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Alpha Mannosidase Inhibitory Effect of Some Iranian Plant Extracts

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Abstract: Alpha 1,2-mannosidase is a key enzyme in N-glycan processing in the endoplasmic reticulum (ER) and Golgi apparatus, have been one of enzyme targets in the development of anti cancer therapies. One hundred species of plants with known and unknown medicinal properties were collected and botanically identified. Methanolic and aqueous extracts prepared by maceration method. Enzyme inhibitory effects against a-mannosidase was determined spectrophotometrically at pH 4.5 and 25°C using 0.5 mM *p*-nitrophenyl- α-D-mannopyranoside as the substrate and 1 units mL^{-1} Jack bean alpha mannosidase in 0.02 M citrate buffer. Among 200 extracts, ten extracts showed more than 20% inhibitory activity on alpha mannosidase; *Punica grantum*, *Damask rose* and *Quercus infectoria* among them showed more than 40%. The kinetic study of the enzyme showed that the inhibition mechanism of the three more active extracts were non competitive. Under the control condition K_m value for the enzyme was 1.59 mmol and V_{max} was 0.039 mmol min^{-1} V_{max} in presence of 4 μg mL^{-1} *Punica grantum*, *Damask rose* and *Quercus infectoria* extracts were 0.020, 0.022 and 0.025 mmol min^{-1}, respectively. The data indicated that these plants are good candidates for therapeutic use and deserve to purify the active agents effective against α- mannosidase. Further *in vitro* and *in vivo* studies are needed to reveal the actual effectiveness of each of them.

Key words: Alpha mannosidase, *Punica grantum*, *Damask rose*, *Quercus infectoria*, inhibitor

INTRODUCTION

In recent years, glycobiology has received an enormous interest due to important roles that carbohydrates play in biological processes. Oligosaccharides and glycoconjugates (e.g., glycoproteins, proteglycans or glycolipids), present on the cellular surface, play key biological roles through molecular recognition events (Perez *et al*., 2008). Over the years, glycosidase inhibitors have received considerable attention in the field of chemical and medicinal research (De Melo *et al*., 2006). They have many potential therapeutic applications because the glycosidase enzyme-catalyzed hydrolysis of complex carbohydrates is a biologically widespread phenomenon in living systems. For example, inhibition of glycosidase enzymes that are involved in the biosynthesis of oligosaccharide chains of the N-linked glycoproteins in the endoplasmic reticulum (ER) and Golgi apparatus has key effects on maturation, transport and secretion of these glycoproteins. This strategy has potential for many therapeutic applications, such as in the treatment of cancer and viral infections (McDonald *et al*., 2006; Mohan and Pinto, 2007).

Many naturally occurring monocyclic and bicyclic amines such as 1-deoxynojirimycin, swainsonine and castanospermine are effective inhibitors of various glycosidase enzymes and have shown potential as therapeutic agents (Asano, 2003). For example, treatment with the indolizidine alkaloid swainsonine a naturally occurring golgi a-mannosidase II inhibitor, which have been isolated from the plant *Swainsona caneescens* (Dorling *et al*., 1980) has led to significant reduction of tumor mass in human patients with advanced malignancies and is a promising drug therapy for patients suffering from breast, liver, lung and other malignancies (Mohan and Pinto, 2007).

The present study was carried out to search for alpha mannosidase inhibitor especially in plants which give rise to a reliable, cheap and safe medicine in management and control of disease.

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MATERIALS AND METHODS

Plants: Different parts of plants, such as flowers, fruits, leaves, aerial parts, roots or seeds (Table 1), were collected during spring-summer 2007 from various states throughout Iran or purchased from the medicinal herbal markets in Kerman city and all of them were botanically identified. A voucher specimen was deposited at the herbarium of the Herbal Medicines Research Center Faculty of Pharmacy, Kerman University of Medical Sciences, Iran (Table 1).

