

Original Research Article

Alpha-Glucosidase Inhibitory and Antioxidant Activity of Solvent Extracts and Fractions of *Typha domingensis* (Typhaceae) Fruit

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Abstract

Purpose: To identify a solvent fraction with potent antiglycosidase and antioxidant activities from the fruit of *Typha domingensis*.

Methods: Extracts were prepared using hexane, chloroform, ethyl acetate, acetone (AE), methanol, and water. Antiglycosidase and 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activities of extracts were assessed. The most active extract was partitioned into chloroform, ethyl acetate, butanol (BF) and water, and the antiglycosidase and radical scavenging activities of the fractions were determined. Mode of inhibition of the strongest antiglycosidase fraction was investigated. Polyphenol, coumarin, proanthocyanidin (TPro), and hydroxycinnamic acid contents of the extracts and fractions were evaluated.

Results: AE had the highest antiglycosidase ($EC_{50} = 12.36 \mu\text{g/mL}$) and radical scavenging ($EC_{50} = 8.57 \mu\text{g/mL}$) activities. Solvent-partitioning of AE resulted in BF, which showed markedly stronger antiglycosidase activity ($EC_{50} = 4.27 \mu\text{g/mL}$) than quercetin ($EC_{50} = 22.18 \mu\text{g/mL}$). BF also had potent radical scavenging activity ($EC_{50} = 7.20 \mu\text{g/mL}$). BF was rich in TPro (735.65 mg/g) and was a competitive glucosidase inhibitor. TPro content correlated with antiglycosidase ($R^2 = 0.709$) and DPPH scavenging activities ($R^2 = 0.838$).

Conclusion: TPro-rich BF of *T. domingensis* fruit is a highly potent glucosidase inhibitor and radical scavenger. The findings demonstrate a potential for the development of natural antihyperglycemic agents with antioxidant effect from *T. domingensis* fruit.

Keywords: *Typha domingensis*, Antiglycosidase, Antioxidant, Proanthocyanidin, Hydroxycinnamic acid, Polyphenol, Coumarin

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INTRODUCTION

Type 2 diabetes is a chronic metabolic disorder characterized by hyperglycemia. Postprandial hyperglycemia is also a key risk factor for microvascular and macrovascular complications

in patients with type 2 diabetes [1]. Thus, antihyperglycemic agents that target postprandial hyperglycemia are recommended for optimal diabetes management and reduction of diabetes-associated complications [1].

α -Glucosidase is well-recognized as a therapeutic target for the modulation of postprandial hyperglycemia. α -Glucosidase inhibitors are used in therapy to delay or inhibit gastrointestinal digestion of oligosaccharides and the subsequent release of glucose. This consequently delays or reduces glucose absorption into the bloodstream following food uptake [2]. Acarbose, miglitol, and voglibose are antiglucosidase drugs that are orally administered for the management of postprandial hyperglycemia. Owing to their undesirable side effects, there is great interest among researchers worldwide to search for alternative glucosidase inhibitors. Minimal side effects and low costs of herbal medicines in the treatment of diabetes have encouraged the search for glucosidase inhibitors of plant origin [2,3].

In this study, we evaluated the potential of medicinal plant *Typha domingensis* Pers. (Typhaceae) as a source of potent, natural α -glucosidase inhibitors. The fruit and inflorescence of several *Typha* species are traditionally used in the treatment of wounds and bleeding in different regions of the world [4,5]. *T. domingensis* fruit is not traditionally used as an antidiabetic remedy. However, our preliminary screening has revealed moderate antiglucosidase and antioxidant activities in the crude water extracts of *T. domingensis* fruit, which were greater in potency compared with the male and female flowers [6]. At present, the antiglucosidase and antioxidant capacities of the *T. domingensis* plant are underexplored in the literature. Searching for concurrent antiglucosidase and antioxidant properties in the *T. domingensis* fruit has practical significance. Diabetic complications that are associated with postprandial hyperglycemia are known to be caused by the induction of oxidative stress [1]. Hence, dual-function antidiabetic agents with concurrent antiglucosidase and antioxidant properties may provide additional benefits when compared with single-function glucosidase inhibitors.

