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Antioxidant Activity and Inhibition of α-Glucosidase by *trans*-Resveratrol, Piceid, and a Novel *trans*-Stilbene from the Roots of Israeli *Rumex bucephalophorus* L.

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The roots of *Rumex bucephalophorus*, collected in Israel, were analyzed for *trans*-stilbenes. Two stilbene-*O*-glycosyl derivatives were identified, in addition to 3,5,4′-trihydroxystilbene (**1**) (resveratrol). The stilbene-*O*-glycosyl derivatives were 5,4′-dihydroxystilbene-3-*O*-β-D-glucopyranoside (**2**) (piceid) and the new 5,4′-dihydroxystilbene-3-*O*-α-arabinopyranoside (**3**), which is being named rumexoid. The structure of rumexoid was elucidated by using spectroscopic data. The antioxidant capacities of stilbenoids **1**−**3** were determined and expressed as trolox equivalent antioxidant capacity (TEAC). TEAC value for *trans*-resveratrol was highest (2.7) and for rumexoid lowest (1.5). In vitro, *trans*-resveratrol and rumexoid demonstrated a potent inhibitory effect on α-glucosidase activity (IC50 < 0.1 and < 0.5 mM, respectively). The commercial antidiabetic agent acarbose was shown to inhibit only 35% of the enzyme activity at 0.5 mM. The addition of piceid to the reaction mixture did not inhibit α-glucosidase in vitro in the range of concentrations used. These findings extend the range of reported beneficial effects of stilbene derivatives, and demonstrate the multifaceted activities that dietary polyphenols may exert in the intestine, where their concentrations are highest in the body.

KEYWORDS: Antioxidants; α-glucosidase; *trans*-resveratrol; piceid; *trans*-stilbene; *Rumex bucephalophorus* L.

INTRODUCTION

Members of the family Polygonaceae are known to produce numerous biologically active secondary metabolites, such as flavonoid glycosides (*1*), anthraquinones (*2*, *3*), tannins (*2*), and other polyphenols (*4*). Hydroxylated stilbenes form one of the most interesting and therapeutically important groups of plant-derived polyphenols. Among them, *trans*-3,5,4′-trihydroxystilbene (**1**) (*trans*-resveratrol) and its well-known glycoside, 5,4′-dihydroxystilbene-3-*O*-β-D-glucopyranoside (**2**) (piceid), are the most studied. *trans*-Resveratrol is reported to provide protection against cardiovascular diseases due to its lipid-lowering activity and by inhibiting lipid peroxidation in humans (*5*, *6*). Moreover, it was found to be a potent inhibitor of tyrosine kinase (p56lck) (*7*), and it has been reported to possess antifungal properties (*8*). These effects could also be due to its structural resemblance to tyrosine (*9*, *10*). *trans*-Resveratrol and piceid were both found to be Cyp3A4 inhibitors (*11*, *12*) and to induce anticarcinogenic effects (*13*, *14*). In addition, piceid has been shown to improve blood microcirculation (*15*).

There is increasing evidence that individual polyphenols or classes of polyphenols may cause other beneficial effects, independent of their antioxidant capacities, by directly influencing the activities of key enzymes. Diabetes mellitus is a chronic disease that is growing in prevalence worldwide, to which nonpharmacologic therapy (e.g., diet, exercise, and weight loss) remains a critical component (*16*). There have been reports that polyphenolic fractions from plants can cause insulin-like effects in glucose utilization (*17*−*22*). Several reports suggest polyphenolic fractions from plants can induce insulin-like effects on glucose utilization (see (*23*) for review). α-Glucosidase (EC 3.2.1.20) catalyzes the final step in the digestive process of carbohydrates, and thus its inhibition can retard the uptake of dietary carbohydrates and suppress postprandial hyperglycemia and could be useful for treating diabetic and/or obese patients (*16*, *17*, *24*).

