J Korean Soc Appl Biol Chem (2012) 55, 47–51
DOI 10.1007/s13765-012-0008-1

ORIGINAL ARTICLE

α-Amylase and α-Glucosidase Inhibitors Isolated from *Triticum aestivum* L. Sprouts

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Received: 1 September 2011 / Accepted: 11 October 2011 / Published Online: 29 February 2012

Abstract Inhibitory activities of the methanol extract from *Triticum aestivum* L. sprouts were examined against α-amylase and α-glucosidase. The active constituents of *T. aestivum* were isolated by chromatographic techniques and identified as γ-aminobutyric acid and ferulic acid on the basis of IR and NMR. γ-Aminobutyric acid and ferulic acid showed the high inhibitory activities with IC_{50} values of 5.4±0.2 and 9.5±0.1 mM against α-amylase, and 1.4±0.4 and 4.9±0.3 mM against α-glucosidase. The methoxy group on the hydroxycinnamic acid of ferulic acid derivatives played important functions in the α-amylase and α-glucosidase inhibitory activities. Based on the IC_{50} values of nitrite-scavenging activity, ferulic acid (98±3.9 μg/mL) was the most effective constituent, followed by γ-aminobutyric acid (182±4.2 μg/mL), sinapic acid (301±2.7 μg/mL), and *p*-coumaric acid (454±2.2 μg/mL). These results indicate that γ-aminobutyric acid and ferulic acid could be useful as preventative agents, and possibly therapeutic modalities for the treatment of metabolic diseases.

Keywords γ-aminobutyric acid · α-amylase · ferulic acid α-glucosidase · *Triticum aestivum* sprouts

Introduction

In order to ameliorate diabetes mellitus by retarding the absorption of glucose, it is necessary to inhibit carbohydrate-hydrolyzing enzymes, such as α-amylase and α-glucosidase (Wang et al., 2010). Well-known enzyme inhibitors, such as acarbose and voglibose, have received a considerable amount of attention (Hollander, 1992; Liu, 2011), largely due to the side effects associated with synthetics, including flatulence, abdominal cramping, and possibly diarrhea (Hollander, 1992; Kim, 2009). In this regard, efforts have been focused on the isolation and identification of α-amylase and α-glucosidase inhibitors from plants, owing to the naturally bioactive compounds (amino acids, polyketides, and terpenes) (Lee, 2005; Kim, 2009). These enzyme inhibitors could be used to effectively treat diabetes mellitus with minimal side effects, develop physiologically functional foods, and lead compounds (Liu et al., 2011). Furthermore, these bioactive inhibitors have been shown to exhibit various functional abilities (Kim, 2009; Liu, 2011).

Triticum aestivum L. is one of the major cereals, and is rich in dietary fiber, minerals, phenolic compounds, starches, and other phytochemicals. These bioactive compounds play important roles in human nutrition and health benefits (Hung, 2009; Jeong, 2010). Previous reports have largely focused on the functionality and nutrition of wheat grains such as flour and bran (Adom et al., 2003). However, relatively few studies have examined the isolation and purification of bioactive compounds from *T. aestivum* sprouts. Therefore, the present study focused on the antidiabetic compounds (α-amylase and α-glucosidase inhibitors) and nitrite-scavenging components isolated from *T. aestivum* sprouts.

Materials and Methods

Chemicals. Acarbose, bovine serum albumin, butylated hydroxyanisole, *p*-coumaric acid, dimethyl sulfoxide, *p*-nitrophenyl-α-D-glucopyranoside, porcine pancreatic α-amylase, sinapic acid, sodium azide, starch azure, and Tris-HCl were purchased from Sigma-Aldrich (St. Louis, MO). All other chemicals were of reagent grade. Acetonitrile, H_2O, and methanol (HPLC grade) were used as the mobile phase for HPLC purification.

Sample preparation. *T. aestivum* L. sprouts were collected from

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the National Institute of Crop Science, Rural Development Administration (Lee et al., 2009). Whole sprout samples (500 g) were washed, homogenized with a high-speed blender (robot coupe USA Inc. Blixer 3, 3450 rpm, Jackson, Ridgeland, MS) to obtain juice, and treated with a cooling system (4°C) for 7 days. After steam-cooking the juice (100°C) for 5 min, the juice was filtered through two layers of gauze. The samples were extracted with methanol (2 L) in a shaking incubator for 24 h at room temperature, and filtered using filter paper (Toyo filter paper No, Toyo Roshi, Tokyo, Japan). Subsequently, the combined filtrate was then concentrated *in vacuo* at 45°C to yield 10.2%.

