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ORIGINAL ARTICLE

A New Sucrase Enzyme Inhibitor from *Azadirachta indica*

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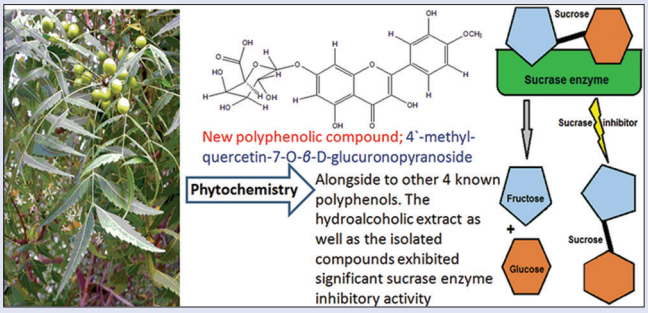
ABSTRACT

Background: Sucrase enzyme inhibitor considered as an oral anti-diabetic therapy that delays the absorption of eaten carbohydrates, reducing the postprandial glucose and insulin peaks to reach normoglycemia. **Materials and Methods:** Chromatographic fractionation of the hydroalcoholic extract of leaves of *Azadirachta indica* growing in KSA, followed by *in-vitro* assay of sucrase enzyme inhibition activity. **Results:** This investigation led to the isolation of a new remarkable sucrase enzyme inhibitor; 4`-methyl Quercetin-7-O-β -D-glucuronopyranoside (1) alongside with four known compounds; 2,3-hexahydroxydiphenoyl-(α/β)-D-$^4C_1$-glucopyranose (2), Avicularin (3), Castalagin (4) and Quercetin-3-*O*-glucoside (5). The structure of the new compound (1) was elucidated on the basis of its spectral data, including ESI-MS, UV, ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H COSY, HSQC, NOESY and HMBC. **Conclusion:** Under the assay conditions, hydroalcoholic extract of *A. indica* and compounds 1-5 exhibited significant sucrase enzyme inhibitory activity.

Key words: *Azadirachta indica*, polyphenols, sucrase inhibitor

SUMMARY

- Chromatographic fractionation of the hydroalcoholic extract of leaves of *Azadirachta indica*, led to the Isolation of a new flavonoid glycoside named 4`-methyl Quercetin-7-O-β-D-glucuronopyranoside, alongside to other 4 known polyphenols. The hydroalcoholic extract as well as the isolated compounds exhibited significant sucrase enzyme inhibitory activity.



Abbreviations used: ESI-MS; electrospray ionization-mass spectrometry, UV; ultraviolet, NMR; nuclear magnetic resonance, 1H-1H COSY; 1H-1H correlation spectroscopy, NOESY; nuclear overhauser effect spectroscopy, and HSQC; heteronuclear multiple bond correlation. *A. indica*; Azadirachta indica.

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INTRODUCTION

Any defect in insulin secretion or action results in hyperglycemia which leads to a metabolic disease, i.e. diabetic mellitus. Medicinal plants have been used since centuries by various cultures worldwide for the treatment of diabetes. Food and herbal control of postprandial hyperglycemia is an essential step in the early treatment of diabetes mellitus as hyperglycemia may induce nonenzymatic glycosylation of various proteins, resulting in the improvement of accompanied complications such as macrovascular and cardiovascular diseases.[1-4] Phytochemical constituents isolated from plants exhibit several hypoglycemic mechanisms, through the inhibition of carbohydrate-metabolizing enzymes, manipulation of glucose transporters, regeneration of α-cell, and enhancement of the insulin-releasing activity.[5,6] Hyperglycemia could be controlled by decreasing the absorption of glucose through the inhibition or decreasing the effect of certain enzymes responsible for the hydrolysis of carbohydrate such as sucrase enzyme in the digestive tract.[7]

