α-glucosidase inhibitors from plants: A natural approach to treat diabetes

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Submitted: 15-05-2010

ABSTRACT

Diabetes is a common metabolic disease characterized by abnormally high plasma glucose levels, leading to major complications, such as diabetic neuropathy, retinopathy, and cardiovascular diseases. One of the effective managements of diabetes mellitus, in particular, non–insulin-dependent diabetes mellitus (NIDDM) to decrease postprandial hyperglycemia, is to retard the absorption of glucose by inhibition of carbohydrate hydrolyzing enzymes, such as α-glucosidase and α-amylase, in the digestive organs. α-Glucosidase is the key enzyme catalyzing the final step in the digestive process of carbohydrates. Hence, α-glucosidase inhibitors can retard the liberation of d-glucose from dietary complex carbohydrates and delay glucose absorption, resulting in reduced postprandial plasma glucose levels and suppression of postprandial hyperglycemia. In recent years, many efforts have been made to identify effective α-glucosidase inhibitors from natural sources in order to develop a physiologic functional food or lead compounds for use against diabetes. Many α-glucosidase inhibitors that are phytoconstituents, such as flavonoids, alkaloids, terpenoids,anthocyanins, glycosides, phenolic compounds, and so on, have been isolated from plants. In the present review, we focus on the constituents isolated from different plants having α-glucosidase inhibitory potency along with IC50 values.

Key words: Alkaloids, anthocyanins, diabetes, flavonoids, α-glucosidase, glycosides, terpenoids

INTRODUCTION

Diabetes mellitus is the most serious, chronic metabolic disorder and is characterized by high blood glucose levels. One therapeutic approach to treat diabetes is to retard the absorption of glucose via inhibition of enzymes, such as α-glucosidase, in the digestive organs.[1,2] α-Glucosidase (α-D-glucoside glucohydrolase) is an exo-type carbohydrase distributed widely in microorganisms, plants, and animal tissues,[3] which catalyzes the liberation of α-glucose from the non reducing end of the substrate. Inhibiting this enzyme slows the elevation of blood sugar following a carbohydrate meal.[4] It is a membrane bound enzyme present in the epithelium of the small intestine, which works to facilitate the absorption of glucose by the small intestine by catalyzing the hydrolytic cleavage of oligosaccharides into absorbable [Figure 1] monosaccharides.[5]

By the inhibition of α-glucosidase in the intestine, the rate of hydrolytic cleavage of oligosaccharide is decreased and the process of carbohydrate digestion spreads to the lower part of small intestine. This spreading of digestion process delays the overall absorption rate of glucose into the blood. This has proved to be one of the best strategies to decrease the postprandial rise in blood glucose and in turn help avoiding the onset of late diabetic complications.[5]

There are reports of the presence of α-glucosidase inhibitors, such as acarbose[6,7] andvoglibose,[8] in microorganisms, and nojirimycin[9-11] and 1-deoxynojirimycin[11] in plants, as well as the effects of α-glucosidase inhibitor in wheat kernels on blood

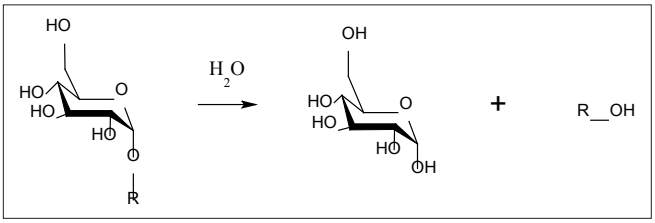

Figure 1: Conversion of oligosaccharide to glucose

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DOI: 10.4103/0973-7847.79096

glucose levels after food uptake.[12]

α-Glucosidase inhibitory potency of plant extracts and isolated compounds from different origins are discussed in Table 1.

α-GLUCOSIDASE INHIBITION BY FLAVONOIDS

The inhibitory activity of six groups of flavonoids against α-glucosidase in yeast and rat small intestine was compared, and the chemical structures of flavonoids responsible for the inhibitory activity were evaluated. Yeast α-glucosidase was potently inhibited by the anthocyanidin, isoflavone, and flavonol groups with the IC_{50} values less than 15 μM. Rat's small intestinal α-glucosidase was weakly inhibited by many flavonoids, and slightly by the anthocyanidin and isoflavone groups.[13]

All the six groups of flavonoids with their chemical structures [Figure 2].

One flavonoid glycoside, quercetin 3-O-β-D-xylopyranosyl (1'''→2'')-β-D-galactopyranoside(7) from *Alstonia scholaris*