Isolation and purification of the active compounds. Bioactive compounds were purified from the methanol extract of the *T. aestivum* sprouts by a bioassay-guide separation. The methanol extract (20 g) dissolved in distilled water was partitioned with *n*-hexane, chloroform, ethyl acetate, *n*-butyl alcohol, and water-soluble solvent, successively. The organic solvent portions were concentrated to dryness using a rotary vacuum evaporator (EYELA autojck NAJ-100, Tokyo, Japan) at 45°C, and the water portion was freeze-dried at −56°C.

The ethyl acetate (5 g) portion was isolated on a silica gel column (Merck 70–230 mesh; 620 g; inside diameter, 8×93 cm, Rahway, NJ) and then consecutively eluted utilizing a gradient step of ethyl acetate-methanol (7:1 to 1:9; v/v). In this step, four fractions (G1-G4) were obtained and bioassayed using antidiabetic and antioxidant activity methods. The bioactive fraction (G2, 2.914 g) was then purified by Prep. HPLC (LC908C-W60, recycling preparative HPLC, Japan Analytical Industry Co., Ltd., Tokyo, Japan). The Jaigel GS column (GS-310 50 cm + GS-220 50 cm, 7.6 mm i.d., 1000 mm long; Japan Analytical Industry Co., Ltd., Tokyo, Japan) was used with in H_2O:methanol (3:7, v/v) at a flow rate of 3 mL/min and detection at 320 nm. This procedure generated five fractions (G21-G25), each of which was bioassayed for their activities. The active fraction (G22, 1.025 g) was then further separated on a Jaigel ODS column (ODS 50 cm, 8.0 mm i.d., 500 mm long) using methanol (100%, v/v) at a flow rate of 3 mL/min for HPLC, from which a potent active compound (G222, 0.098 g) was isolated. Subsequently, the bioactive water-soluble (5 g) portion was then purified by Prep. HPLC (LC908C-W60, recycling preparative HPLC, Japan Analytical Industry Co., Ltd.). The Jaigel ODS column (ODS 50 cm, 8.0 mm i.d., 500 mm long; Japan Analytical Industry Co., Ltd.) was used with H_2O:acetonitile (9:1, v/v) at a flow rate of 5 mL/min and detection at 294 nm. This procedure generated 4 fractions (F1-F4), each of which was bioassayed for its biological activities. The active fraction (F3, 3.097 g) was then further separated on Jaigel GS column (GS-310 50 cm + GS-220 50 cm, 7.6 mm i.d., 1000 mm long; Japan Analytical Industry Co., Ltd.), with methanol (100%, v/v) at a flow rate of 3 mL/min for HPLC. For further separation of the active F37 fraction (0.801 g), Jaigel W series column (W-253 50 cm + W-252 50 cm, 20.0 mm i.d., 1000 mm long) using H_2O (100%, v/v) at a flow rate of 5 mL/min for HPLC were used. The eluates were examined for their biological activities. The active F372 fraction was subjected to this procedure twice in succession. Finally, a potent active compound (F3721, 0.443 g) was isolated. The structures of ferulic acid (G222) and γ-aminobutyric acid (F3721) were then determined by spectroscopic analyses. To accomplish this, the IR spectra were recorded on a ThermoNicolet/NEXus 870 FT-IR apparatus. Spectra were run in the 4000–400 cm^{-1} region. The ^1H- and ^{13}C-NMR spectra of the compound were recorded in deuterium oxide with a NJM-LA 400F7 spectrometer (JEOL, Tokyo, Japan) at 400 and 100 MHz (TMS as an internal standard), respectively. The chemical shifts were given in δ (parts per million). G222, FT-IR (wavenumber cm^{-1}); 1207, 1750, 2926, 3102, 3020; ^1H-NMR (D_2O, 400 MHz) δ 3.80, 5.29–5.35, 6.28, 6.72–6.91, 7.15–7.39, 10.87; ^{13}C-NMR (D_2O, 100 MHz); 55.62, 111.78, 115.92, 116.13, 122.76, 127.42, 144.63, 147.51, 148.96, 170.33. F3721, FT-IR (wavenumber, cm^{-1}); 1397, 1596, 2594, 2955; ^1H-NMR (D_2O, 400 MHz) δ 1.65–1.79, 2.01–2.10, 2.77–2.80, 4.65, 10.55; ^{13}C-NMR (D_2O, 100 MHz); 24.38, 35.15, 40.03, 182.29.