Methanolic and aqueous extracts were prepared from 20 g of air-dried tissue of each plants pulverized by maceration in 200 mL methanol or distillated water at room temperature for 24 h. After filtration achieved methanolic extracts were air dried and aqueous extracts dried at 40°C in the incubator. The resulted dried materials either powdered or waxy shape compound were kept in dark vials at -20°C.

Enzyme assay: P-Nitrophenyl-α-D-mannopyranoside (PNPM) and Jack Bean α-mannosiadse was purchased from Sigma, USA.

The enzymatic activities of α-mannosidase were determined colorimetrically by monitoring the release of p-nitrophenol from the P-Nitrophenyl-α-D-mannopyranoside (Li *et al*., 2005). The assay mixtures for these experiments contained 5 μmol PNPM, enzyme

Table 1: Plants and their inhibitory effect on alpha mannosidase

Plants	Family	Used parts	Methanolic (%)	Aqueous (%)
Acantholepis orientalis	Asteraceae	Aerial parts	-3±0.1	4±0.2
Achillea eriophora	Asteraceae	Aerial parts	6±1.0	3±1.0
Achillea wilhelmsii	Asteraceae	Aerial parts	8±0.2	4±0.3
Acroptilon repens	Asteraceae	Aerial parts	-2±0.3	-2±0.1
Alhagi camelorum	Fabaceae	Aerial parts	1±3.0	19±0.3
Alpinia officinarum	Zingiberaceae	Rhizomes	8±3.0	11±4.0
Arctium lappa	Asteraceae	Roots	1±0.1	17±3.0
Artemisia santolina	Asteraceae	Aerial parts	1±0.3	0±0.0
Berberis integrimma	Berberidaceae	Aerial parts	-1±0.2	11±0.2
Berberis integrimma	Berberidaceae	Roots	3±0.4	1±0.4
Biebersteinia multifida	Bibersteiniaceae	Aerial parts and fruits	2±0.1	2±0.2
Brassica nigra	Brassicaeae	Seeds	-2±0.1	4±0.0
Bryonia aspera	Cucurbitaceae	Aerial parts	6±0.1	13±0.0
Bunium persicum	Apiaceae	Seeds	7±2.0	0±0.0
Camellia sinensis	Theaceae	Leaves	5±3.0	-1±1.0
Cannabis sativa	Cannabaceae	Seeds	8±0.6	1±3.0
Cardaria draba	Brassicaeae	Aerial parts andflowers	-2±3.0	1±0.0
Carthamus oxyacantha	Asteraceae	Aerial parts	0±0.0	3±0.2
Chaerophyllum khorassanicum	Apiaceae	Aerial parts	3±0.2	14±2.0
Cichorium intybus	Asteraceae	Roots	9±0.4	8±0.3
Ciunamomum zeylanicum	Lauraceae	Derm	21±3.0	28±2.0
Citrus anrantium	Rutaceae	Flowers	3±0.0	10±7.0
Citrus sineusis	Rutaceae	Fruits hull	2±1.0	3±0.2
Convolvulns pilosellaefolius	Concolvulaceae	Aerial parts	3±0.2	2±0.3
Cordia mixa	Boraginaceae	Fruits	3±0.3	5±0.3
Crocus sativa	Iridaceae	Leaves	2±0.5	0±0.0
Cuminum cyminum	Apiaceae	Seads	0±0.0	0±0.2
Ducrosia assadii	Apiaceae	Aerial parts	1±0.2	1±0.0
Echium amoenum	Boraginaceae	Flowers	8±0.3	7±0.4
Equisetum arveuse	Equisetaceae	Whole the plant	4±1.0	2±0.2
Eremostachys laciniata	Lamiaceae	Whole the plant	-2±0.0	2±0.5
Eremurus persicus	Liliaceae	Aerial parts	2±0.3	3±1.0
Eremurus persicus	Liliaceae	Flowers	-1±0.2	4±2.0
Eremurus persicus	Liliaceae	Fruits	-1±0.3	-2±0.9
Euphorbia hebecarpa	Euphorbiaceae	Aerial parts andflowers	-6±1.0	0±1.0
Ferula assa-foetida	Apiaceae	Aerial parts andflowers	7±1.0	14±3.0
Ferula oopoda	Apiaceae	Aerial parts	10±0.1	15±3.0
Ferulago angulata	Apiaceae	Aerial parts	-3±1.0	-2±2.0
Ficus carica	Moraceae	Leaves	4±0.3	4±0.5
Foeniculum vulgare	Apiaceae	Fruits	0±0.0	1±0.3
Francoeuria undulata	Asteraceae	Aerial parts	7±0.3	6±0.4
Fumaria parviflora	Fumariaceae	Aerial parts	3±0.2	3±0.3
Glycyrrhiza glabra	Fabaceae	Aerial parts	4±3.0	7±2.0
Gundelia tournefortii	Asteraceae	Aerial parts	1±0.0	0±0.0