As an extension to our previous screening work [6], a more detailed investigation was undertaken where bioassay-guided fractionation was performed on *T. domingensis* fruit. The antiglucosidase and radical scavenging activities of *T. domingensis* fruit extracts prepared by using extraction solvents differing in polarity were compared in this study. The most potent extract was further solvent-partitioned into different fractions and their antiglucosidase and radical scavenging activities were established. The

contents of bioactive phytochemicals (polyphenols, coumarins, proanthocyanidins, and hydroxycinnamic acids) in the solvent extracts and fractions were determined and their correlations with antiglucosidase and radical scavenging activities were analyzed. Enzyme kinetic study was also performed to understand the possible mode of inhibition exerted by the solvent fraction exhibiting the most potent antiglucosidase activity.

EXPERIMENTAL

Plant sample

Healthy, mature fruits of *Typha domingensis* were collected in May 2013 from a population of *T. domingensis* inhabiting a lakeshore at the Universiti Tunku Abdul Rahman (UTAR) campus. The species of the plant was authenticated by Professor Hean-Chooi Ong, a plant taxonomist at University of Malaya, Malaysia. A herbarium specimen has been stored at UTAR's Faculty of Science for future reference.

Preparation of solvent extracts

Fruits of *T. domingensis* were cleaned by rinsing in distilled water and then blotted dry with tissue paper. The samples were then oven-dried at 45 °C to constant weight. The dried sample was pulverized using a Waring blender. Solvent extracts were prepared by first mixing the pulverized samples with hexane, chloroform, ethyl acetate, acetone, methanol, or autoclaved deionized water at a 1:10 (dry weight: volume) ratio. Each of the mixtures was incubated at 25 °C for 48 h on an orbital shaker (100 rpm). The mixtures were subsequently vacuum-filtered and the filtrates were centrifuged at 8600 g and 4 °C for 10 min. The supernatants obtained from the hexane extract (HE), chloroform extract (CE), ethyl acetate extract (EAE), acetone extract (AE), methanol extract (ME), and water extract (WE) were collected, whereas the pellets were discarded. The organic solvent extracts were concentrated by rotary evaporation *in vacuo* and then taken to dryness in an oven at 35 °C; WE was freeze-dried. The solid residues recovered from HE, CE, EAE, AE, and ME were dissolved in dimethyl sulfoxide (DMSO), whereas the solid residue of WE was redissolved in water. Aliquots of 50 mg/mL were prepared and stored at -20 °C until further use.

Determination of antiglucosidase activity

Glucosidase inhibitory activity was determined as previously described [6]. Quercetin was used as a reference compound as its effectiveness as a

glucosidase inhibitor *in vivo and in vitro* has been established [7,8]. EC_{50} , defined as the extract/fraction concentration required to achieving 50 % antiglucosidase activity, was determined by using linear regression analysis.

Determination of 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging activity

DPPH radical scavenging assay was carried out as previously described [9]. Ascorbic acid was used as the positive control. EC_{50} , defined as extract/fraction concentration required to achieve 50 % DPPH scavenging activity, was determined by using linear regression analysis.

Antiglucosidase and radical scavenging activities of different fractions

Fractionation of AE was carried out by suspending the solid residue of AE (2 g) in 100 mL of deionized water, followed by sequential partitioning into chloroform, ethyl acetate, and butanol by using a separatory funnel. Chloroform fraction (CF), ethyl acetate fraction (EAF), butanol fraction (BF), and water fraction (WF) were obtained. CF, EAF, and BF were concentrated by rotary evaporation *in vacuo* and then taken to dryness in an oven at 35 °C; WF was freeze-dried. The yield of CF, EAF, BF, and WF was 20.2, 20.1, 22.8, and 3.4 % w/w, respectively. The solid residues recovered from CF, EAF, and BF were dissolved in DMSO, whereas the solid residue of WF was redissolved in water. Aliquots of 50 mg/mL were prepared and stored at -20 °C until used. Antiglucosidase and DPPH scavenging activities of fractions were determined as described above. Their EC_{50} values were also determined by using linear regression analysis.