Isolation of α-glucosidase from sprague dawley rats. α-Glucosidase was isolated according to the procedure described previously by Lee (2005) with a slight modification. Briefly, α-glucosidase was prepared from the small intestines of 4-week-old Sprague Dawley male rats (each weighing 180–200 g). The rats were starved for 16-18 h prior to the study except for water provided *ad libitum*. The small intestinal brush border was removed from rats and carefully homogenized for 5 min in 5 volumes (w/v) of 5 mM EDTA (pH 7.0) containing 0.5 M sodium chloride and 0.5 M potassium chloride using a Potter-Elvehjem homogenizer (Wheaton Co., Millville, NJ). The homogenate was centrifuged at 20,000 × *g* for 30 min. The precipitate was then dissolved with 5 mM EDTA (pH 7.0) and centrifuged at 20,000 × *g* for 30 min. The precipitate was then redissolved with 5 volumes of 0.9% sodium chloride and centrifuged at 1,000 × *g* for 30 min. The supernatant was retained as an enzyme preparation. All procedures were carried out at 4°C.

Assay for α-amylase inhibitory activity. The porcine pancreatic α-amylase inhibitory activity was assayed according to the procedure described by Wang et al. (2010) with a slight modification. The enzyme solution (6.25 U/mL) was prepared by dissolving α-amylase (Sigma Co., St. Louis, MO) in 0.5 M Tris-HCl buffer (pH 6.9). The starch azure (8 mg) was suspended in 0.5 M Tris-HCl buffer containing 0.01 M calcium chloride and soaked in boiling water for 5 min followed by preincubation at 37°C for 10 min. The enzyme solution (100 μL) and sample (100 μL) in 50% dimethyl sulfoxide were mixed in a 96-well microtiter plate. After 10 min of incubation at 37°C, 50 μL of 50% acetic acid was then added to stop the reaction. The absorbance of the reactants was measured at 595 nm with a microplate reader (Model ASYS UVM 340, Biochrom Ltd., Cambridge, England). Acarbose was used as a positive control. All reaction tests were replicated three times. The inhibition percentage (%) was determined using the following equation: Inhibition (%) = $[1-(A_{sample}/A_{control})]\times 100$. The IC_{50} values were calculated by applying logarithmic regression

analysis.

Assay for α-glucosidase inhibitory activity. α-Glucosidase inhibitory activity was assayed according to the procedure described by Shinde et al. (2008) with a slight modification. The formation of *p*-nitrophenol was measured using α-glucosidase after reaction with *p*-nitrophenyl-α-D-glucopyranoside (NPG). The enzyme solution (0.6 U) was prepared by dissolving α-glucosidase in 0.1 M phosphate buffer (pH 7.0) containing 2 g/L bovine serum albumin and 0.2 g/L sodium azide. The enzyme solution (50 μL) and sample (10 μL) dissolved in dimethyl sulfoxide were mixed and placed in a 96-well microtiter plate. After 15 min of preincubation at 37°C, 5 mM NPG (50 μL) in the same buffer was added, and the mixture was incubated for 10 min at 37°C. Forty microliters of 0.1 M Sodium carbonate were subsequently added to stop the reaction. The absorbance of the reactants was measured at 405 nm using a microplate reader (Model ASYS UVM 340, Biochrom Ltd.). Acarbose was used as a positive control. All reaction tests were replicated three times. Inhibition percentage (%) was determined using the following equation: Inhibition (%) = $[1-(A_{sample}/A_{control})]\times100$. The IC_{50} values were calculated by applying logarithmic regression analysis.