Table 1: Continued

Plants	Family	Used parts	Methanolic (%)	Aqueous (%)
Heracleum persicum	Apiaceae	Fruits	0±0.0	6±0.2
Hibiscus gossypifolius	Malvaceae	Flowers	0±0.0	5±0.0
Hyoscyamus senecionis	Solanaceae	Aerial parts and flowers	2±0.2	4±0.4
Hypecoum pendulum	Fumariaceae	Aerial parts	0±0.5	5±0.6
Juglans regia	Juglandaceae	Fruits hull	5±0.6	4±0.2
Juglans regia	Juglandaceae	Leaves	6±0.0	13±4.0
Laurus nobilis	Lauraceae	Leaves	6±0.9	7±0.4
Lawsonia inermis	Lythraceae	Leaves	11±4.0	10±2.0
Levisticum officinale	Apiaceae	Roots	32±2.0	26±3.0
Linum usitatissimum	Liliaceae	Seeds	0±0.0	0±0.0
Malva sylvestris	Malvaceae	Flowers	0±0.4	2±2.0
Marrubium anisodon	Lamiaceae	Aerial parts	11±0.2	11±0.5
Mentha longifolia	Lamiaceae	Aerial parts	8±1.0	28±4.0
Mentha piperita	Lamiaceae	Leaves	0±0.0	4±2.0
Myrtus communis	Myrtaceae	Leaves	30±3.0	22±3.0
Nepeta crispa	Lamiaceae	Aerial parts	0±0.0	6±0.9
Nepeta saccharata	Lamiaceae	Whole the plant	1±0.0	5±0.7
Nigella sativa	Ranunculaceae	Seeds	4±0.0	-1±0.3
Onobrychis viciifolia	Fabaceae	Aerial parts	5±0.0	1±0.1
Otostegia persica	Lamiaceae	Aerial parts	0±0.0	11±0.1
Outreya carduiformis	Asteraceae	Aerial parts	0±0.0	0±0.0
Peganum harmala	Nitrariaceae	Aerial parts	8±0.0	4±0.0
Peucedanum aucheri	Apiaceae	Roots	5±0.0	10±0.2
Pimpinella anisum	Apiaceae	Seeds	0±0.0	2±0.1
Piper nigrum	Pipereaceae	Fruit	-4±0.3	3±0.3
Pistacia vera	Anacardiaceae	Fruits hull	2±4.0	1±2.0
Punica granatum	Lythraceae	Fruits hull	70±1.0	20±4.0
Quercus infectoria	Fagaceae	Galls	29±2.0	42±4.0
Rosa damascena	Rosaceae	Floret	57±1.0	26±3.0
Rosmarinus officinalis	Lamiaceae	Aerial parts	-2±2.0	8±5.0
Rubia tinctorium	Rubiaceae	Roots	4±2.0	5±0.1
Salvadora persica	Salvadoraceae	Wood	6±5.0	0±0.0
Salvia rhytidea	Lamiaceae	Whole the plant	2±0.0	8±0.0
Scrophularia frigida	Scorophulariaceae	Aerial parts	3±2.0	8±0.3
Sangnisorba minor.	Rosaceae	Aerial parts	-6±3.0	-2±8.0
Scrophularia striata	Scorophulariaceae	Aerial parts	8±0.0	5±0.9
Solanum dulcamara	Solanaceae	Fruits	6±0.0	7±0.0
Sonchus asper	Asteraceae	Aerial parts	1±0.2	6±0.2
Sophora alopecuroides	Fabaceae	Aerial parts	0±0.4	1±0.0
Stachys inflata	Lamiaceae	Aerial parts	1±0.3	1±0.3
Stachys lavandulifolia	Lamiaceae	Aerial parts	6±0.4	7±0.4
Terminalia chebulla	Combretaceae	Fruits	17±3.0	29±2.0
Tencrium polium	Lamiaceae	Aerial parts	0±0.3	0±0.0
Tencrium scordium	Lamiaceae	Aerial parts	4±0.9	1±0.0
Thymus serpyllum	Lamiaceae	Aerial parts	0±0.0	7±3.0
Trigonella foenum graecum	Fabaceae	Seeds	13±0.3	4±0.5
Urtica dioica	Urticacea	Aerial parts	0±0.2	0±0.3
Urtica ureus	Urticacea	Aerial parts	7±0.3	6±2.0
Vaccinium arcto-staphylus	Ericaceae	Fruits	32±3.0	13±4.0
Valeriana hispida	Valerinaceae	Rhizomes	2±0.9	3±0.4
Verbascum kermaneusis	Scrophulariaceae	Leaves	0±3.0	2±9.0
Verbascum songaricum	Scrophulariaceae	Aerial parts	1±0.0	3±0.9
Zataria multiflora	Lamiaceae	Aerial parts	7±0.0	3±3.0
Zhumeria majdae	Lamiaceae	Leaves	0±0.4	4±4.0
Zingiber officinale	Zingiberaceae	Rhizomes	2±3.0	-5±1.0
Ziziphus spina-christi	Rhamnaceae	Leaves	24±4.0	8±3.0