Azadirachta indica A. Juss is a famous plant of the *Meliaceae* family. It is native to the Indian subcontinent and grows in many countries of the world such as Egypt and the Kingdom of Saudi Arabia (KSA). A massive cultivation of this tree occurred in the plains of Arafat, holy Makkah, the KSA. In 1971, approximately, 50,000 neem trees were cultivated to provide shade for the millions of pilgrims.[8] It has enormous therapeutic, biological activity, and ethno-medicinal significance, so it is considered as a source of many biological active agents, due to its contents of various active constituents with diverse medicinal properties. It was practiced by different types of vaidyas and traditional healers in almost all the countries in the world such as the KSA, China, India, Egypt, Rome, and Greek.[9-15] Anti-diabetic activity of medicinal plants has a strong relationship with their antioxidant property and polyphenolic contents.[16,17] Our previous study revealed that the leaves of *A. indica* contain a considerable amount of polyphenolic compounds with significant antioxidant and cytotoxic activity.[18] Hence, it is interesting to investigate the *in vitro* anti-diabetic activity of alcoholic extract of *A. indica* and the isolated polyphenolic compounds through the performance of sucrase inhibitory activity test.

MATERIALS AND METHODS

Equipment and materials

Pure samples were measured separately as MeOH solutions and various diagnostic shift reagents, Shimadzu ultraviolet (UV) 240 spectrophotometer,[19] and with sprayed Naturstoff reagent.[20] Nuclear

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magnetic resonance (NMR) analyses were run on Varian Mercury 300 MHz and Bruker 500 MHz spectrometers relative to TMS in different deuterated solvents. Electrospray ionization-mass spectrometry (ESI-MS) spectra were measured according to previously published conditions.[18]

Extraction and isolation

Leaf samples *of A. indica* were freshly collected from Bahra in the KSA and identified by Dr. Kadry Abdelkhaliq, Faculty of applied sciences, Umm Al-qura University, Makkah, the KSA. These samples were dried and grinded to get 1000 g which were extracted with hot 80% aqueous ethanol (2.5 L × 5 L) at 70°C. After evaporation of solvent under reduced pressure, the residue (115 g) was defatted with petroleum ether. The methanolic extract of the defatted residue was preliminarily fractionated on a polyamide 6S (Riedel De Haen AG, Seelze, Hannover, Germany) column (C) (300 g, 120 cm × 5 cm) using a step gradient of H_2O–MeOH 100: 0–0:100 for elution to give 25 fractions of 1 L each, which were collected and monitored by Comp-PC using Whatman No. 1 paper (systems S_1 and S_2); S_1: *n*-BuOH-AcOH-H_2O (4:1:5, top layer) and S_2: 15% aqueous AcOH and UV-light into three major collective fractions. Fraction I (180 mg) was subjected to repeated column chromatography (CC) on microcrystalline cellulose (E. Merk, Darmstadt, Germany) using *n*-BuOH-isopropanol-H_2O BIW, 4:1:5, organic layer as an eluent followed by repeated and separate cellulose column for each major subfraction using methanol/BIW (50%) to give pure samples of compound 1 (17 mg), compound 3 (27 mg), and compound 5 (17 mg). Fraction II (85 mg) was chromatographed on a Sephadex LH-20 CC and eluted with MeOH, then pure compound 4 (26 mg) was obtained by precipitation from MeOH by excess EtOAc. The rest was dried (20 g) and then it was re-dissolved in water:methanol (1:10), filtered and dried under vacuum to give 15.5 g dry residue. Therefore, it was fractionated on cellulose CC (70 cm × 5 cm) using MeOH (10%), then it was chromatographed on Sephadex C (10% aqueous MeOH as eluent) followed by Sephadex LH-20 CC and eluted with 10% MeOH to give pure compound 2 (16 mg). These compounds were visualized by spraying with Naturstoff (for flavonoids) and nitrous acid or KIO_3 reagents (for tannins) as illustrated previously by Abdelhady *et al.*, 2015.[18]

Assay of sucrase inhibitory activity

A sucrase enzyme solution of rat intestine has been prepared according to Dahlqvist's method. It occurred as a complex of sucrase and isomaltase, this hydrolyzes sucrose into glucose and fructose.[21] Honda and Hara created a method to assay the effect of samples on sucrase enzyme activity.[22] Enzyme solutions (10 µL) were incubated together with buffered solubilized sample (25–200 µg/ml in maleate buffer with pH 6.0) for 10 min at 37°C, while the volume was completed to 200 µL with maleate buffer (pH 6.0) in case of control, then the reaction was initiated by the addition of 100 µL of sucrose solution (60 mM). About 30 min later, the reaction was stopped by the addition of 200 µL of 3, 5-dinitrosalysilic acid reagent. The mixture was incubated in a boiling water bath for 5 min. The absorbance of each reaction was read at 540 nm. The percentages of inhibitory activities were calculated using the following formula:

$$\% \text{ Inhibition} = \frac{\text{Abs control} - \text{Abs sample}}{\text{Abs control}} \times 100$$

Abs control represents the absorbance of the control reaction (containing all reagents except the tested sample), whereas the Abs sample is the absorbance of the tested sample. An untreated enzyme solution was used as control. All experiments were carried out 3 times.