Nitrite-scavenging activity. Nitrite-scavenging activity was processed according to the procedure described by Lee and Lee (2010) with slight modification. One millimole sodium nitrite (1 mL) and sample (1 mL) dissolved in 0.1 N hydrogen chloride (pH 1.2) were mixed in a 10-mL tube. After 2 h of preincubation at 37°C, 2% acetic acid (5 mL) and Griess reagent (0.4 mL) were added, and the mixture was incubated for 15 min at room temperature. The absorbance of the reactants was measured at 520 nm using a spectrophotometer (Model DR-4000U, HACH Co., Loveland, CO). Butylated hydroxyanisole (BHA) (Sigma Co.) was used as a positive control. All reaction tests were replicated three times. To determine the nitrite-scavenging activity percentage (%), we used the equation: (%) = $[1-(A_{sample}-A_{control}/B_{1\ mM\ sodium\ nitrite})]\times100$.

Results and Discussion

Antidiabetic activities of the methanol extract from *T. aestivum* sprouts against α-amylase and α-glucosidase were measured at 1,500 μg/mL (Table 1). The inhibiting percentages of the methanol extract against α-amylase and α-glucosidase were 30.4±0.2 and 58.2±0.7%, respectively. In the case of nitrite-scavenging activity, the methanol extract showed 92.5±0.5% at 1,000 μg/mL and 59.7±0.5% at 500 μg/mL (Table 2). Due to the potent activity of the methanol extract derived from the *T. aestivum* sprouts, the extract (20 g) was fractionated into *n*-hexane (yield 0.344 g), chloroform (0.896 g), ethyl acetate (6.235 g), *n*-butyl alcohol (4.253 g), and water-soluble portions (8.272 g), after which five portions were evaluated for the inhibitory activities of α-amylase and α-glucosidase. At 1,500 μg/mL, the inhibitory activities of five fractions against α-amylase were as follows: the water-soluble fraction (48.4±1.3%) > ethyl acetate fraction (28.6 ±0.9%) > *n*-butyl alcohol fraction (16.4±0.5%) > chloroform fraction (9.5±0.8%) > *n*-hexane fraction (1.3±1.9%) (Table 1). Furthermore, the inhibitory activities of the five fractions against α-glucosidase were as follows: water-soluble fraction (68.1± 0.2%) > ethyl acetate fraction (32.8±0.6%) > *n*-butyl alcohol fraction (17.3±1.5%) > chloroform fraction (13.6±0.8%) > *n*-hexane fraction (9.1±1.6%) at 1,500 μg/mL. The nitrite-scavenging activities of five fractions at 1,000 μg/mL ranged from 17.3±0.8 to 89.5±0.6 μg/mL, and increased in the following order (Table 2): water-soluble fraction (89.5±0.6 μg/mL) > ethyl acetate fraction (53.2±1.1 μg/mL) > *n*-butyl alcohol fraction (37.1±0.9 μg/mL) > *n*-hexane fraction (21.9±1.4 μg/mL) > chloroform fraction (17.3± 0.8 μg/mL). In particular, the ethyl acetate and water-soluble fraction had higher α-amylase inhibitory activity, α-glucosidase inhibitory activity, and nitrite-scavenging activity than the other fractions.

Table 1 α-Amylase and α-glucosidase inhibitory activities of various fractions obtained from the methanol extract of *T. aestivum* sprouts

Samples[a]	α-Amylase inhibitory activities (%)	α-Glucosidase inhibitory activities (%)
Methanol extract	30.4±0.2	58.2±0.7
n-Hexane fraction	1.3±1.9	9.1±1.6
Chloroform fraction	9.5±0.8	13.6±0.8
Ethyl acetate fraction	28.6±0.9	36.1±0.6
n-Butyl alcohol fraction	16.4±0.5	17.3±1.5
Water-soluble fraction	48.4±1.3	68.1±0.2
Acarbose[b]	59.3±0.6	70.2±1.9

