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Phytochemicals, Antioxidant and Inhibitory Activity against α-Glucosidase in *Uncaria sclerophylla* Twigs and Stems

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Abstract

The medicinal plant *Uncaria sclerophylla* Roxb has been used as a traditional antidiabetic drug by the people of Kalimantan, Indonesia. However, scientific data on this plant as an antidiabetic has never been reported. This research aims to investigate the antidiabetic activity of the twigs and stems of *U. sclerophylla* as an inhibitor of α-glucosidase, and its antioxidant activity, including phytochemical screening. Four-graded maceration was used as the extraction method, thin-layer chromatography was used as a screening method, and all bioassays were conducted by spectrophotometric principles to determine inhibition of α-glucosidase and antioxidant activity from n-hexane, dichloromethane, ethyl acetate and methanol extracts of twigs and stems. The research results showed that *U. sclerophylla* twigs and stems contain alkaloids, phenols, and flavonoids. Inhibitory activity against α-glucosidase was shown from both twigs and stems of the plant, with the most active extract being n-hexane extract from twigs with an IC_{50} of 84.44 µg/mL. The best antioxidant activity was shown by methanol extract from both twigs (IC_{50} 28.76 µg/mL) and stems (IC_{50} 27.76 µg/mL). The assay results have underlined that the twigs and stems of this species have the potential to be developed in the treatment of diabetes mellitus through α-glucosidase inhibition and antioxidant activity.

Keywords: Antidiabetes; *Uncaria sclerophylla*; Antioxidant; α-glucosidase; Phytochemical content

Introduction

The α-glucosidase inhibitors have been widely used in treating diabetes mellitus as first-line drugs and combinations. This class of antidiabetic therapy has effectiveness in reducing HbA1C (0.3 to 1%) and reducing postprandial glucose concentrations (40 to 50 mg/dL) (Dipiro *et al*. 2011). The α-glucosidase has the ability to reduce and control blood sugar levels by inhibiting carbohydrate breakdown due to its inhibition of the enzyme α-glucosidase as a carbohydrate breakdown. Hence, this class of antidiabetic therapy provides benefits in the treatment of diabetes (Ibrahim *et al*. 2017; Prasad *et al*. 2019; Zaidi *et al*. 2019). *In vivo* studies have shown that α-glucosidase inhibitors can slow down the dysfunction of insulin secretion and positively affect the progress of the control of diabetes (Fukaya *et al*. 2009). This therapy class is also positively related to an increase in GLP-1, which is an inducer of insulin secretion, which will reduces post-prandial hyperglycemia (Dabhi *et al*. 2013).

Various studies have explained the role of antioxidants in helping overcome the condition of diabetes mellitus, and this is related to the oxidative stress that occurs in diabetes due to an increase in free radicals level (Burgos-moron *et al*. 2019; Singh *et al*. 2022). In diabetes, there is a decrease in the concentration of endogenous enzymatic and non-enzymatic antioxidants. This is accompanied by an increase in the levels of advanced oxidation products, which exacerbate oxidative stress (Rajendiran *et al*. 2018; Kanwugu *et al*. 2021). Increased reactive oxygen species (ROS) during diabetes can modulate insulin signaling pathways, thereby contributing to the progression of diabetes and the development of diabetic vascular complications (Ghasemi-Dehnoo *et al*. 2020; Akpoveso *et al*. 2023). Various studies showed that antioxidant therapy helps repair beta cell damage caused by oxidative stress, and the antioxidants help improve insulin sensitivity and reduce the diabetes complications (Rajendiran *et al*. 2018; Ghorbani *et al*. 2019; Dinić *et al*. 2022).