RESULTS

The dried residue of 80% EtOH extract, which was extracted with pet-ether for defatting, was chromatographed on a polyamide column followed by successive separation on Sephadex LH-20 CC and cellulose CC for purification. The isolated pure compounds were identified by different chromatographic and spectral techniques such as UV, ^{1}H, ^{13}C NMR, two-dimensional NMR, and negative ESI-MS. As discussed in the published data,[18] the isolated known compounds have been identified as 2, 3-hexahydroxydiphenoyl-(*α*/*β*)-D-$^4C_1$-glucopyranose (2), avicularin (3), castalagin, (4) and quercetin-3-*O*-glucoside (5). In addition to the new compound isolated for the 1st time from nature identified as 4'-methyl quercetin-7-O-*β*-D-glucuronopyranoside (1) is identified according to the following:

Compound 1 was obtained as pale yellow amorphous powder (17 mg) with the following chromatographic properties: Rf values; 0.32 (S_1), 0.51 (S_2); purple color under UV light turned to green color with $FeCl_3$ and orange color with Naturstoff spray reagents. UV-spectral data λ_{max} (nm) (MeOH): 281, 352; (+NaOMe): 287, 382; (+NaOAC): 280, 351; (+$AlCl_3$): 280, 302 (sh), 352, 391; (+$AlCl_3$/HCl): 281, 301 (sh), 348, 390. ^{1}H NMR (500 MHz, DMSO-*d*6): *δ* ppm 12.49 (1H, s, H-bonded OH-5), 7.58 (2H, dd, *J* = 8.1, 2.4 Hz, 1H-6'), 7.47 (1H, d, *J* = 2.0 Hz, H-2'), 7.12 (1H, d, *J* = 8.4 Hz, H-5'), 6.74 (1H, d, *J* = 1.9 Hz, H-8), 6.67 (1H, d, *J* = 1.9 Hz, H-6), 5.68 (1H, d, *J* = 6.1 Hz, H-1"), 3.76 (3H, s, O-Me), 4.29-2.85 (remaining sugar protons). ^{13}C NMR (125 MHz, DMSO-*d*6): *δ* ppm 177.24 (C-4), 172.02 (C-6"), 164.2 (C-2), 163.21 (C-5), 156.22 (C-7), 156.06 (C-9), 148.65 (C-4'), 148.60 (C-3'), 131.71 (C-3), 121.21 (C-6'), 120.07 (C-1'), 116.24 (C-5'), 113.63 (C-2'), 104.06 (C-10), 100.85 (C-1"), 97.65 (C-6), 96.48 (C-8), 78.63 (C-3"), 76.45 (C-5"), 71.06 (C-2"), 70.26 (C-4"), 54.78 (OCH_3-4')-ve ESI-MS: m/z 491.18 $(M-H)^-$, 477.39 $(M-CH_3)^-$, 315.44 (M-deoxyglucuronide)$^-$, 300.43 (quercetin-H)$^-$.

Results of the anti-diabetic activity (sucrase-inhibitory activity)

The effect of the hydroalcoholic extract of *A. indica* and its selected isolated polyphenolic compounds on carbohydrate-hydrolyzing enzyme, namely rat intestinal sucrase, has been studied using *in vitro* model system.[22] These samples significantly inhibited ($P > 0.05$) sucrase activity [Table 1 and Figure 1]. The sucrase inhibitory activity of hydroalcoholic extract of *A. indica* and the isolated polyphenolic compounds supposed to be due to the presence of hydrolysable tannins and flavonoids.[17,23] It was observed that compound 1 exhibited the highest sucrase inhibitory activity with IC_{50} (68.45 µg/ml) followed by compound 5 with IC_{50} (90.26 µg/ml), compound 3 with IC_{50} (94.31 µg/ml), compound 4 with IC_{50} (138.3 µg/ml), total extract with IC_{50} (160.6 µg/ml), and then compound 2 with IC_{50} (195.62 µg/ml).