Phytochemical contents and correlation with bioactivities

Total phenolic (TP), total proanthocyanidin (TPro), and total hydroxycinnamic acid (THA) contents of extracts/fractions were determined as described in [6]. The three parameters were expressed as mg gallic acid equivalents (GAE)/g sample, mg leucocyanidin equivalents (LE)/g sample and mg caffeic acid equivalents (CAE)/g sample, respectively. Total coumarin (TCou) content was determined as described in [10] and expressed as mg coumarin equivalents (CE)/g sample. Correlation analyses were carried out between phytochemical contents of all extracts and fractions and the $1/EC_{50}$ values of antiglucosidase and DPPH scavenging activities.

Coefficient of determination (R^2) was determined from the analyses.

Evaluation of mode of α -glucosidase inhibition by butanol fraction

The antiglucosidase assay described above was carried out in the presence or absence of BF (4.27 and 5.34 μ g/mL) using 0 - 2 mM of the p-nitrophenyl α -D-glucopyranoside (p-NPGP) substrate (S). The amount of p-nitrophenol formed during the reactions was determined by using a p-nitrophenol standard curve. Reaction velocity (v) was calculated as the amount of p-nitrophenol formed (mM) per reaction duration (min). A Lineweaver-Burk plot was prepared. The mode of inhibition of glucosidase by BF was determined by analyzing the double reciprocal ($1/v$ versus $1/[S]$) plot using the Michaelis-Menten kinetics. V_{max} (maximum velocity) and k_m (substrate concentration that yields a half-maximal velocity) were determined from the plot.

Data analysis

All experiments were carried out in triplicates and data are expressed as mean \pm standard error of the mean (SEM). Statistical analyses were performed using SAS (Version 9.2). Data were analyzed by one-way ANOVA test and means of significant differences were separated using Fisher's Least Significant Difference (LSD) test or Student's t test at $\alpha = 0.05$. Linear regression and correlation analyses were carried out using Microsoft Office Excel 2003.

RESULTS

All solvent extracts of *T. domingensis* fruit, except HE, exhibited concentration-dependent increases in antiglucosidase activity when tested at 20, 40, 60, 80, and 100 μ g/mL (data not shown). No antiglucosidase activity was detected in HE. The EC_{50} value of antiglucosidase activity of AE (12.36 μ g/mL) was the lowest among all the solvent extracts (Table 1). The EC_{50} values of AE and ME are 44 % and 37 % lower than that of quercetin, respectively. The EC_{50} values of CE and EAE are 162 % and 488 % higher than that of quercetin. The EC_{50} value of WE was not statistically different from that of quercetin.

All six extracts of *T. domingensis* fruit showed an increase in DPPH scavenging activity in a concentration-dependent manner when tested at 20, 40, 60, 80, and 100 μ g/mL (data not shown).

Table 1: EC₅₀ values of antiglycosidase and DPPH scavenging activities of solvent extracts

Extract	EC ₅₀ value (µg/mL)	
	Antiglycosidase activity	DPPH scavenging activity
HE	nd	929.30 ± 22.29*
CE	58.15 ± 4.46*	63.98 ± 0.79*
EAE	130.33 ± 0.69*	43.84 ± 0.35*
AE	12.36 ± 0.05*	8.57 ± 0.20*
ME	14.03 ± 0.55*	11.64 ± 0.42*
WE	24.11 ± 0.68	11.77 ± 0.18*
Positive control	22.18 ± 0.88 (Quercetin)	3.56 ± 0.12 (Ascorbic acid)

Data are mean ± SEM (n = 3). The asterisks (*) denote values that are significantly different (p < 0.05) compared with the positive control, as determined by using Student's t test. nd = not determined. HE had no detectable antiglycosidase activity; hence, EC₅₀ value was not calculated

AE had the lowest EC₅₀ value for DPPH scavenging activity (8.57 µg/mL) among all the solvent extracts (Table 1). The EC₅₀ value of AE was 2.4-fold greater than that of ascorbic acid. HE had the highest EC₅₀ value among the extracts, which is also 260-fold higher than that of ascorbic acid.