The roots and aerial parts of members of the *Polygonaceae* family, including those of *Rumex*, have been, and are still being used in ancient and current traditional herbal medicines throughout the world for a variety of therapeutic purposes. Several *Rumex* species, including *R. pictus* Forsk., *R. cyprius* Murb., *R. pulcher* L., *R. occultans* Sam., and *R. bucephalophorus* L. are native to Israel, a country with a long-documented history of traditional medicine (*25*, *26*). In a single report demonstrating

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the effect of extract from a member of *Polygonaceae* on glucose metabolism, stilbenoids and other compounds from the Himalayan rhubarb *Rheum emodi* displayed mild yeast as well as mammalian intestinal α-glucosidase inhibitory activity (*22*).

We have recently isolated and characterized several stilbenoids from *R. bucephalophorus* L. (*27*). In a continuing investigation of this plant, we have isolated a new *trans*-stilbene, named rumexoid (**3**), together with piceid (**2**) from the roots. To the best of our knowledge, a plant stilbene substituted with an arabinopyranosyl moiety, forming an α-directed glycosidic bond, has not been previously isolated. The antioxidant capacity and the in vitro α-glucosidase inhibitory activity of the isolated stilbenoids were determined.

MATERIALS AND METHODS

Materials. HPLC grade solvents, other solvents, and sodium acetate were purchased from BDH (Poole, UK). Acetic acid was purchased from J. T. Baker (Phillipsburg, NJ). Recombinant α-D-glucosidase from *Saccharomyces cerevisiae* expressed in unspecified host EC 3.2.1.20 (G-0660), *p*-nitrophenyl-α-D-glucopyranoside, and bovine serum albumin, were purchased from Sigma Chemical Co. (St. Louis, MO).

Plant Material. Whole plant of *R. bucephalophorus* L. was collected in April 2002 from the coastal region of Israel, 60 km southwest of Jerusalem, and a voucher specimen has been deposited at the first author's research laboratory at the Institute of Biochemistry, Food Science, and Nutrition of the Hebrew University of Jerusalem.

Extraction and Isolation. Roots and leaves were separated, freeze-dried, and ground prior to extraction. The powders (1 g) were extracted three times consecutively with 10 mL of acidified ethyl acetate (0.1% formic acid) at room temperature. Next, the extract was centrifuged at 12 000 g for 15 min, and the supernatant was collected and evaporated under a nitrogen stream. The dry residues were dissolved in 500 μL of 30% MeOH in water and chromatographed by RP-HPLC. Finally, fractions with a characteristic *trans*-resveratrol absorption spectrum were collected and pooled for spectral analyses.

Spectral Analyses. A Bruker DRX-500 NMR spectrometer, operating at 500 MHz for ^{1}H and at 125 MHz for ^{13}C, was used for the NMR experiments; chemical shifts are expressed in δ (parts per million), referring to the solvent peaks δ_H 3.34 and δ_X 49.0 for CD_3OD; coupling constants, *J*, are in Hz. DEPT ^{13}C, ^{1}H−^{1}H COSY, ^{1}H−^{13}C HMQC, and HMBC NMR experiments were carried out by using the conventional pulse sequences as described in the literature.

Mass spectra were recorded on an Esquire HCT Ion Trap LC/MS^n (Bruker Daltonics, Bremen, Germany), operated by Esquire, and DataAnalysis version 3.0 software. Isolated compounds were introduced by using direct infusion with a syringe pump at a flow rate of 4 μL/min.

Reversed Phase Chromatography. The HPLC system (Thermo Separation Products, Riviera Beach, FL) consisted of an autosampler (AS3000), an injector (100 μL), a column oven (30 °C), a pump (P3000), a diode array detector (UV6000), and a reverse-phase (RP) C18 column (25 × 4.6 mm, Goldsil, Teknokroma, Barcelona, Spain). A linear gradient using water and methanol, both acidified with 0.01% (v/v) formic acid, at a flow rate of 1 mL/min, was used, following 2 min at 40% methanol and reaching 55% methanol in 8 min. The column was then washed with 90% methanol for 2 min, and the column was then equilibrated at 40% methanol for 5 more min. Stilbenoids were monitored at 306 nm.