[a]Sample concentration: 1,500 μg/mL
[b]Positive control

Owing to the potent activities of the ethyl acetate and water-soluble fractions against α-amylase and α-glucosidase, their active components were subjected to silica gel chromatography and isolation by prep HPLC. Structural determination of the isolates (G222 and F3721) was made by spectroscopic analysis techniques, including FT-IR, ^{1}H- and ^{13}C-NMR. Based on the results of these analyses, the active compounds were identified as ferulic acid (G222) and γ-aminobutyric acid (F3721). Ferulic acid (G222, $C_{10}H_{10}O$): MW (Molecular weight) 194.2; FT-IR (wave number cm^{-1}); 1207 (CO), 1750 (COOH), 2926 (CH_3), 3102 (CH), 3020 (benzene); ^{1}H-NMR (D_2O, 400 MHz) δ 3.80 (3H, s, CH_3), 5.29–5.35 (OH, d, OH), 6.28 (1H, s, CH), 6.72–6.91 (1H, m, CH), 7.15–7.39 (1H, m, CH), 10.87 (OH, s, OH); ^{13}C-NMR (D_2O, 100 MHz); 55.62 (2-OCH_3), 111.78 (C-1), 115.92 (C-8), 116.13 (C-4), 122.76 (C-5), 127.42 (C-6), 144.63 (C-7), 147.51 (C-3), 148.96 (C-2), 170.33 (C-9). γ-Aminobutyric acid (F3721, $C_4H_9NO_2$): MW (Molecular weight) 103.1; FT-IR (wavenumber, cm^{-1}); 1397 (CH_2), 1596 (C=C), 2594 (COOH), 2955 (NH_2); ^{1}H-NMR (D_2O, 400 MHz) δ 1.65–1.79 (2H, m, CH_2), 2.01–2.10 (2H, t, CH_2), 2.77–2.80 (2H, t, CH_2), 4.65 (NH2, s, NH_2), 10.55 (OH, s, OH); ^{13}C-NMR (D_2O, 100 MHz); 24.38 (C-2), 35.15 (C-3), 40.03 (C-1), 182.29 (C-4). The spectroscopic data generated by

Table 2 Nitrite-scavenging activities of various fractions obtained from the methanol extract of *T. aestivum* sprouts

Samples	Nitrite-scavenging activities (%)		
	200 (μg/mL)	500 (μg/mL)	1,000 (μg/mL)
Methanol extract	12.6±0.6	59.7±0.5	92.5±0.2
n-Hexane fraction	ND[a]	ND	21.9±1.4
Chloroform fraction	ND	ND	17.3±0.8
Ethyl acetate fraction	11.4±0.7	37.3±0.8	53.2±1.1
n-Butanol fraction	ND	3.8±1.4	37.1±0.9
Water-soluble fraction	42.8±1.2	67.4±0.3	89.5±0.6
BHA[b]	57.1±0.5	98.3±0.7	99.8±0.2

[a]ND: not detected
[b]Positive control

the analysis of ferulic acid and γ-aminobutyric acid in this study were in agreement with the previously reported data (Sonnewald, 1993; Bunzel, 2005; Kulik, 2009).

Antidiabetic activities of γ-aminobutyric acid, ferulic acid, ferulic acid derivatives (*p*-coumaric acid, sinapic acid), and acarbose as a positive control were examined by comparing the IC_{50} values generated against α-amylase and α-glucosidase. With regard to α-amylase inhibitory activities, γ-aminobutyric acid (5.4±0.2 mM) was less potent than acarbose (2.4±0.3 mM), followed by ferulic acid (9.5±0.1 mM), sinapic acid (12.3±0.3 mM), and *p*-coumaric acid (>30 mM). Against α-glucosidase, γ-aminobutyric acid (1.4±0.4 mM) was more effective than acarbose (1.7±0.1 mM), followed by ferulic acid (4.9±0.3 mM), sinapic acid (6.1±0.8 mM), and *p*-coumaric acid (>30 mM), respectively (Table 3). These results show that γ-aminobutyric acid and ferulic acid evidenced effective inhibitory activities against α-amylase and α-glucosidase and could be used as safe inhibitors for preventing digestion of carbohydrates, with the aim of developing them for clinical applications in the dietary control of type 2 diabetes mellitus. However, further study on the action mode of γ-aminobutyric acid and ferulic acid related to control of type 2 diabetes mellitus are needed for the *in vivo* bioassay methods.