Phytochemical analysis revealed that AE, ME, and WE generally contained higher levels of TP, TCou, TPro, and THA contents, relative to HE, CE, and EAE (Table 2). The four classes of phytochemicals were detected in all six solvent extracts, with the exception that THA was not detectable in HE. Among the six extracts, ME

had the highest TCou, TPro, and THA contents, whereas AE had the highest TP content.

Among the organic and water fractions partitioned from AE, concentration-dependent increase in antiglycosidase activity was detected when BF, EAF, and WF were tested at 2, 4, 6, 8, 10, 15 and 20 µg/mL (data not shown). EC₅₀ values of the antiglycosidase activity of organic and water fractions of AE ranged between 4.27 and 28.68 µg/mL (Table 3). BF had the lowest EC₅₀ value, which is about 5-fold lower than the EC₅₀ value of quercetin.

Table 2: Phytochemical contents of organic solvent and aqueous extracts

Extract	Phytochemical content			
	TP (mg GAE/g)	TCou (mg CE/g)	TPro (mg LE/g)	THA (mg CAE/g)
HE	2.38 ± 0.04 ^a	14.37 ± 0.50 ^a	0.14 ± 0.03 ^a	nd
CE	14.01 ± 0.44 ^b	33.07 ± 0.70 ^b	0.80 ± 0.06 ^a	4.13 ± 0.18 ^a
EAE	61.24 ± 0.29 ^c	26.05 ± 0.47 ^c	50.40 ± 2.67 ^b	50.81 ± 0.52 ^b
AE	574.07 ± 7.80 ^d	75.04 ± 1.97 ^d	298.96 ± 23.06 ^c	291.85 ± 7.07 ^c
ME	401.46 ± 5.77 ^e	92.00 ± 2.94 ^e	416.87 ± 11.79 ^d	306.67 ± 6.42 ^d
WE	192.79 ± 5.10 ^f	41.55 ± 0.19 ^f	332.35 ± 16.91 ^c	266.67 ± 1.28 ^e

Data are mean ± SEM (n = 3). Values in the same column that are followed by different superscript letters are significantly different (p < 0.05), as determined by using Fisher's LSD test. nd = not detectable

Table 3: EC₅₀ values of the antiglycosidase and DPPH scavenging activities of the solvent fractions of AE

Fraction	EC ₅₀ value (µg/mL)	
	Antiglycosidase activity	DPPH scavenging activity
CF	nd	309.95 ± 53.49*
EAF	27.72 ± 2.68	7.33 ± 0.46*
BF	4.27 ± 0.03*	7.20 ± 0.42*
WF	28.68 ± 2.01*	90.85 ± 6.65*
Positive control	22.18 ± 0.88 (Quercetin)	3.56 ± 0.12 (Ascorbic acid)

Data are mean ± SEM (n = 3). The asterisks (*) denote values that are significantly different (p < 0.05) compared with the positive control, as determined by using Student's t test. nd = not determined. Chloroform fraction showed an erratic trend in antiglycosidase activity; hence, EC₅₀ value was not calculated

Table 4: Phytochemical contents of the solvent fractions of AE

Fraction	Phytochemical content			
	TP (mg GAE/g)	TCou (mg CE/g)	TPro (mg LE/g)	THA (mg CAE/g)
CF	27.16 ± 3.57 ^a	49.84 ± 2.55 ^a	1.11 ± 0.25 ^a	10.49 ± 0.04 ^a
EAF	844.20 ± 26.47 ^b	25.42 ± 0.31 ^b	418.43 ± 8.20 ^b	549.63 ± 7.41 ^b
BF	640.96 ± 11.06 ^c	36.60 ± 0.13 ^c	735.65 ± 43.63 ^c	554.81 ± 1.96 ^b
WF	165.67 ± 0.78 ^d	6.72 ± 0.22 ^d	2.19 ± 0.24 ^a	159.48 ± 0.93 ^c