TEAC. The total antioxidant capacity of resveratrol and its derivatives was measured by the ABTS$^{\bullet+}$ radical cation decolorization assay involving preformed ABTS$^{\bullet+}$ radical cation (*28*). Briefly, **1**−**3** (100 μL) were added to 1 mL of working solution of ABTS$^{\bullet+}$, stirred continuously, and absorbance (at 734 nm) was measured after 10 min. An appropriate solvent blank was run, and absorbance of the samples was subtracted from the blank. All determinations were performed in triplicate.

Acid Hydrolysis of 2 and 3. Compounds **2** and **3** were heated with 2 M HCl at 121 °C for 40 min. The hydrolyzed compounds were extracted with EtOAc. Next, the EtOAc extract was collected and evaporated under a nitrogen stream. Finally, the dry residues were dissolved in 30% MeOH in water and chromatographed by RP-HPLC.

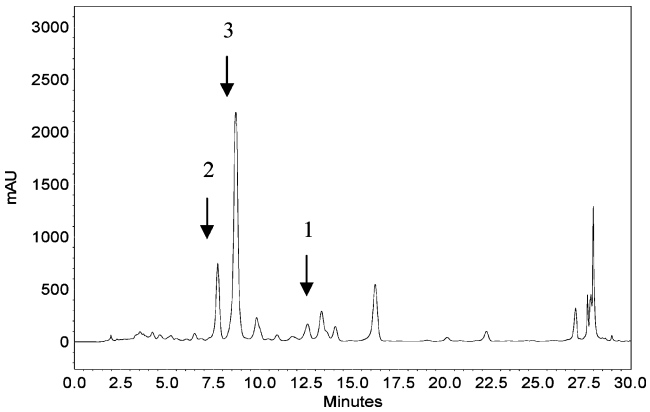
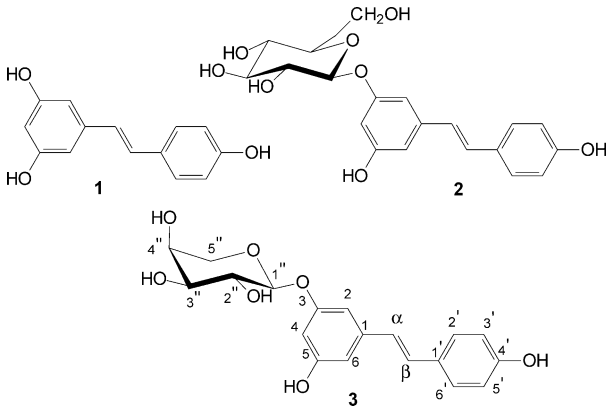


Figure 1. HPLC Chromatogram of *R. bucephalophorus* roots extract. Absorbance at 306 nm is shown. Resveratrol (**1**), piceid (**2**), and rumexoid (**3**).

Scheme 1. Structures of Resveratrol (**1**), Piceid (**2**), and Rumexoid (**3**)



Assay for α-Glucosidase. α-Glucosidase activity was assayed according to the method described by Lee (*29*) with slight modifications. α-Glucosidase (0.6 U) was dissolved in 100 mM phosphate buffer (pH 7.0) containing 2 g/L bovine serum albumin and 0.2 g/L NaN_3 and used as an enzyme solution. *p*-Nitrophenyl-α-D-glucopyranoside (5 mM) in the same buffer (pH 7.0) was used as a substrate solution. The enzyme solution (50 μL) and test extracts (10 μL) dissolved in dimethyl sulfoxide at a concentration of 1 mM were mixed in a well of a microtiter plate and measured for titer (Abs 405 nm) at zero time by using a microplate reader (ELX 800, Bio-Tek Instruments). Following 5 min preincubation at room temperature, the substrate solution (50 μL) was added and incubated for an additional 5 min at room temperature. The increase in absorbance from zero time was measured. Averages of five replicates are presented.