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Various medicinal plants have been used traditionally in the treatment of diabetes (Ghorbani 2013; Alam *et al*. 2021; Salleh *et al*. 2021). These plants have been used for generations by the local community, one of which is the *Uncaria sclerophylla* plant, which is known for its efficacy in the treatment of diabetes mellitus by people of Kalimantan, Indonesia. The genus *Uncaria* itself is known to contain various phytoconstituents such as flavonoids, alkaloids, phenols, and terpenoids (Hoyos *et al*. 2015; Sakti *et al*. 2019; Qin *et al*. 2021) and has shown much potential in the treatment of diabetes, both *In vivo* and *In vitro* assays as both α-glucosidase inhibitor and antioxidant (Apea-Bah *et al*. 2009; Ahmad *et al*. 2011; Aprely *et al*. 2021). The species *U. sclerophylla* has never been reported for its scientific data as antidiabetic, even though this species has been consumed for generations to help treat diabetes mellitus. Exploration of scientific data on *U. sclerophylla* is urgently needed because of its widespread traditional use. This research investigated phytochemical content (alkaloid, phenol, and flavonoid) where various studies show the potential of these phytoconstituents as inhibitors of α-glucosidase as well as antioxidants (Sarian *et al*. 2017; Famuyiwa *et al*. 2019; Junejo *et al*. 2020; Wairata *et al*. 2022).

Materials and Methods

Plant material

Stems and branches of *U. sclerophylla* were collected from Meratus Forest, South Kalimantan, Indonesia. Plant authenticity was determined, and a voucher specimen was deposited in the Faculty of Pharmacy, Universitas Indonesia (voucher specimen number 237/LB/XI/2021). Stems and twigs were cleaned, dried at 16˚C, powdered, and sieved using 40 mesh; the powdered material was stored at 16˚C until it was time to be extracted.

Chemical and instrumentations

Chemicals: n-hexane (SmartLab), dichloromethane (SmartLab), ethyl acetate (SmartLab), methanol (SmartLab), TLC Plate 254GF (Merck). Dragendorff reagent, 1% ethanolic $AlCl_3$ (Merck), folin-ciocalteu reagent (Merck), quercetin (Sigma Aldrich), 96% ethanol (Merck). Enzyme α-glucosidase (Sigma Aldrich), para-nitrophenyl-α-D glucopyranoside (Sigma Aldrich), acarbose (Sigma Aldrich), bovine serum albumin (Sigma Aldrich), potassium dihydrogen phosphate, sodium carbonate (Merck), dimethylsulfoxide. 1,1-diphenyl-2-picrylhydrazyl (DPPH) (Sigma-Aldrich). **Instruments:** rotary evaporator (IKA), UV lamp (Camag), micropipette (Eppendorf), microplate reader (Glomax, Promega), pH meter (Eutech 510 Instrument).

Extraction

Extraction of the stems and twigs of *U. sclerophylla* was carried out using a four-stage maceration, adopting the method from (Triadisti *et al*. 2018) with modifications to the number of solvent types. Solvents with increasing polarity were used for extraction, including n-hexane, dichloromethane, ethyl acetate, and methanol in a ratio of 1:20 between simplicia and solvent to obtain n-hexane extract, dichloromethane extract, ethyl acetate extract and methanol extract. Evaporation of the extract was assisted by a rotary evaporator and finished with a dehydrator. The extract was stored at 16˚C until it was time to be analyzed.

Thin layer chromatography for alkaloids, phenols, and flavonoids identification

Identification of the extracts' alkaloid, phenol, and flavonoid phytoconstituent content was carried out using the adopted method with slight modification (Maya *et al*. 2019). Alkaloids were detected using Dragendorff's reagent to spray the TLC plate containing the eluted extract. A yellow-orange color in visible light indicated a positive result. Phenol was detected using a 10% Folin-ciocalteau spray reagent on the TLC plate, where a positive result was shown by the presence of a blue color in visible light. The presence of flavonoids was detected using a 1% ethanolic $AlCl_3$ spray reagent which was shown by yellowish fluorescence under UV light 366/365.

α-glucosidase enzyme inhibition activity assay

The α-glucosidase inhibitory activity assay was carried out using the spectrophotometric method, where the absorbance was read with a microplate reader (Triadisti *et al*. 2017). The solution mixture consisting of 30 µL of sample solution, 36 µL of phosphate buffer pH 6.8, and 17 µL of pNP-G substrate (5 mM) was incubated for 5 min at 37°C then added 17 µL of α-glucosidase enzyme solution (0.12 Unit/mL) and incubated for 15 min at 37˚C. After 15 minutes of incubation, 100 µL of 267 mM Na_2CO_3 was added to stop the enzyme reaction, and the absorbance of the p-nitrophenol produced from the enzyme reaction was read using a microplate reader. In the sample control solution, the Na_2CO_3 solution was added before adding the α-glucosidase enzyme so that the reaction did not occur. Each assay was carried out three times (triplication), and the standard deviation was measured for each sample. The percentage of α-glucosidase inhibition was calculated by the formula:

$$\alpha - \text{glucosidase inhibition } (\%) = \frac{(\text{AB blank} - \text{AB sample})}{\text{AB blank}} \times 100$$

where AB blank is the absorption of enzyme activity without inhibitor corrected by blank control, and AB sample is the absorbance of sample corrected by sample control. The IC_{50} value was calculated by the formula: (50 – a)/b.