Table 1: Extracts/phytoconstituents having α-glucosidase inhibition activity

Plant	Part	Extract/active constituent	IC_{50}	References
Acosmium panamense (Onychiuroidea)	Bark	Butanolic extract	109 μg/mL	29
Adhatoda vasica Nees (Acanthaceae)	Leaves	Vasicine Vasicinol	125 μM 250 μM	15
Alstonia scholaris (Apocynaceae)	Leaves	quercetin 3-O-β-D-xylopyranosyl (1 →2″)-β-D-galactopyranoside (-)-lyoniresinol 3-O-β-D-glucopyranoside	1.96 mM (m) 1.95 mM (s) 1.43 mM (m)	14
Bergenia ciliate (Saxifragaceae)	Rhizome	(-)-3-O-galloylepicatechin (-)-3-O-galloylcatechin	560 μM (s), 334 μM (m) 297 μM (s), 150 μM (m)	19
Cassia auriculata	Flowers	Methanolic extract	0.023 mg/mL	30
Cecropia obtusifolia (Cecropiaceae)	Leaves	Butanolic extract	14μg/mL	31
Chinese aloe (Asphodelaceae)	Leaves	Aloeresin A	11.94 mM (s) 2.16 mM (m)	32
Cleistocalyx operculatus (Myrtaceae)	Flower buds	Aqueous extract	68.2 ± 3.4% inhibition by 100 mg	33
Commelina communis (Commelinaceae)	Aerial parts	Isoquercitrin Isorhamnetin-3-O-rutinoside Isorhamnetin-3-O-β-D-glucoside Glucoluteolin Chrysoriol-7-O-β-D-glucoside Orientin Vitexin Isoorientin Isovitexin Swertisin Flavocommelin 1-Deoxynojirimycin DMDP	2.4×10^{-4} M 5.1×10^{-4} M $\geq 1.0 \times 10^{-3}$ M $\geq 1.0 \times 10^{-3}$ M $\geq 1.0 \times 10^{-3}$ M $\geq 1.0 \times 10^{-3}$ M 4.2×10^{-4} M $\geq 1.0 \times 10^{-3}$ M $\geq 1.0 \times 10^{-3}$ M 3.7×10^{-4} M $\geq 1.0 \times 10^{-3}$ M 1.5×10^{-4} M 5.8×10^{-5} M	34
Crataegus oxyacantha (Rosaceae)	Leaves	Apigenin Vitexin Isovitexin Luteolin Orientin Isoorientin	21.85 μM 25.11 μM 23.26 μM 13.07 μM 23.30 μM 19.68 μM	35
Cuscuta reflexa (Convolvulaceae)		7′-(3′,4′-dihydroxyphenyl)-*N*-[(4methoxyphenyl ethyl] propenamide 7′-(4′-hydroxy,3′-methoxyphenyl)-*N*-[(4-butylphenyl) ethyl] propenamide 6,7-dimethoxy-2*H*-1-benzopyran-2-one 2-(3-hydroxy-4-methoxyphenyl)-3,5-dihydroxy-7-*O*-β-D-glucopyranoside-4H-1-benzopyrane-4-one	103.58 μM 45.67 μM 0.44 mM 0.24 mM	36

Table 1 (contd...)

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Derris indica (Fabaceae)	Root	30,40-dihydroxy-4H-furo[2,3- h]chromen-4-one	25.6 ± 0.341 µg/mL.	37
		3,30,40-trihydroxy- 4H-furo[2,3-h]chromen-4-one	37.9 ± 2.6 µg/mL	
		Karanjin	26.3 ± 1.8 µg/mL	
		Pongapin	21.4 ± 0.7 µg/mL	
		Pongaglabrone	8.6 ± 0.1 µg/mL	
		Pongamol	58.2 ± 0.2 µg/mL	
		Ovalitenone	29.7 ± 0.5 µg/mL	
		Pongachromene	22.8 ± 5.5 µg/mL	
		Fisetin tetramethyl ether	19.7 ± 0.3 µg/mL	
		3-Methoxy-7-hydroxy-30,	36 ± 1.8 µg/mL	
		40-methylenedioxyflavone	28.7 ± 1.8 µg/mL	
		7-Omethylchrysin		
		7,4′-dimethoxy-5-hydroxyflavone	4.4 ± 0.1 µg/mL	
		Pinnatin	36.5 ± 5.9 µg/mL	
		Pongapinone-B	1.2 ± 0.2 µg/mL	
		Piperonylic acid	18.4 ± 2.2 µg/mL	
Derris scandens (Fabaceae)		Scandenin A	25.17 ± 0.6 µg/mL	38
		Scandenone	34.74 ±0.60 µg/mL	
		Scandinone	33.83 ±1.32 µg/mL	
		4, 5, 7-Trihydroxybiprenylisoflavone	45.14 ± 1.13 µg/mL	
		Chloroform extract	6.28 ± 1.02 µg/mL	
		Hexane extract	10.63 ± 0.319µg/mL	
Dorstenia psilurus (Moraceae)	Roots	Dorsilurin F	4.13 ± 0.12 µM	39
		Dorsilurin G	7.51 ± 0.17 µM	
		Dorsilurin H	24.01 ± 0.46 µM	
		Dorsilurin I	21.49 ± 0.71 µM	
		Dorsilurin J	16.91 ± 0.68 µM	
		Dorsilurin K	43.95 ± 0.46 µM	
		Dorsilurin C	11.17 ± 0.15 µM	
Duranta repens (Verbenaceae)	Whole plant	7-*O*-D-glucopyranosyl-3,5-dihydroxy-3′-(4″-acetoxy-3″-methylbutyl)-6,4′-dimethoxyflavone	65.5 ± 2.5 µM	40
		3,7,4′-trihydroxy-3′-(8″-acetoxy-7″-methyloctyl)-5,6-dimethoxyflavone	757.8 ± 65.5 µM	
		(-)-6β-hydroxy-5β ,8β ,9β ,10α-cleroda-3,13-dien-16,15-olid-18-oic acid	577.7 ± 19.0 µM	
Ecklonia stolonifera (Laminariaceae)	Leaves	Water extract	0.026 mg/mL	41
		Methanol extract	0.022 mg/mL	
Elaeodendron transvaalense (Celastraceae)	Stem bark	Acetone extract	50.62 ± 0.351 µg/mL	42
Euclea undulata (Ebenaceae)	Root bark	Acetone extract	49.95 ± 0.007 µg/mL	42
Fagara tessmannii (Rutaceae)	Stem bark	vanillic acid	69.4 ± 0.8 µM	26
		2,6-dimethoxy-1,4-benzoquinone	900.0 ± 3.5 µM	
		3β-acetoxy-16β-hydroxybetulinic acid	7.6 ± 0.6 µM	
Ferula mongolica (Umbelliferae)	Roots	Baigene A	56.6 µM	5
		Baigene B	32.21 µM	
		Baigene C	63.68 µM	
		7′-Methoxybaigene C	79.87 µM	
		Mongolin B	60.0 µM	
		4′-Methoxydshamirone	82.41 µM	
		Baigene B	20.5 µM	
		Dshamirone	29.15 µM	
		Mongolin C	4.36 µM	
		Mongolin D	9.31 µM	
Grateloupia elliptica (Halymeniaceae)	Algae	2,4,6-tribromophenol (S)	60.3 µM	1
		2,4,6-tribromophenol (B)	130.3 µM	
		2,4-dibromophenol (S)	110.4 µM	
		2,4-dibromophenol (B)	230.3 µM	
Gypsophila oldhamiana (Caryophyllaceae)	Root	Segetalic acid	23.1 ± 1.8 µM	27
		28-O-α-L-arabinopyranosyl-(1→4)-α-L-arabinopyranosyl-(1→3)-β-D-xylopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→2)-β-D-fucopyranosyl ester	65.5 ± 4.5 µM	
		3-keto,16α-hydroxy, 24-noroleanolic acid	15.2 ± 1.8 µM	