solution (0.1 unit), in 900 μL of sodium citrate buffer (50 mM), pH 4.5 in final volume was 1 mL. One hundred micrograms of each extract was dissolved in 20 μL of distillated water and added to the test mixture before adding the substrate. Blank sample contained whole test mixture and extract without enzyme solution.

The mixture was incubated for 30 min at 25°C, the reaction was terminated by the addition of 3 vol. of NH_4OH solution (0.05 M). The absorbance at 405 nm was determined by NOVA spectrophotometer (LKB, Sweden).

The inhibitory activity calculated using following formula (Bhandari *et al*., 2008):

$$\text{Inhibitory activity (\%)} = (OD_{control} - OD_{test}) / OD_{control} \times 100$$

Each test performed 3 times and mean value was used for inhibitory activity of the plants extract.

Kinetics of inhibition against alpha mannosidase by *Punica granatum, Rosa damascene and Quercus infectoria*: In order to examine the inhibition mode by methanolic extract of *Punica granatum, Rosa damascene* and aqueous extract of *Quercus infectoria*, alpha-mannosidase activity was measured with increasing concentrations of PNPM (0.125, 0.25, 0.5 and 1 mM) in the absence or presence one mentioned extract at different concentrations (0, 4 and 10 μg mL^{-1}). Optimal doses of extracts were determined based on the results from inhibitory activity assay as described above. Inhibition type for these extracts was determined by Lineweaver–Burk plot analysis of the data resulted from enzyme assays containing various concentrations of PNPM and extracts according to Michaelis-Menten kinetics (Kim *et al*., 2005; Shim *et al*., 2003).

RESULTS

Plants with alpha mannosidase inhibition properties: We found that methanolic extract *Punica granatum, Rosa damascene* and aqueous extract of *Quercus infectoria,* have 70, 57 and 42% inhibitory effect on alpha mannosidase, respectively.