Antioxidant activity assay

The antioxidant activity assay method used was the DPPH

Table 1: Extracts yield from various solvents

Plant Sample	Solvent	Simplisia weight (g)	Extract weight (g)	Yield (%)
Stems	n-Hexane		0.1590	0.1590
	Dichloromethane	100	0.3720	0.3720
	Ethyl acetate		1.0820	1.0820
	Methanol		21.3640	21.3640
Twigs	n-Hexane		0.1000	0.1000
	Dichloromethane	100	0.4310	0.4310
	Ethyl acetate		0.7499	0.7499
	Methanol		10.7981	10.7981

Table 2: Alkaloid, phenol, and flavonoid content of *U. sclerophylla* stem extract

Solvent	Presence of alkaloids		Presence of phenols		Presence of flavonoids	
	TLC	Result	TLC	Result	TLC	Result
n-Hexane	-	Not detected	-	Not detected	-	Not detected
Dichloromethane		Detected		Detected	-	Not detected
Ethyl acetate		Detected		Detected		Detected
Methanol		Detected		Detected		Detected

free radical scavenging method adopted with slight modifications (Bobo-garcía *et al*. 2014). A 20 µL sample solution, was pipetted in a Eppendorf tube and then 180 µL of 150 µmol/L DPPH solution was added to each solution. The control solution consisted of 20 µL methanol and 180 µL of 150 µmol/L DPPH solution, while the blank solution consisted of 200 µL methanol p.a. The solution was shaken for 60 sec and then incubated at room temperature in a dark room for 40 min. Each assay solution was then measured for its absorbance at a wavelength of 517 nm. Each assay was carried out in triplicate, and the standard deviation was measured for each sample.

The EC_{50} value was calculated based on the percentage of DPPH scavenging from each sample solution concentration with the formula:

$$\text{DPPH scavenging (\%)} = \frac{(\text{Absorbance of control solution} - \text{Absorbance of Sample})}{\text{Absorbance of control solution}} \times 100$$

After obtaining the percentage of DPPH scavenging for each concentration, the equation y = a + bx is determined by a regression calculation where x is the concentration (µg/mL) and y is the percentage of DPPH scavenging (%). Antioxidant activity is expressed by an Effective Concentration of 50% (EC_{50}).

Table 3: Alkaloid, phenol, and flavonoid content of *U. sclerophylla* twigs extract

Solvent	Presence of alkaloids		Presence of phenols		Presence of flavonoids	
	TLC	Result	TLC	Result	TLC	Result
n-Hexane		Detected	-	Not detected	-	Not detected
Dichloromethane		Detected	-	Not detected	-	Not detected
Ethyl acetate	-	Not detected		Detected		Detected
Methanol	-	Not detected		Detected		Detected

Statistical analysis

The data from each assay (% α-glucosidase inhibition and DPPH scavenging) is analyzed for standard deviation, and the displayed data represents the mean ± standard deviation.

Results

Identification of phytochemicals in *U. sclerophylla* extract

Extracts with different polarities were detected for their alkaloid, phenol, and flavonoid content using TLC (Table 1). The results of detecting these phytoconstituents can be seen in Table 2–3. Phytochemical screening revealed the presence of alkaloids, phenols, and flavonoids in the n-hexane, dichloromethane, and methanol extracts obtained from the stem. The twigs were found to contain alkaloids in n-hexane and dichloromethane extracts and phenols and flavonoids in the ethyl acetate and methanol extracts.