Table 1 (contd...)

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Hyssopus officinalis (Lamiaceae)	Leaves	1-O-beta-D-6′-O-cinnamoylglucopyranosyl-3-(3", 5"-dimethoxy-4"-hydroxyphenyl)-1,2,3-propanetriol 1-O-beta-D-glucopranosyl-3-(3",5"-dimethoxy-4"-hydroxyphenyl)-1,2,3-propanetriol	3×10^{-3} M 3×10^{-3} M	43
Ipomoea batatas (Convolvulaceae)	Roots	Peonidin (m) 6-O-Caffeoylsophorose (s) 6-O-Caffeoylsophorose (m)	200 ± 4.1 µM 874 ± 39.0 µM 699 ± 17.1 µM	44
Lobelia chinensis (Campanulaceae)		Radicamines A Radicamines B	$6.7\ x10^{-6}$ M $9.3x10^{-6}$ M	45
Machilus philippinensis (Lauraceae)	Leaves	Kaempferol-3-O-α-L-rhamnopyranoside 3″,4″-di-E-p-coumaroic acid ester 3″-E,4″-Z-di-p-coumaroic acid ester Quercetin-3-O-rhamnopyranoside Kaempferol-3-O-rhamnopyranoside	6.10 ± 0.28 µM 1.00 ± 0.01 µM 33.05 ± 2.68 µM 228.11 ± 9.50 µM	46
Malmea depressa (Annonaceae)	Root	butanolic extract	21 µg/mL	47
Malpighia emarginata	Fruit	Aceronidin (leucocyanidin-3-O-β-D-glucoside)	100 µM	48
Mangifera indica (Malpighiaceae)	Bark	Ethanolic extract	314 µg/mL	49
Morus alba (Moraceae)	Leaves	1-deoxynojirimycin (s) 1-deoxynojirimycin (m)	7.7×10^{-5} mM 1.7×10^{-4} mM	50
Origanum majorana (Labiatae)	Leaves	6-hydroxyapigenin 6-hydroxyapigenin-7-O-β-D-glucopyranoside 6-hydroxyluteolin-7-O-β-D-glucopyranoside 6-hydroxyapigenin-7-O-(6-O-feruloyl)-β-D-glucopyranoside 6-hydroxyluteolin-7-O-(6-O-feruloyl)-β-D-glucopyranoside	12 µM ≥500 µM 300 µM ≥500 µM ≥500 µM	51
Penares schulzei	Bark	Schulzeines A Schulzeines B Schulzeines C	48–170 nM 48–170 nM 48–170 nM	52
Pharbitis nil (Convolvulaceae)		Pelargonidin	60 µM	53
Phyllanthus amarus (Phyllanthaceae)	Whole plant	Hexane extract	32 µg/mL	54
Pine (Pinaceae)	Bark	Pine bark extract (Pycnogenol)	5 µg/mL	55
Pine needle (Pinaceae)	bark	Ethanolic extract	155 µg/mL	56
Piper longum (Piperaceae)	Fruit	Methanol extract Pipataline Pellitorine Sesamine Brachystamide B Guineensine Deoxynojirimycin (std)	112.90 ± 30.53 µg/mL 32.10 ± 0.36 µg/mL 34.39 ± 0.97 µg/mL 36.39 ± 0.58 µg/mL 34.09 ± 4.89 µg/mL 19.26 ± 1.70 µg/mL 12.23 ± 1.41 µg/mL	57
Piper umbellatum (Piperaceae)	Branches	Piperumbellactams A Piperumbellactams B Piperumbellactams C	98.07 ± 0.44 µM 43.80 ± 00.56 µM 29.64 ± 00.46 µM	16
Psidium guajava (Myrtaceae)	Leaves	Aqueous extract	60.8 ± 2.1 µg/mL	58
Pteronia divaricata (Compositae)	Entire plant	Acetone extract	31.22 ± 0.154 µg/mL	43
Salacia reticulate (Hippocrateaceae)	Roots	Mangiferin (s) Mangiferin (m) (-)-epicatechin (s) (-)-epigallocatechin (s) (-)-4′-O-Methylepigallocatechin (s) Salacinol (s) Kotalanol (s)	87 µg/mL >300 µg/mL 277 µg/mL 130 µg/mL >300 µg/mL 0.84 µg/mL 0.58 µg/mL	59
Scutellaria baicalensis (Lamiaceae)	Root	Baicalein	2.6×10^{-4} M	60