RESULTS AND DISCUSSION

A preliminary analysis using PDA-RP-HPLC of the ethyl acetate extracts of *R. bucephalophorus* roots revealed that the root extract contains, in addition to *trans*-resveratrol ((**1**), **Scheme 1**), two substances (**2** and **3**) with absorbance spectra characteristic of *trans*-stilbenes (two absorption bands with maxima at 280 and 306 nm). Acid hydrolysis confirmed the characterization of the two additional compounds as *trans*-resveratrol analogues. The three components were isolated by RP-HPLC for further spectral analysis and identification (**Figure 1**). By using standards of *trans*-resveratrol and previously prepared piceid (*10*), we were able to ascribe the latest eluting *trans*-stilbene (Rt = 12.7 min) to *trans*-resveratrol (**1**) and the stilbene eluting at Rt = 7.4 min to piceid (**2**).

Table 1. NMR Data for Rumexoid (**3**)

position	δ (^{13}C)	δ (^{1}H)	HMBC
		Resveratrol Fragment	
1	141.34(C)		
2	107.80(CH)	6.74(1H, dd, 1.4,2.1)	C_α, C_3, C_4, C_6
3	160.31(C)		
4	104.16(CH)	6.45(1H, dd, 2.1)	C_2, C_3, C_5, C_6
5	159.60(C)		
6	108.80(CH)	6.64(1H, dd, 1.4,2.1)	C_α, C_2, C_4, C_5
α	126.69(CH)	6.86(1H, d, 16.0)	C_1, C_2, C_6, $C_{1'}$
β	129.90(CH)	7.02(1H, d, 16.0)	C_α, C_1, $C_{1'}$, $C_{2'}$, $C_{6'}$
1′	130.29(C)		
2′(6′)	128.89(CH)	7.38(2H, d, 8.5)	C_β, $C_{6'}(C_{2'})$, $C_{4'}$
3′,5′	116.51(CH)	6.79(2H, d, 8.5)	$C_{1'}$, $C_{5'}(C_{3'})$, $C_{4'}$
4′	158.50(C)		
		Arabinopyranoside Moiety	
1″	102.83(CH)	4.85(1H, d, 7.0)	$C_{2''}$, $C_{3''}$, $C_{5''}$, C_3
2″	72.28(CH)	3.82(1H, dd, 7.0, 9.0)	$C_{1''}$, $C_{3''}$, $C_{4''}$
3″	74.18(CH)	3.65(1H, dd, 9.0, 3.5)	$C_{1''}$, $C_{2''}$, $C_{5''}$
4″	69.60(CH)	3.90(1H, ddd, 3.5,2.5,1.5)	$C_{2''}$, $C_{3''}$,$C_{5''}$
5″	67.16(CH_2)	3.96(1H, dd, 12.5, 2.5)	$C_{1''}$, $C_{3''}$, $C_{4''}$
		3.74(1H, dd, 12.5, 1.5)	

The chemical structures of compounds **1** and **2** were further confirmed by comparing the ^{1}H and ^{13}C NMR spectral data of the isolated compounds to those of standards. The third *trans*-stilbene (compound **3**) was identified by using NMR: ^{1}H NMR, ^{13}C NMR, DEPT, ^{1}H−^{1}H−COSY, HMQC, HMBC, and NOE spectra as a new resveratrol derivative, 5,4′-dihydroxystilbene-3-*O*-α-arabinopyranoside (**3**). Quantitation of the amounts of compound **1** and the two other *trans*-stilbenes (compounds **2** and **3**) was based on suggested similarity in the response factor of piceid and *trans*-resveratrol (*30*). The level of **1** was determined to be 25 μg/g root d.w., and the levels of **2** and **3** were 175 and 400 μg/g d.w., respectively.