Data are mean ± SEM (n = 3). Values in the same column that are followed by different superscript letters are significantly different (p < 0.05), as determined by using Fisher's LSD test

When evaluated at 4, 8, 12, 16 and 20 µg/mL, a concentration-dependent increase in DPPH scavenging activity was observed among the fractions of AE, particularly in BF, EAF, and WF (data not shown). EC₅₀ values of the DPPH scavenging activity of organic and water fractions of AE ranged between 7.20 and 309.95 µg/mL (Table 3). Among the fractions, BF had the lowest EC₅₀ value, which is about 2-fold greater than the EC₅₀ value of ascorbic acid. CF had the highest EC₅₀ value among the fractions, which is also 87-fold higher than that of ascorbic acid.

Different levels of TP, TCou, TPro, and THA contents were detected in the organic and water fractions of AE (Table 4). Overall, EAF and BF had the highest TP, TPro, and THA contents, whereas CF had the lowest. CF, nevertheless, had the highest TCou content. EAF had the highest TP content, which is 31-fold greater compared with CF. BF had the highest TPro content, which is 663-fold greater compared with CF. Notably, on the basis of leucocyanidin equivalents, BF contained about 74 % proanthocyanidins by weight. Both BF and EAF contained the highest and similar levels of THA content, which is about 53-fold higher compared with CF.

Correlation analyses of all extracts and fractions found 1/EC₅₀ values of antiglycosidase activity to be correlated significantly (p < 0.05) with only TPro and THA contents, with R² of 0.709 and 0.476, respectively. 1/EC₅₀ values of DPPH scavenging activity correlated significantly (p < 0.05) with TP, TPro, and THA contents, with R² of 0.864, 0.838, and 0.883, respectively. TPro content is the phytochemical parameter that simultaneously correlated with both antiglycosidase and DPPH scavenging activities at high R² values (> 0.70).

In order to determine the mode of inhibition of glucosidase by BF, a Lineweaver-Burk plot was prepared (figure not shown). The plot indicates that the inhibition of glucosidase by BF followed

that of competitive kinetics. An increase in k_m and unaltered V_{max} values were detected when glucosidase-catalyzed cleavage of p-NPGP occurred in the presence of BF (Table 5).

Table 5: k_m and v_{max} values for glucosidase activity in the presence or absence of BF

Sample	k _m (mM)	v _{max} (mM/min)
Control	1.93 ± 0.13 ^a	0.046 ± 0.005 ^a
4.27 µg/mL BF	2.61 ± 0.12 ^b	0.044 ± 0.005 ^a
5.34 µg/mL BF	3.91 ± 0.17 ^c	0.037 ± 0.007 ^a

Data are mean ± SEM (n = 3). Values in the same column that are followed by different superscript letters are significantly different (p < 0.05), as determined by using Fisher's LSD test

DISCUSSION

Our results indicate that the active constituents of *T. domingensis* fruit which exhibited antiglycosidase and radical scavenging activities are likely to be relatively polar in nature. AE, ME, and WE had higher antiglycosidase and DPPH scavenging activities compared with extracts prepared with less polar solvents, such as HE and CE. The three extracts also had higher phytochemical contents relative to extracts prepared with the other solvents. When fractions of AE were compared, BF and EAF had higher antiglycosidase and DPPH scavenging activities than CF. With the exception of TCou, the phytochemical contents of BF and EAF were also higher compared with that partitioned into CF. Collectively, these results suggest that polar solvents were effective for extracting glucosidase inhibitors and radical scavengers from *T. domingensis* fruit.

Similar to our findings, polar solvent ethyl acetate was more effective in extracting antiglycosidase agents from *Callistephus chinensis* in comparison with hexane and chloroform [11]. By contrast, chloroform extract of *Psoralea corylifolia* was a more potent α-glucosidase inhibitor than extracts prepared with 50 % ethanol, ethanol, methanol, and water [12]. Our

observations, together with the aforementioned findings, suggest that optimal solvent polarity for the extraction of antiglucosidase agents from plant samples may not be easily predicted and is likely to be species or sample-dependent.