Livisticum officinale, Vaccinium arcto-staphylus, Myrtus communis, Terminalia chebulla, Mentta longifolia, Ziziphus spina-christi and *Cinnamomum zeylanicum* extracts showed 20-30% inhibitory effect on alpha mannosidase. The rest of the plants extracts showed <10% or no inhibitory activity in this study. No extract was found to enhance the enzyme activity.

Kinetic analysis of alpha mannosidase inhibition: The inhibition mode of three strong active plants (*Punica granatum, Rosa damascene* and *Quercus infectoria*) against alpha-mannosidase was analyzed by Lineweaver–Burk plots. Double-reciprocal plots of enzyme kinetics demonstrated noncompetitive inhibition of alpha-mannosidase activity by these extracts (Fig. 1, 2, 3). The Km value of PNP-glycoside for Jack bean alpha-mannosidase was 1.59 mM and the Ki value of 4.08, 5.15 and 6.70 μg mL^{-1} for *Punica granatum, Rosa damascene* and *Quercus infectoria*, respectively. V_{max} in presence of 4 μg mL^{-1} of each of the above extracts were 0.020, 0.022 and 0.025 mmol min^{-1}, respectively (Fig. 1, 2, 3).

DISCUSSION

We found that methanolic extracts of *Punica granatum and Rosa damascene* and aqueous extract of *Quercus infectoria* have strong inhibitory effect on alpha mannosidase.

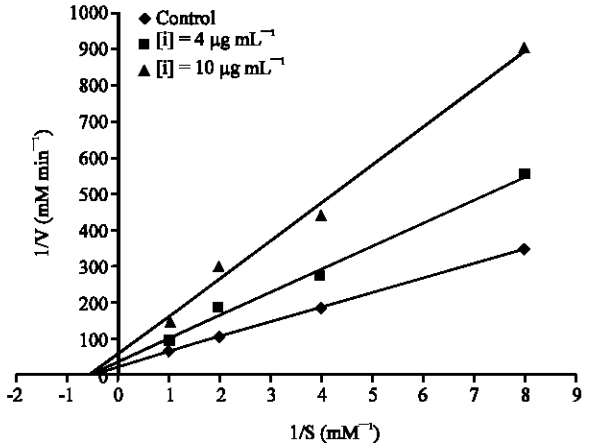

Fig. 1: Lineweaver-Burk plot of kinetic analysis of alpha-mannosidase inhibition by galls of *Quecus infectoria*. Alpha-mannosidase was treated with each designated concentration of PNP-glycoside (0.125-2 mM) in the absence or presence of extract at two different concentrations (4 and 10 μg mL^{-1}). The enzyme reaction was performed by incubating the mixture at 25°C for 15 min

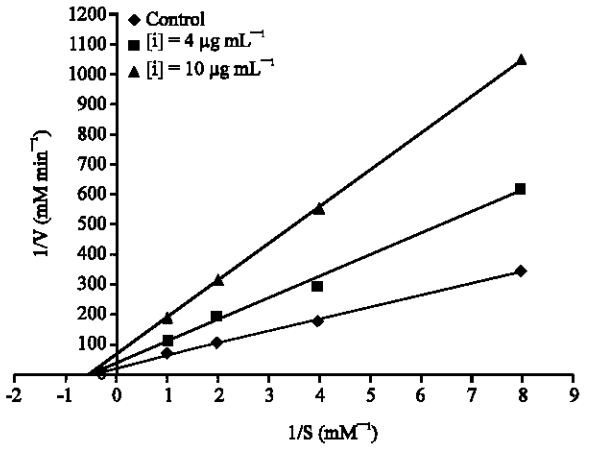

Fig. 2: Lineweaver-Burk plot of kinetic analysis of alpha-mannosidase inhibition by floret of *Rosa damascena*. Alpha-mannosidase was treated with each designated concentration of PNP-glycoside (0.125-2 mM) in the absence or presence of extract at two different concentrations (4 and 10 μg mL^{-1}). The enzyme reaction was performed by incubating the mixture at 25°C for 15 min

Alpha mannosidase II inhibitor, has led to reduction of tumor mass in human patients with advanced malignancies and is a promising drug therapy for patients suffering from breast, liver, lung and other malignancies (Mohan and Pinto, 2007).

