the world, particularly in non developed countries, and other agents such as alcohol and non steroidal anti-inflammatory drugs gain importance in developed countries. Nowadays the main line of approach in the treatment of peptic ulceration is the eradication of *H. pylori* infection. In developed countries however, where the prevalence of *H. pylori* infection is lower, there is a significant incidence of *H. pylori* negative duodenal ulceration and also of recurrent ulceration after *H. pylori* eradication, in which case two main approaches for treatment remain. The first deals with reducing the production of gastric acid and the second with re-enforcing gastric mucosal protection (Hoogerwerf and Pasricha, 2001; Valle, 2005). There has been a rapid progress in the understanding of the pathogenesis of peptic ulcer and treatment. Modern approaches are proton pump inhibitors, histamine receptor blockers, drugs affecting the mucosal barrier and prostaglandin analogs (Manonmani *et al.*, 1995). Nonetheless, even with these treatments relapses do occur, and there still remains a need for other methods of treatment. This has been the basis for the development of new antiulcer drugs, which includes herbal drugs.

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Azadirachta indica A. juss (Meliaceae), commonly known as Neem is well known for its medicinal properties. The fruit is a smooth olive-like drupe which varies in shape from elongate oval to nearly roundish, and when ripe are 1.4–2.8 cm (0.55–1.1 in) by 1.0–1.5 cm (0.39–0.59 in). The fruit skin is thin, and the bitter-sweet pulp is yellowish-white and very fibrous. The white, hard inner shell of the fruit encloses one, rarely two or three, elongated seeds. *A. indica* has been used as traditional medicine for the treatment of various diseases. It has been largely used in ayurveda, unani and homeopathic medicine for various ailments. The Sanskrit name of the neem tree is 'Arishtha' meaning 'reliever of sickness' and hence is considered as 'Sarbaroganibarini'. The tree is still regarded as 'village dispensary' in India (Schmutterer, 1995; Singh *et al.*, 1996). The leaves, seed, roots and bark of the plant possess bitter principles in different concentrations (Oliver-Bever, 1986). The efficacy of *A. indica* extract against malarial (Iwu *et al.*, 1986) and bacterial and viral infections (Okpaniyi and Ezeukwu, 1981) had been reported. The plant also had insecticidal properties (Nwude, 1986; Oliver-Bever, 1986). Moreover, the antifertility (Prakash *et al.*, 1988; Bardhan *et al.*, 1991; Upadhyay *et al.*, 1993) and hypotensivity with minimal negative chronotropic (Thompson and Anderson, 1978) effects of *A. indica* have also been reported.

Neem oil, bark and leaf extracts have been therapeutically used as folk medicine in the treatment and control of leprosy, intestinal helminthiasis, respiratory disorders, constipation, blood morbidity, rheumatism, biliary infections, itching, ulcers and many more along with a general health promoter (Kirtikar and Basu,