Acid hydrolysis of glycosides **2** and **3** yielded *trans*-resveratrol as the sole product. The assignment of the signals in the ^{13}C and ^{1}H NMR spectra (**Table 1**) of compound **3** is based on splitting patterns of signals in the ^{1}H NMR, ^{1}H−^{1}H COSY, HMQC, and HMBC spectra. The ^{13}C NMR spectrum of **3** showed 17 different signals, of which 12 belong to *trans*-resveratrol aglycone (taking into account that, in one of the aromatic rings, there are two pairs of equivalent carbon atoms) and five others to a sugar moiety. The latter afforded a very well-resolved ^{1}H NMR spectrum, which together with the HMBC data and NOE results, led to the suggestion that glycoside **3** is 5,4′- dihydroxystilbene-3-*O*-α-arabinopyranoside. The signal at δ 4.85 (J = 7.0 Hz) was attributed to the anomeric proton H-1″. This is in accord with the chemical shift of C-1″ −102.83 (compared with the results exhibited by α-*O*-arabinopyranosides of various flavonols) (*31*−*33*). Following the connectivities from the splitting patterns and the ^{1}H−^{1}H COSY spectrum, the two doublets of doublets at δ 3.82 (J = 7.0, 9.0 Hz) and δ 3.65 (J = 9.0, 3.5 Hz) were assigned to H-2″ and H-3″, respectively. The multiplet at δ 3.90 (J = 3.5, 2.5, 1.5 Hz) was ascribed to H-4″ because it coupled with both H-3″ and two nonequivalent methylene (based on HMQC spectrum) protons: H-5″-*R* at δ 3.96 (J = 12.0, 2.5 Hz) and H-5″-*S* at δ 3.74 (J = 12.0, 1.5 Hz). According to the HMBC data, the sugar moiety has a pyranose ring (**Table 1**). H-1″, H-2″, and H-3″ are axial based on their large coupling constants. The small hyperfine coupling constants observed for H-4″ indicated that it is equatorially oriented. Irradiation of the anomeric proton in a NOE experiment revealed a strong absorption at δ 3.65 (H-3″), 3.74 (H-5″-*S*), 3.82 (H-2″), 6.45 (H-4, trisubstituted aromatic ring), and 6.74 (H-2, trisubstituted aromatic ring).

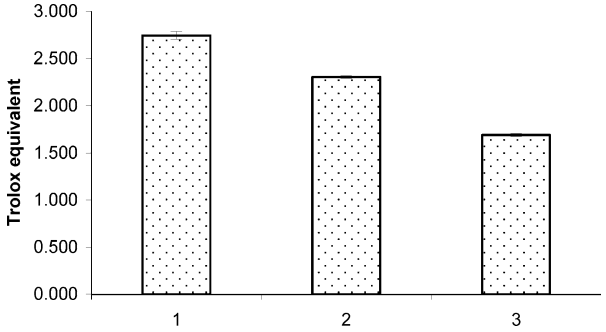


Figure 2. Trolox equivalent antioxidant capacity (TEAC) of stilbenes from the roots of *R. bucephalophorus.* Each value is the mean of triplicates ± standard deviation.

These results indicated that H-5″-*S*, like H-1″, is axial, and that the sugar moiety is attached to the 3-*O*-atom of the trisubstituted aromatic ring. The latter conclusion was also confirmed by the HMBC spectrum in which a ^{13}C−^{1}H long-range cross-peak was observed between C-3 and H-1″. On the basis of the foregoing NMR spectral data, we found that compound **3** could be either one of two enantiotropic isomers: 5,4′-resveratrol-3-*O*-α-L-arabinopyranoside in the $^{4}C_1$ conformation or 5,4′-resveratrol-3-*O*-α-D-arabinopyranoside in the $^{1}C_4$ conformation.