Data were analyzed using two-factorial analysis of variance (ANOVA), including first-order interactions (two-way ANOVA), followed by

Table 1: Percentage sucrase inhibitory activity using Honda and Hara assay

	Conc. 25 µg/ml	Conc. 50 µg/ml	Conc. 100 µg/ml	Conc. 200 µg/ml
Total extract	31.72±1.63	34.64±1.54	41.34±2.37	55.63±2.88
Compound 1	37.52±0.92	42.56±3.08	62.72±1.83	71.35±3.21
Compound 2	33.27±2.02	36.43±1.87	43.67±1.47	50.29±2.65
Compound 3	28.62±1.07	31.47±0.86	52.38±2.46	58.34±1.64
Compound 4	25.73±0.77	28.43±1.43	48.28±2.37	52.77±2.04
Compound 5	21.39±2.14	30.82±1.06	54.64±1.34	61.36±3.02

Data were analyzed using two-factorial ANOVA, including first-order interactions (two-way ANOVA), followed by the Tukey's *post hoc* test for multiple comparisons. $P<0.05$ indicated statistical significance. Conc.: Concentration of the tested sample; ANOVA: Analysis of variance

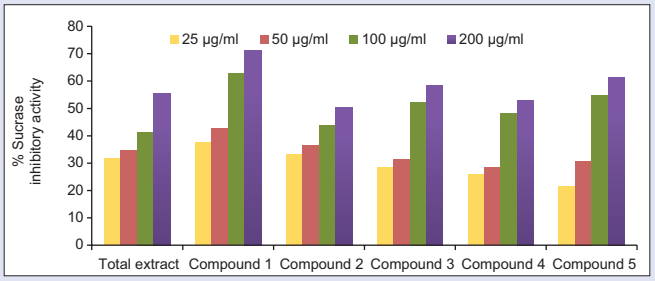

Figure 1: Sucrase enzyme inhibition activity

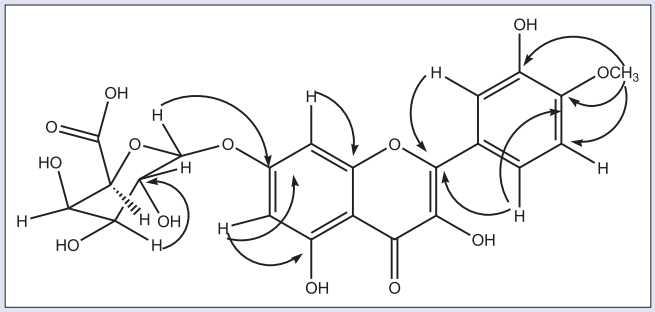

Figure 2: Heteronuclear multiple bond correlation correlations for compound 1

the Tukey's *post hoc* test for multiple comparisons. $P < 0.05$ indicated statistical significance.

DISCUSSION

According to the chromatographic properties and UV-spectral data, compound 1 was expected to be 4', 7-quercetin derivative. The UV spectrum in MeOH exhibited the two characteristic absorption bands at λ_{max} (nm) 281 nm (band II) and 352 nm (band I) of quercetin nucleus. Upon addition of NaOAc, no bathochromic shift of band II was observed which is diagnostic of a substituted 7-OH group. The remaining diagnostic shift reagents were in complete agreement with the 3', 5 dihydroxy-4'-7 disubstituted flavonol structure.[19] Negative ESI-MS spectrum exhibited the molecular ion peak at m/z 491 $[M-H]^-$ which corresponds to a molecular weight of 492 and a molecular formula of $C_{22}H_{20}O_{13}$. In addition, a fragment ion peak at m/z 477 after a loss of a methyl moiety indicates a methyl quercetin glucuronide structure. Mild acid hydrolysis and CoPC showed the presence of glucuronic acid in the aqueous phase and quercetin in the organic phase. ^{1}H NMR spectrum showed the AM coupling system of the two meta-coupled doublets at δ ppm 6.74 and 6.67 assignable for H-8 and H-6, respectively, characteristic for ring-A of flavonol, in addition to the signals at δ ppm 7.58 (dd), 7.47 (d), 7.12 (d), assignable to H-6', H-2', and H-5', respectively, of ring-B with the absence of H-3' resonance signal suggesting the presence of quercetin moiety. The resonance singlet signal which integrated for three protons at δ ppm 3.76 was indicative for the presence of methoxy group, the location of the methoxy group on C-4'(ring-B) was deduced from the downfield shift of H-5' at δ ppm 7.12 (≈+0.3), in comparison with previously published data describing related structures.[24,25] This was approved by the heteronuclear multiple bond correlation (HMBC) that showed $^{2,3}J_{CH}$ coupling between O-Me protons at δ ppm 3.76 with C-4' at δ ppm 148.65. Further, structure confirmation was proved by the two-dimensional spectrums of ^{1}H-^{1}H COSY, HSQC, NOESY and HMBC, and by comparison with related compounds reported in published data.[24-28] This complete assignment confirmed the structure of compound 1 to be 4'-methyl Quercetin-7-O-β-D-glucuronopyranoside, which has not been reported previously in nature [Figure 2].

