

RESEARCH ARTICLE

Characterization of nimbidiol as a potent intestinal disaccharidase and glucoamylase inhibitor present in *Azadirachta indica* (neem) useful for the treatment of diabetes

Abhishek Mukherjee and Subhabrata Sengupta

Department of Biotechnology, Heritage Institute of Technology, Kolkata, India

Abstract

Azadirachta indica, used in antidiabetic herbal drugs, was reported to contain α -glucosidase inhibitor. Bioassay guided purification characterized the inhibitor as nimbidiol (a diterpenoid), present in root and stem-bark of the tree. Nimbidiol inhibited intestinal (mammalian) maltase-glucoamylase, sucrase-isomaltase, lactase, trehalase and fungal α -glucosidases. Nimbidiol showed a mixed competitive inhibition on intestinal carbohydrases. IC_{50} , K_i and K_i' (μM) were 1.35 ± 0.12 , 0.08 ± 0.01 , 0.25 ± 0.11 , respectively, for maltase-glucoamylase (maltotetraose as substrate). Nimbidiol was more potent inhibitor of isomaltase (IC_{50} $0.85 \pm 0.035 \mu M$), lactase (IC_{50} $20 \pm 1.33 \mu M$) and trehalase (IC_{50} $30 \pm 1.75 \mu M$) than acarbose, voglibose, salacinol, kotalanol and mangiferin. K_i and K_i' values (μM) for intestinal sucrase were 0.7 ± 0.12 and 1.44 ± 0.65 , respectively. Development of nimbidiol as an antidiabetic drug appears to be promising because of broad inhibition spectrum of intestinal glucosidases and easy synthesis of the molecule.

Keywords: glucosidase inhibitor, glucoamylase inhibitor, mixed competitive inhibition, root extract, intestinal lactase

Introduction

One of the most direct and beneficial types of therapy for non-insulin dependent diabetes is lowering of blood glucose level by delaying glucose absorption in blood after taking a carbohydrate meal. Inhibition or lowering of activities of some intestinal membrane bound carbohydrases like maltase-glucoamylase and sucrase-isomaltase by suitable inhibitors, slow-down absorption of glucose into the blood stream. During the last 40 years, a large number of glucosidase inhibitors have been isolated from plants and micro-organisms¹ and some of these were developed as drugs to control type II or non-insulin dependent diabetes². Different inhibitors isolated from plants and microorganisms include diverse types of compounds like acarbose, isoacarbose, cyclodextrins, acarviosine-glucose and hibiscus acid³⁻⁶. Although the list of α -glucosidase inhibitors isolated from various

biological sources are long, yet the bioactive molecules of traditional antidiabetic herbal drugs characterized are few in number. We recently reported that the medicinal plant *Tinospora cordifolia*, which according to old ayurveda system of medicine contains antidiabetic agents, has α -glucosidase inhibitory activity⁷. The inhibitor molecule present in the plant was purified and identified to be saponarin⁸. Neem (*Azadirachta indica*) tree is native to India and Burma; it grows in much of Southeast Asia and West Africa. Neem is a fast growing tropical evergreen tree and lives for long years. Neem has been used extensively in ayurvedic medicine for various purposes like: twigs for cleaning teeth, juice of leaves in healing skin disorders, as a tonic, as insect repellent etc. Various parts of the plant are used for the treatment of fever and infections. Hypoglycaemic effect of *Azadirachta indica* leaf extracts and seed oil was observed in normal and

Address for Correspondence: Subhabrata Sengupta, Department of Biotechnology, Heritage Institute of Technology, Anandapur, East Kolkata Township, Kolkata 700107, West Bengal, India. Tel: 91-33-24430445. Fax: 91-33-24430455. E-mail: profs_sengupta@yahoo.ca

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