We found DPPH scavenging activity to be correlated with TP, THA and TPro contents to similar degrees. This concurs with previous reports of correlations between DPPH scavenging activity and TP and THA contents in other plants [13-15]. Positive correlations between DPPH scavenging activity and TPro were also reported for rhizome extracts of highland ferns [14]. When previously screening hot water extracts of *T. domingensis* fruit and flowers for antiglucosidase and antioxidant activity, we found the highest activities in the fruit extract, which also had the highest TPro content [6]. In this study, the antiglucosidase activity of *T. domingensis* fruit extracts and fractions correlated more strongly with TPro content and weakly with THA content. Likewise, in highland ferns, THA content was either less strongly or not correlated to antiglucosidase activity when compared with TPro content [14]. Taking into account our current results and reported evidence in the literature, TPro of *T. domingensis* fruit is a promising source of both glucosidase inhibitors and radical scavengers. On the other hand, THA of *T. domingensis* fruit is likely an important contributor of radical scavenging activity only.

Among all extracts and fractions analyzed, BF stood out as a dual-function antiglucosidase and radical scavenging agent of high potency. BF was a stronger inhibitor of α -glucosidase when compared with quercetin. In addition, based on the comparison of EC₅₀ values, the potency of BF as a radical scavenger was in the same order of magnitude as that of ascorbic acid. BF had the highest TPro content among all extracts and fractions analyzed. Thus, TPro is likely responsible for the potent dual bioactivities in the TPro-rich BF. Our findings corroborate with the reports of concurrent antiglucosidase and antioxidant activities in proanthocyanidins isolated from black chokeberry [16] and persimmon peel [17].

Our enzyme kinetic study suggests that TPro-rich BF contained active constituents that were possibly able to bind to the catalytic site of α -glucosidase, thus acting as competitive inhibitors. Acetone extract of the leaves of *Picralima nitida* was also reported to be a competitive inhibitor of α -glucosidase [18], although there are more reports of plant extracts and natural products as non-competitive [19,20]

and mixed-type [21] α -glucosidase inhibitors. Our study revealed that BF differs in its mode of inhibition from quercetin, which exerts either non-competitive [22] or mixed-type [23,24] inhibition on α -glucosidase. Notably, the mode of glucosidase inhibition by BF is the same as that of acarbose, miglitol, and voglibose, three oral antihyperglycemic drugs [25]. An advantage of competitive inhibitors is that their inhibitory action is reversible, thus allowing undesirable effects to be readily mitigated by decreasing the dosage of inhibitors used [26].

In this study, we used yeast α -glucosidase for the evaluation of antiglucosidase activity. Yeast α -glucosidase is available in pure form from commercial sources and has been widely used as a model for investigating antiglucosidase properties of natural products. In grape skin and pomace extracts, inhibition against yeast α -glucosidase correlated with inhibition against mammalian α -glucosidase and suppression of postprandial hyperglycemia in Streptozocin-induced diabetic mice [27]. To assess the radical scavenging activity of *T. domingensis* fruit extracts and fractions, we have used the DPPH radical scavenging assay. The assay is widely used for antioxidant screening since it is rapid and simple, using DPPH radicals which are stable and commercially available. However, DPPH radicals have very little similarity to the highly reactive and transient oxygen radicals, such as hydroxyl, peroxy and superoxide anion radicals, which occur in biological systems [28]. Thus the ability of the *T. domingensis* extracts and fractions to scavenge biologically relevant radicals should be investigated.

CONCLUSION

In this study, we found that *T. domingensis* fruit is rich in polar bioactive constituents, as evidenced by the high phytochemical contents and strong bioactivities of extracts prepared with polar solvents. Correlation analysis suggests that proanthocyanidins of *T. domingensis* fruit are a promising source of both antiglucosidase inhibitors and radical scavengers. Proanthocyanidins-rich butanol fraction of acetone extract showed more potent antiglucosidase activity than quercetin and strong radical scavenging activity comparable to that of ascorbic acid. The results provide a strong rationale for future exploration of *T. domingensis* fruit as a novel source of antihyperglycemic agent with concurrent antioxidant activity.

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