The type 2 diabetes mellitus including hyperglycemia has been shown to increase superoxide anion and hydrogen peroxide production in vascular tissue (Gokce and Haznedaroglu, 2008). Wang et al. (2010) reported that seven flavonoids isolated from the guava leaves showed strong inhibitory activity against α-glucosidase, and also had more effective free radical-scavenging activity. Furthermore, berry polyphenols were found to possess antidiabetic and antioxidative activities (McDougall and Stewart, 2005). Generally, plants have long been recognized as sources of antidiabetic and antioxidative compounds due to their ability to bind to naturally bioactive compounds (such as amino acid and phenolic compounds) (Kwon et al., 2008; Lee et al., 2009; Lee, 2010; Wang et al., 2010; Liu et al., 2011). Therefore, the antioxidative activity as measured by nitrite-scavenging activity was examined. In the nitrite-scavenging activity, the antioxidative activities of γ-aminobutyric acid, ferulic acid, ferulic acid

Table 3 α-Amylase and α-glucosidase inhibitory activities of isolated compounds and IC_{50} values (mM)[a] of their derivatives

Samples	α-Amylase inhibitory activities	α-Glucosidase inhibitory activities
γ-Aminobutyric acid	5.4±0.2	1.4±0.4
p-Coumaric acid	>30	>30
Ferulic acid	9.5±0.1	4.9±0.3
Sinapic acid	12.3±0.3	6.1±0.8
Acarbose[b]	2.4±0.3	1.7±0.1

[a]IC_{50} value: The 50% inhibitory concentration
[b]Positive control

Table 4 Nitrite-scavenging activities of isolated compounds and its derivatives for IC_{50} value (μg/mL)[a]

Samples	Nitrite-scavenging activities
γ-Aminobutyric acid	182±4.2
p-Coumaric acid	454±2.2
Ferulic acid	98±3.9
Sinapic acid	301±2.7
BHA[b]	160±0.5

[a]IC_{50} value: The 50% inhibitory concentration
[b]Positive control

derivatives, and BHA as a positive control were examined via comparison of the IC_{50} values. Based on the IC_{50} values, ferulic acid (98±3.9 μg/mL) was the most effective constituent, followed by γ-aminobutyric acid (182±4.2 μg/mL), sinapic acid (301±2.7 μg/mL), and *p*-coumaric acid (454±2.2 μg/mL) (Table 4). These results showed that γ-aminobutyric acid and ferulic acid exhibit potent scavenging activity against nitrite as a radical acceptor. Previously, ferulic acid was shown to have the most effective free radical-scavenging and SOD-like activities (Lee et al., 2009).

T. aestivum sprouts contain bioactive nutrient, vitamin, and mineral components (Nagaoka, 2005). In particular, some parts of *T. aestivum* such as the bran, germ, and young leaf contain a number of bioactive materials such as ferulic acid, folic acid, iron, linoleic acid, niacin, and vitamin B_1, B_6, B_{12}, although the material contents of each part differed (Nagaoka, 2005). In the present study, γ-aminobutyric acid and ferulic acid isolated from *T. aestivum* sprouts were found to exert more profound inhibition effects against α-amylase and α-glucosidase, and showed potent antioxidative activity in the nitrite-scavenging assay. Furthermore, the structural relationships of ferulic acid and its derivatives were examined. Ferulic acid is one of the phenolic compounds containing various functional groups on hydroxycinnamic acid. In particular, ferulic acid and sinapic acid, which belong to the hydroxycinnamic acid backbone-containing methoxy groups, showed effective α-amylase and α-glucosidase inhibitory and antioxidative activities. However, *p*-coumaric acid exhibited a relatively weak inhibitory response against α-amylase and α-glucosidase, as well as weak nitrite-scavenging activity.

In conclusion, antidiabetic activities of γ-aminobutyric acid and

ferulic acid against α-amylase and α-glucosidase indicate that the *T. aestivum* sprouts may have pharmacological values. Our findings demonstrate that ferulic acid derivatives have structural relationships related to α-amylase inhibitory activity, α-glucosidase inhibitory activity, and nitrite-scavenging activity. However, further work will be necessary to definitively determine if this activity is sufficient in evaluating these potent compounds for clinical applications.

Acknowledgments. This work was supported by a grant from Korea Institute of Planning and Evaluation for Technology of Food, Agriculture, Forestry, and Fisheries, through Chonbuk National University, to Hoi-Seon Lee (108156-03-1-SB010).

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