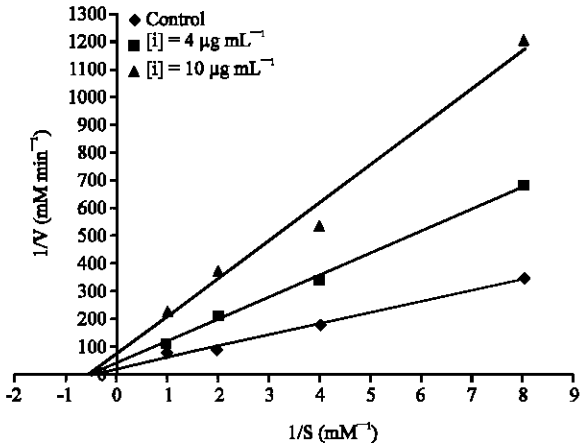

Fig. 3: Lineweaver-Burk plot of kinetic analysis of alpha-mannosidase inhibition by *Punica granatum*. Alpha-mannosidase was treated with each designated concentration of PNP-glycoside (0.125-2 mM) in the absence or presence of extract at two different concentrations (4 and 10 μg mL^{-1}). The enzyme reaction was performed by incubating the mixture at 25°C for 15 min

The N-linked oligosaccharide moieties present on many endoplasmic reticulum synthesized proteins have been shown to play a crucial role in the quality control which guarantees the endoplasmic reticulum accumulation of misfolded proteins in the lumen (Fagioli and Sitia, 2001). Branched chain N-linked oligosaccharides are co-translationally added to luminal asparagine residues of proteins as preassembled Man9GlcNAc2 precursors. ER and Golgi a1, 2-mannosidases, which are classified as class I α-mannosidases specifically hydrolyze a1, 2-mannose residues, catalyze the trimming of the 'high mannose' chains involving four α1, 2-linked mannose residues and this process generates Man5GlcNAc2. 1-Deoxymannojirimycin (DMJ), a mannose analogue, specifically inhibits the class I α-mannosidases, resulting in the accumulation of glycoproteins containing mainly high mannose type N-glycan (Man8GlcNAc2), while swainsonine (SW) specifically inhibits the class II α-mannosidases in the golgi (Bischoff and Kornfeld, 1984; Elbein, 1987; Tulsiani *et al*., 1982).

Several mannosidase inhibitors had been synthesized chemically or isolated from different sources. These include D-mannonlactam amidrazon, Swainsonine and Plantagoside (Dorling *et al*., 1980; Pan *et al*., 1992; Yamada *et al*., 1989) with different specificities.

In the present investigation attempt was made to identify new α-mannosidase inhibitors from plants with or without any known medicinal properties. Ten out of 200 extracts prepared from 100 plants exhibited anti α-mannosidase activity more than 20% with no record for such properties so far. The anti HIV activity of *Rosa damascena* showed by Mahmood *et al*. (1996) could be explain by the effect of the extract on α- mannosidase. The inhibition of the later enzyme by this plant extract might be responsible for such a phenomena. Nine compounds with moderate anti-HIV activity were found from Rosa damascene, assuming one with viral protease inhibitory action (Mahmood *et al*., 1996). Nature of α-mannosidase inhibitor and active fractions of the two other crude extracts should be revealed.

Mode of action of three active extracts on Jack Bean α-mannosiadse was a non- competitive action which was in contrast to that of swainsonine at low inhibitor concentration (Kang and Elbein, 1983; Tulsiani *et al*., 1985). The inhibition mode of these extracts on enzymes from different sources remains to be determined.

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