Table 1 (contd...)

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Sophora flavescens (Fabaceae)	Roots	Kushenol A (—)-kurarinone Sophoraflavanone G 2′-methoxykurarinone Kurarinol Isoxanthohumol Kuraridin Maackian	45 μM 68 μM 37 μM 155 μM 179 μM 358 μM 57 μM 185 μM	61
Spiraea cantoniensis (Rosaceae)	Flower	Quercetin 3-*O*-(6-*O*-caffeoyl)-*β*-galactoside Kaempferol 3-*O*-(6-*O*-caffeoyl)-*β*-galactoside Kaempferol 3-*O*-(6-*O*-caffeoyl)-*β*-glucoside	0.085 mM 0.35 mM 0.47 mM	62
Syagrus romanzoffiana (Arecaceae)	Seed	13-hydroxykompasinol A scirpusin C	6.5 uM 4.9 uM	24
Syzygium cumini (Myrtaceae)	Seed kernel	70% Ethanol extract Acetone extract Ethyl acetate extract 1-Butanol extract	24.6 ± 0.7 μg/mL 19.5 ± 0.4 μg/mL 16.6 ± 0.3 μg/mL 8.3 ± 0.2 μg/mL	63
Syzygium malaccense (Myrtaceae)	Bark	Casuarine 6-O-β-glucoside	5.7 μg/mL	64
Terminalia chebula (Combretacea)	Fruit	Chebulanin Chebulagic acid Chebulinic acid	690 μM 97 μM 36 μM	18
Terminalia superb (Combretacea)	Stem bark	Gallic acid Methyl gallate Ellagic acid Ellagic acid 3,30-dimethyl ether Ellagic acid-4-o-b-Dxylopyranoside-3,30-dimethyl ether	5.2 ± 0.2 μM 11.5 ± 0.1 μM 194.1 ± 0.2 μM 184.6 ± 0.9 μM 118.7 ± 0.1 μM	65
Tournefortia hartwegiana (Boraginaceae)	Aerial parts	Methanolic extract	3.13 mg/mL	66
Tussilago farfara (Asteracerae)	Flower buds	3,4-Dicaffeoylquinic acid 3,5-Dicaffeoylquinic acid 4,5-Dicaffeoylquinic acid 1,2,3,4,6-Penta-O-galloyl-b-D-glucopyranose (standard)	0.91 mM 0.90 mM 0.89 mM 0.14 mM	17
Viburnum dilatatum (Caprifoliaceae)	Fruits	Cyanidin 3-sambubioside 5-Caffeoyl quinic acid Cyanidin 3-glucoside 5-Caffeoyl-4-methoxy quinic acid Cyaniding Quercetin	3.19 mM 82.18 mM 25.55 mM 11.12 mM 63.29 mM 29.41 mM	67

Maltase (m); Sucrase (s), 2R,3R,4R,5R)2,5-bis(hydroxymethyl)-3,4-dihydroxypyrrolidine (DMDP); 1-deoxynojirimycin (DNJ)

inhibited only maltase with IC_{50} values of 1.96 mM.[14]

ALKALOIDS

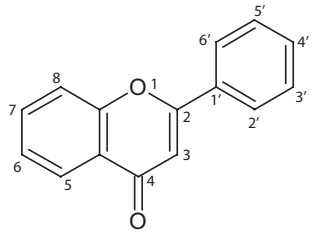
Methanolic extract of *Adhatoda vasica Nees* was tested in screening experiments for rat intestinal α-glucosidase. Vasicine (8) and Vasicinol (9), which were isolated by assay-guided fractionation of this extract, showed a high sucrase inhibitory activity with IC_{50} values 125 and 250 μM, respectively. Both of these compounds were shown to be reversible inhibitors of sucrase.[15]