It is appeared worldwide that the drugs used for anti-diabetic effect with complementary mechanisms should be developed to control and inhibit the hydrolysis of carbohydrates in a reversible way. These consequently reduce the rise of postprandial blood glucose in diabetics.[3] Medicinal plants suggested to inhibit sucrase activity due to several possible factors such as the presence of polyphenolic constituents.[17,23] Anti-diabetic activity of medicinal plants has a strong relationship with their antioxidant property.[17] Hence, hydroalcoholic extract of *A. indica* and the isolated polyphenolic compounds may have anti-diabetic activity, due to their significant antioxidant and reducing power activities, as approved in the previous investigation.[18] Hence, the tested samples (i.e. *A. indica* and compounds 1–5) may offer a support in the treatment of diabetic disease. In the present investigation, the effect of the tested samples on carbohydrate-hydrolyzing enzyme, namely rat intestinal sucrase, has been studied using *in vitro* model systems. The hydroalcoholic extract of *A. indica* and its selected isolated polyphenolic compounds; 4'-methyl quercetin-7-O-β-D-glucuronopyranoside (1), 2,3-hexahydroxydiphen oyl-(α/β)-D-$^4C_1$-glucopyranose (2), avicularin (3), castalagin (4), and quercetin-3-*O*-glucoside (5) significantly decreased the sucrase enzyme activity [Figure 1]. These findings are in accordance with the previous study as the sucrase-inhibitory activity of tested plants supposed to be due to the presence of flavonoid glycosides and/or hydrolysable tannins.[16] Due to the rise in the incidence of diabetic patients around the world, it appears that more anti-diabetic drugs with complementary actions should be discovered and improved to reduce the blood glucose level by inhibiting the hydrolysis of carbohydrates in a reversible way. The World Health Organization suggested the evaluation of traditional plant treatments for diabetes as they are effective, less toxic, with fewer side effects, and are considered to be excellent candidates for oral therapy.[29] The antihyperglycemic activity of the plants is mainly due to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or inhibiting the intestinal absorption of glucose or to the facilitation of metabolites in insulin-dependent processes. Glycosides, flavonoids, and carotenoids, from the plants, are frequently implicated in having anti-diabetic effect.[30] In the present study, the hydroalcoholic extract of *A. indica* and its isolated polyphenolic compounds 1–5 may have anti-diabetic activity due to their potent inhibitory activity against sucrase enzyme as shown in Figure 1.

CONCLUSION

The hydroalcoholic extract of the leaves of *A. indica* (family *Meliaceae)* and the tested compounds; 4'-methyl quercetin-7-O-β-D-glucuronop yranoside (1), 2,3-hexahydroxydiphenoyl-(α/β)-D-$^4C_1$-glucopyranose (2), avicularin (3), castalagin (4), and quercetin-3-*O*-glucoside (5) exhibited a significant *in vitro* anti-diabetic activity using sucrase enzyme inhibitory activity test. The hydroalcoholic extract of the leaves of *A. indica* contains a considerable amount of polyphenolic compounds that have significant antioxidant, cytotoxic,[18] and sucrase-inhibitory activities, thus have a great potential as a source for natural health products. Hence, the authors recommend *in vitro* and *in vivo* toxic tests to be done to evaluate the safety of *A. indica* to be used as a complementary medicine.

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Conflicts of interest

There are no conflicts of interest.

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