A negative ion electron spray mass spectrum of **3** (**Figure 3A**) gave an intense $[M - H]^-$ ion peak at *m*/*z* 359 that is in line with the molecular formula of $3C_{19}H_{20}O_7$, M = 360. The fragmentation pattern of the ion with *m*/*z* 359 obtained by the MS^2 procedure (**Figure 3B**) involves formation of a fragment ion at *m*/*z* 227 that corresponds to loss of the anhydroarabinose moiety from the $[M - H]^-$ ion. No ions characteristic of the sugar moiety were observed in the negative ion mode. The fragmentation pattern of the ion peak at *m*/*z* 227 (obtained by MS^3 procedure, **Figure 3C**) is similar to that obtained from negative ion MS of standard *trans*-resveratrol and confirms the structure of aglycone.

The antioxidant capacities of compounds **1**−**3** were determined as the percentage scavenging of the radical cation of ABTS compared to the water-soluble vitamin E analogue Trolox C (expressed as Trolox C equivalent antioxidant capacity, TEAC). The TEAC values for resveratrol and the two stilbene-*O*-glycosyl derivatives are presented in **Figure 2**. *trans*-Resveratrol (**1**) and piceid (**2**) showed higher antioxidant capacities than rumexoid (**3**). The wide range of biological activities exhibited by plant stilbenes are thought to be due to their powerful antioxidant properties (*34*). Indeed, we found that the TEAC value of each molecule of resveratrol is equal to 2.7 molecules of Trolox. In fact, even the weaker derivative studied here was more potent than Trolox. The simultaneous production of both glycosidic antioxidants in a single tissue may suggest different biological activities (*10*). We are currently studying the affinity of **3** toward tyrosine-dependent enzymes.

A promising beneficial effect of polyphenolic fractions from plants is the alteration of glucose utilization in mammals, leading to reduced symptoms of diabetes mellitus and its accompanying increased risk of cardiovascular disease (CVD). The inhibitory activity toward α-glucosidase by stilbenes **1**−**3** is presented in **Table 2**. Frequently, yeast α-glucosidase is used to identify its inhibitors from traditional medicinal plants and food items (*22*). At 0.1, *trans*-resveratrol showed 58% inhibition of α-glucosidase, and 0.5 mM of rumexoid were required to inhibit 57% of the enzyme activity. Interestingly, the inhibition potency of the parent nonglycosilated stilbene *trans*-resveratrol was five times as high as that of the newly isolated rumexoid (i.e., at 0.1 and