Three alkaloids named piperumbellactam A (10), piperumbellactam B (11) and piperumbellactam C (12) were isolated from branches of *Piper umbellatum* and these compounds showed moderate α-glucosidase enzyme inhibition with IC_{50} values 98.07 ± 0.44, 43.80 ± 0.56, and 29.64 ± 0.46, respectively.[16]

The methanolic extract from flower buds of *Tussilago farfara* showed the highest maltase inhibitory activity, with maltose as a substrate. Enzyme assay-guided fractionation of this extract afforded 3,4-dicaffeoylquinic acid (13), 3,5-dicaffeoylquinic acid (14), and 4,5-dicaffeoylquinic acid (15). Comparison of the activities of these three compounds with others, such as chlorogenic acid (16), quinic acid (17), and caffeic acid (18), suggested that the number of caffeoyl groups attached to a quinic acid core were important for the potency.[17]

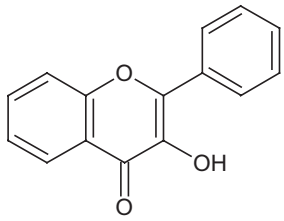
Phenolics

The dried *Terminalia chebula* (Combretaceae) fruits were extracted using 70% methanol at room temperature and its mammalian α-glucosidase inhibitory activity was investigated. It was found to have a potent rat intestinal maltase inhibitory activity. Three active ellagitannins, identified as chebulanin (19), chebulagic acid (20), and chebulinic acid (21) were isolated using bioassay-guided



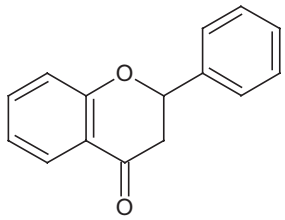
(1) Flavone

Luteolin: 5, 7, 3′, 4′ = OH
Apigenin: 5, 7, 4′ = OH
Baicalein: 5, 6, 7= OH



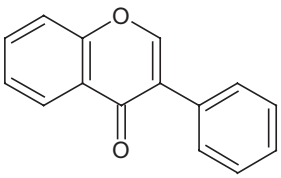
(2) Flavonol

Myricetin: 5, 7, 3′, 4′, 5′ = OH
Quercetin: 5, 7, 3′, 4′ = OH
Kaempferol: 5, 7, 4′ = OH
Fisetin: 7, 3′, 4′ = OH



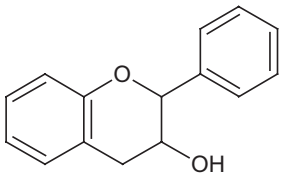
(3) Flavanone

Naringenin: 5, 7, 4′ = OH
Hesperetin: 5, 7, 3′ = OH
4′ = OCH_3



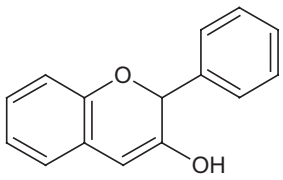
(4) Isoflavone

Daidzein: 7, 4′ = OH
Genistein: 5, 7, 4′ = OH



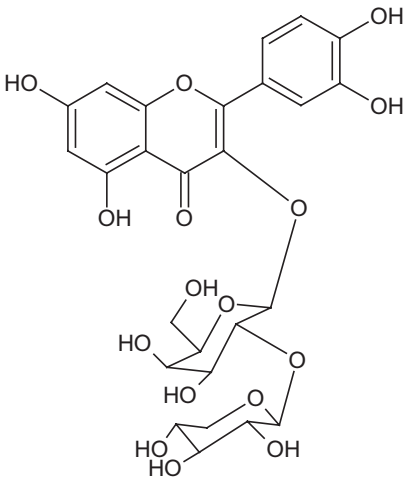
(5) Flavan-3-ol

(+)- Catechin (2R, 3S): 5, 7, 3′, 4′ = OH
(-)- Epicatechin (2R, 3S): 5, 7, 3′, 4′ = OH
(-)- Epigallocatechin (2R, 3R): 5, 7, 3′, 4′, 5′ = OH
(-)- Epigallocatechin gallate (2R, 3R): 5, 7, 3′, 4′, 5′ = OH



(6) Anthocyanidin

Cyanidin: 5, 7, 3′, 4′ = OH



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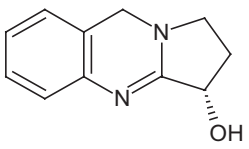

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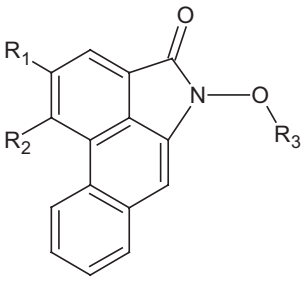

(10) →R_1 = R_2 = OCH3, R_3 = H
(11)→R_1 = OCH3, R_2 = OH, R_3 = H
(12)→R_1 = R_2 = OH, R_3 = CH3

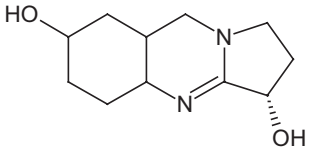

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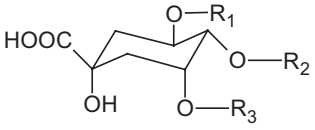
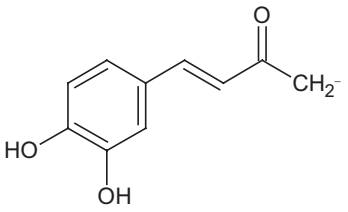
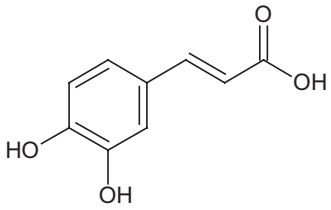
Figure 2: Some of the phytochemicals with their chemical structures





Caffeoyl



(13) R_1= H, R_2 = R_3 = Caffeoyl

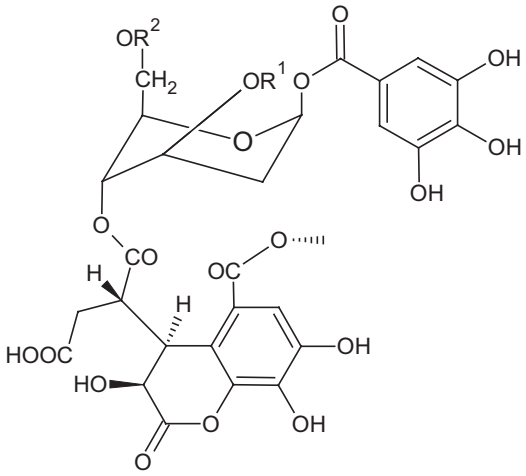
(14) R_1 = R_3 = Caffeoyl, R_2 = H

(15) R_1 = R_2 = Caffeoyl, R_3 = H

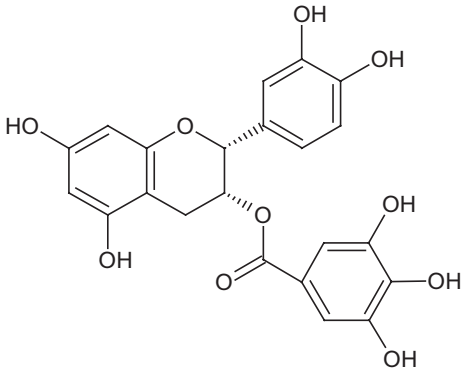
(16) R_1 = Caffeoyl, R_2 = R_3 = H

(17) R_1 = R_2 = R_3 = H

(18)

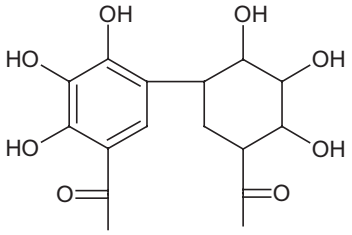


(19) R_1, R_2 =H



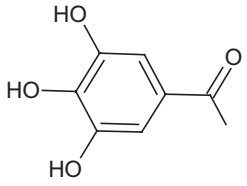
(22)

(20) R_1, R_2= HHDP

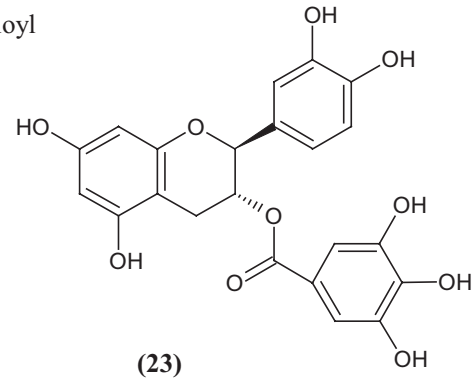


HHDP

(21) R_1, R_2 = galloyl



Galloyl



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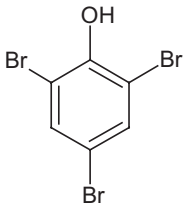

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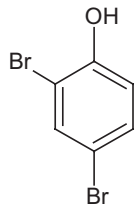
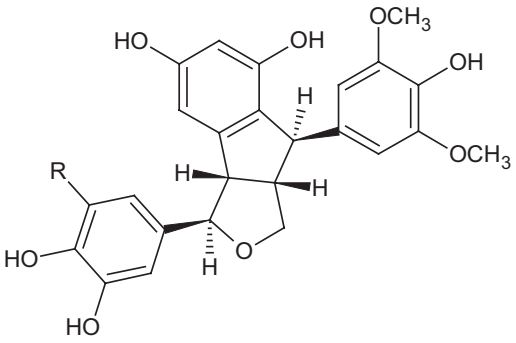
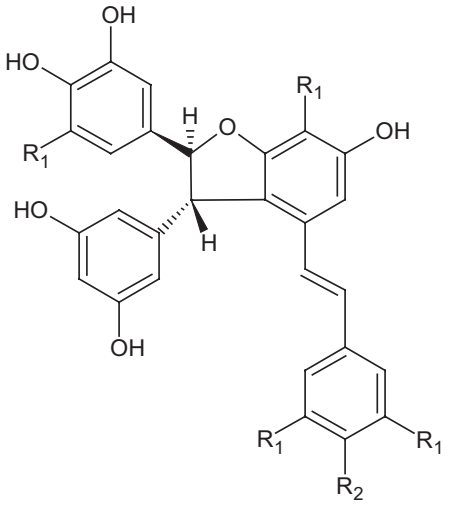


(25)

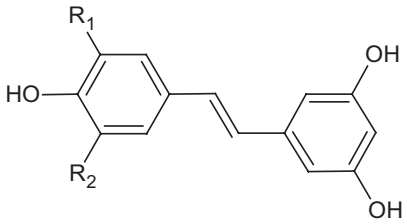
Figure 2 (contd..)