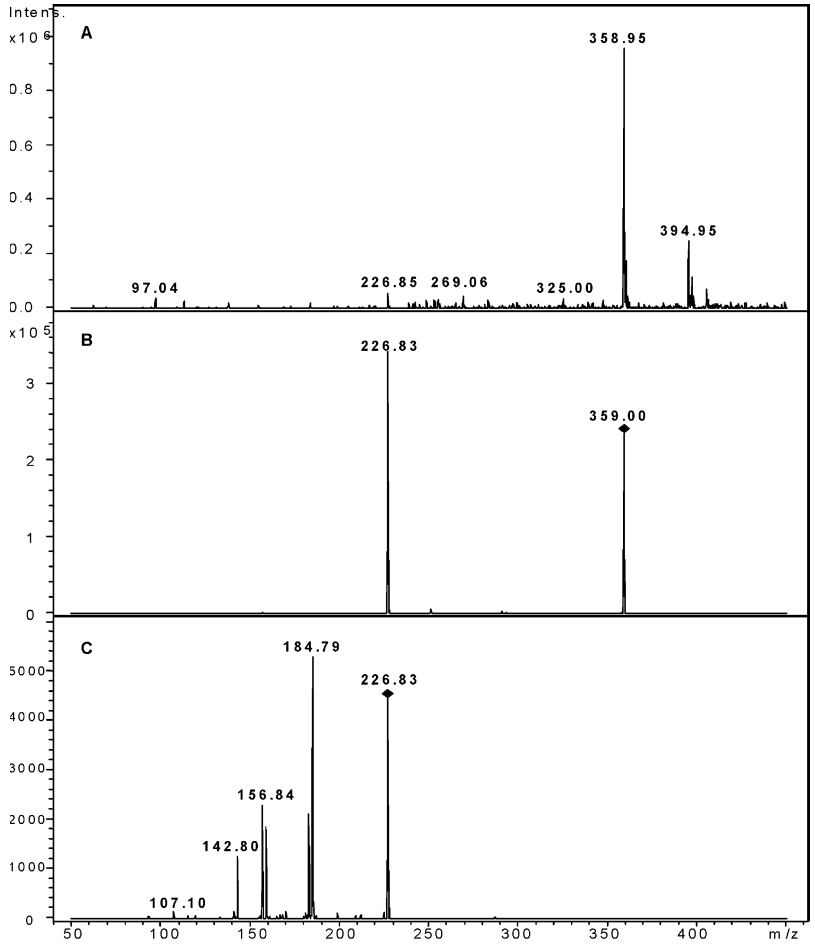


Figure 3. (–)-ESI-ion trap mass spectrum of rumexoid (**A**); MS^2 spectrum of the ion of *m*/*z* 359 (**B**); MS^3 spectrum of the ion of *m*/*z* 227 (**C**).

Table 2. α-Glucosidase Inhibitory Activity of Resveratrol, Rumexoid, and Piceid from *R. bucephalophorus* Roots and of Commercial Acarbose[a]

compound	final concentration (mM)	α-glucosidase inhibition (%)
resveratrol	0.2	71 ± 2.22
	0.1	58 ± 2.97
	0.05	41 ± 0.66
rumexoid	1	74 ± 6.21
	0.5	57 ± 2.76
	0.2	43 ± 1.12
	0.1	27 ± 0.46
piceid	0.2	NI[b]
	0.1	NI
	0.05	NI
acarbose	0.5	35 ± 1.09
	0.125	18 ± 0.29
	0.06	10 ± 0.26

[a] Each value is the mean of five replicates ± standard deviation. [b] NI, no inhibition.

0.5 mM) and much higher than that of the more abundant glucosylated-stilbene, namely piceid.

Inhibition of α-glucosidase by other stilbene analogues, isolated from rhizomes of *Rheum palmatum* and *Rheum emodi (Polygonacea)* has been reported (*22*, *35*). Stilbene analogues of resveratrol (desoxyrhaponticin and rhapontigenin), which were isolated from *R. emodi* (Indian rhubarb), were reported to have a yeast α-glucosidase inhibitory activity (*22*), similar to that found for rumexoid in this work. Roots and leaves of *Rumex*, like the rhizome of *R. emodi*, have been consumed as food, culinary, and medicine for long time. Thus, observations of the varied nature and behavior of compounds in this report for α-glucosidase inhibition needs further detailed studies for their use in prevention and treatment of hyperglycemia and, consequently, diabetes mellitus.

Indeed, both *trans*-resveratrol and rumexoid were also found to be more potent inhibitors of the yeast α-glucosidase than acarbose. Currently, four α-glucosidase inhibitors exist: acarbose, miglitol, voglibose, and emiglitate. Of these, acarbose is by far the most prescribed drug (*36*). The results presented here may add to our understanding of how *trans*-resveratrol and other stilbenes exert beneficial health effects in human, although being hardly absorbed. Moreover, together with vast literature demonstrating various activities of stilbenes, and specifically *trans*-resveratrol (*13*, *17*, *37*), this work suggests a promising therapeutic potential of stilbene analogues in controlling hyperglycemia through either diet or drug development, using the *trans*-stilbene skeleton. The demonstrated potent inhibition of α-glucosidase, together with potent antioxidant capacity, may act in parallel in the gastrointestinal tract.

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