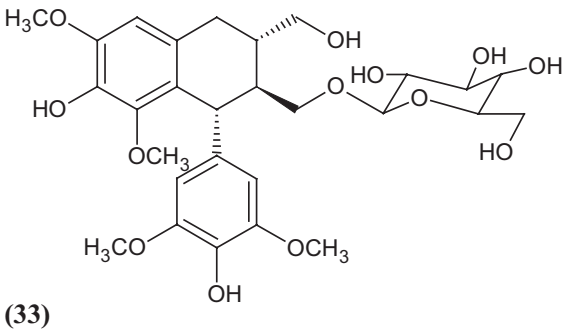
(26) R = OH, racemate **(27)** R = H, racemate



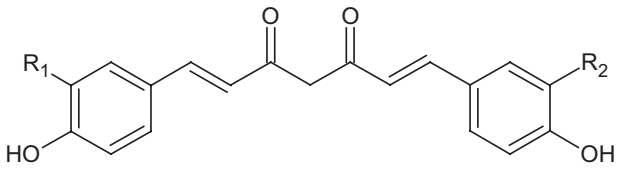
(28) $R_1 = H$, $R_2 = OH$ **(29)** $R_1 = OH$, $R_2 = H$



(30) $R_1 = R_2 = OH$ **(31)** $R_1 = OH$, $R_2 = H$ **(32)** $R_1 = R_2 = H$



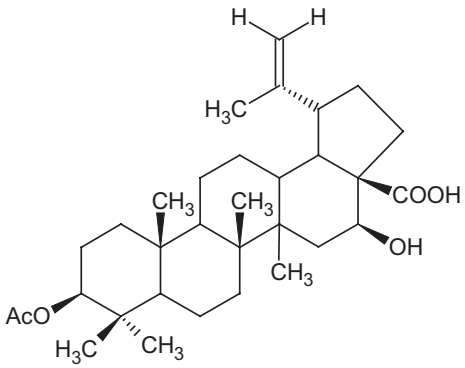
(33)



(34) $R_1 = R_2 = OCH_3$

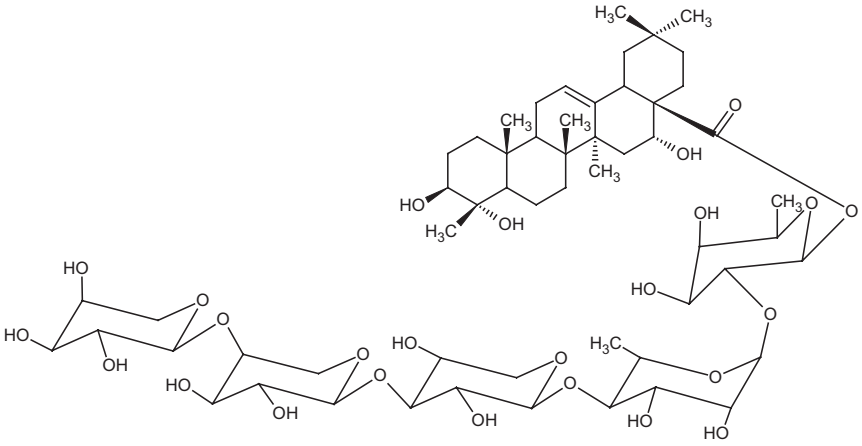
(35) $R_1 = OCH_3$, $R_2 = H$

(36) $R_1 = R_2 = H$

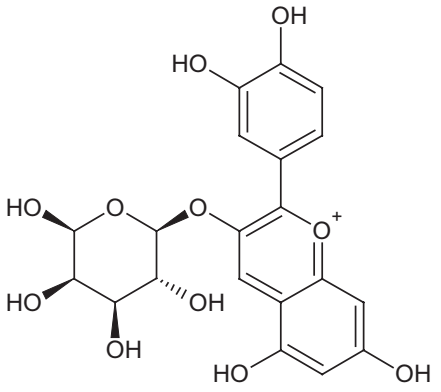


(37)

Figure 2 (contd..)



(38)



(39)

Figure 2 (contd..)

separation. All the three compounds were shown to possess potent intestinal maltase inhibitory activity with IC_{50} values of 690, 97, and 36 μM, respectively.[18]

The extraction and fractionation of 50% aqueous methanolic extracts of *Bergenia cilata* led to the isolation of two active compounds, namely, (-)-3-O-galloylepicatechin (22) and (-)-3-O-galloylcatechin (23). These isolated compounds demonstrated significant dose dependent enzyme inhibitory activities against rat intestinal α-glucosidase. The IC_{50} values of (-)-3-O-galloylepicatechin are 560 and 334 μM for sucrose and maltase, respectively, and that of (-)-3-O-galloylcatechin are 297 and 150 μM for sucrose and maltase, respectively.[19]

Miscellaneous

Two bromophenols, 2,4,6-tribromophenol (24) and 2,4-dibromophenol (25), were purified from *Grateloupia elliptica*. α-Glucosidase inhibitory activity of these compounds against α-glucosidases was determined compared with acarbose and voglibose. The IC_{50} values of compounds (24) and (25) against *Saccharomyces cerevisiae* α-glucosidase were 60.3 and 110.4 μM, respectively, which were lower than the 130.3 and 230.3 μM that was presented against the *Bacillus stearothermophilus* α-glucosidase.[20] The α-glucosidase inhibitory activities of compound (24) against *S. cerevisiae* and *B. stearothermophilus* α-glucosidases were also higher than that for compound (25).[1] It is to be concluded that inhibitory potencies of bromophenol increased with increasing degree of bromo-substitution per benzene ring and with decreasing degree of methyl-substitution.[20] Voglibose and acarbose had high inhibitory effects on mammalian α-glucosidase, but no inhibitory activity against *S. cerevisiae* α-glucosidase.[21-23]

Bioassay-guided screening indicated that the defatted EtOH extract of the seeds of *Syagrus romanzoffiana* showed 55% inhibitory activity against α-glucosidase at a concentration of 10 μg/mL. Further fractionation indicated the active ingredients to be concentrated in the BuOH soluble fraction, having 73% inhibition at 10 μg/mL level. This fraction was further separated over Sephadex LH-20 and low pressure RP-18 columns that eventually yielded eight active compounds Of these, seven are stilbenoids, and two of them, 13-hydroxykompasinol A (26) and scirpusin C (27), possess potent inhibitory activity against α- glucosidase type IV from *B. stearothermophilus* with the IC_{50} value of 6.5 and 4.9 μM, respectively. The IC_{50} values of other less potent α-glucosidase inhibitors from this plant are kompasinol A (28) (IC_{50} = 11.2), scirpusin A (29) (IC_{50} = 8.3), pentahydroxystilbene (30) (IC_{50} = 19.2), Piceatannol (31) (IC_{50} = 23.2), and resveratrol (32) (IC_{50} = 23.9).[24]

One lignan glucoside, (–)-lyoniresinol 3a-O-b-D-glucopyranoside (33), from *Alstonia scholaris* exhibited an inhibitory activity against both sucrase and maltase with IC_{50} values of 1.95 and 1.43 mM, respectively.[14]

Curcuminoids

Natural curcumin (34), demethoxycurcumin (35) and bisdemethoxycurcumin (36) isolated from *Curcuma longa* (turmeric) were evaluated in vitro for the α-glucosidase inhibitory activity via UV and circular dichroism spectroscopy. The results indicated that natural curcuminoid compound **36** showed a remarkable inhibitory effect with IC_{50} of 23.0 μM.[25]

Terpinoids

3b-Acetoxy-16b-hydroxybetulinic acid (37) was isolated from *Fagara tessmannii*, and it was found to be a potent α-glucosidase inhibitor with IC_{50} value 7.6 ± 0.6.[26]

A new triterpenoid saponin Segetalic acid 28-O-α-L-arabinopyranosyl-(1→4)-α-L-arabinopyranosyl-(1→3)-β-D-xylopyranosyl-(1→4)-α-L-rhamnopyranosyl-(1→2)-β-D-fucopyranosyl ester (38) has been isolated and elucidated from the roots of *Gypsophila oldhamiana* and has been evaluated for its α-glucosidase inhibition activity with the IC_{50} values of about 23.1 ± 1.8 μM.[27]

Anthocyanins

Cyanidin-3-galactoside (39), a natural anthocyanin, was also

investigated for its α-glucosidase inhibitory activity. The IC_{50} value of cyanidin-3-galactoside was 0.50 ± 0.05 mM against intestinal sucrase. A low dose of cyanidin-3-galactoside showed a synergistic inhibition on intestinal α-glucosidase (maltase and sucrase) when combined with acarbose.[28]

Maltase (m); Sucrase (s), 2*R*,3*R*,4*R*,5*R*)2,5-bis(hydroxymethyl)-3,4-dihydroxypyrrolidine (DMDP); 1-deoxynojirimycin (DNJ)

DISCUSSION

Diabetes is one of the world's greatest health problems, affecting about 171 million people and most of these will be dominated by those suffering from type 2 diabetes.[68] This increasing trend in type 2 diabetes mellitus has become a serious medical concern worldwide, which accounts for 9% of deaths that prompts every effort in exploring for new therapeutic agents to stem its progress. Although the drug treatment for type 2 diabetes mellitus has been improved to some extent during the last decade, drug resistance is still a big concern that needs to be dealt with effective approaches. One of the strategies to monitor blood glucose for type II diabetes mellitus is to either inhibit or reduce the production of glucose from the small intestine. α-Glucosidase inhibitors interfere with the digestion of carbohydrates, achieving better glycemic control. Thus, natural products of great structural diversity are still a good source for searching for such inhibitors, thereby motivating to explore biologically active compounds from the highly diverse plants.

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Source of Support: Nil, **Conflict of Interest:** None declared