α-glucosidase enzyme inhibitory activity of *U. sclerophylla* extract

Assay results on *U. sclerophylla* extracts at various polarities showed that inhibition of the α-glucosidase enzyme at a assay concentration of 75 µg/mL, where good inhibition was shown by n-hexane and methanol extracts

Table 4: α-glucosidase enzyme inhibitory activity of *U. sclerophylla* extract (75 µg/mL)

Plant part	Solvent maceration	% α-glucosidase inhibition			Mean ± SD
		Data 1	Data 2	Data 3	
Twigs	n-Hexane	47.83	45.39	43.36	45.53 ± 2.2388
	Dichloromethane	12.47	11.11	13.96	12.51 ± 1.4233
	Ethyl Acetate	20.17	19.68	21.77	20.54 ± 1.0933
	Methanol	35.92	32.23	31.49	33.21 ± 2.3724
Stem	n-Hexane	4.88	8.67	6.78	6.78 ± 1.8970
	Dichloromethane	10.70	8.81	8.54	9.35 ± 1.1813
	Ethyl Acetate	26.08	28.17	36.04	30.09 ± 5.2537
	Methanol	28.54	25.22	22.26	25.34 ± 3.1383

Data are mean ± SD or % ± SD for triplicate measurements

Table 5: IC_{50} α-glucosidase inhibition of Acarbose and *U. sclerophylla* twigs n-hexane extract

Sample	Concentration (µg/mL)	α-glucosidase inhibition (%)	R^2	IC_{50} (µg/mL)
Acarbose	45	45.48 ± 1.7415		
	60	48.53 ± 3.5557		
	90	55.96 ± 1.2512	0.9986	65.12
	105	59.39 ± 1.2848		
	120	62.33 ± 0.1959		
n-Hexane extract of twigs	75	43.08 ± 2.2007		
	105	62.63 ± 4.3385		
	120	73.78 ± 6.2537	0.9901	84.44
	135	81.20 ± 2.8391		
	150	87.40 ± 2.4306		

Data are mean ± SD or % ± SD for triplicate measurements

from twigs, also ethyl acetate and methanol extracts from stems with inhibition percentages of 45.53% ± 2.2388, 33.21% ± 2.3724, 30.09% ±5.2537 and 25.34% ± 3.1383, respectively (Table 4). Acarbose, as a positive standard, still showed better activity with an IC_{50} of 65.12 µg/mL compared to n-hexane extracts from twigs as the most active extract with an IC_{50} of 84.44 µg/mL (Table 5).

Antioxidant activity of *U. sclerophylla* extract

Assays for antioxidant activity using the DPPH methods showed that the highest antioxidant activity was shown by methanol extract, both from twigs and stems, with IC_{50} 28.76 and 27.76 µg/mL, respectively (Table 6–7). This is in line with the results of the flavonoid content screening, which showed that flavonoids was present in methanol extracts from both twigs and stems.

Discussion

Several studies show the potential of alkaloids, phenols, and flavonoids in antidiabetic and antioxidant activity (Sarian *et al*. 2017; Famuyiwa *et al*. 2019; Junejo *et al*. 2020; Wairata *et al*. 2022). Screening of alkaloid, phenol, and flavonoid phytoconstituents using thin-layer chromatography has been widely used in various studies (Maya *et al*. 2019). Screening of *U. sclerophylla* extracts showed the presence of alkaloids in dichloromethane, ethyl acetate, and methanol extracts from stems, as well as in n-hexane and dichloromethane extracts from twigs. Phenol content was seen in all extracts except the n-hexane (both from stems and twigs) and dichloromethane extracts from twigs, and flavonoids were seen in ethyl acetate and methanol extracts, both from twigs and stems (Table 2–3). Various alkaloid, phenolic, and flavonoid compounds have been reported as inhibitors of α-glucosidase, and as antioxidants (Yin *et al.* 2014; Kim *et al.* 2017; Sharma *et al*. 2019; Kumar *et al.* 2021; Sakulkeo *et al.* 2022). The TLC screening results showed the presence of alkaloids, phenols, and flavonoids of these extracts.

Alkaloid have been reported to have antidiabetic and antioxidant activity, including: the compound vindolysin from *Catharanthus roseus* with the activity of inducing glucose uptake in TC6 cells and C2C12 cells and showing antioxidant activity (Tiong *et al*. 2013); the compound vindoline from *Catharanthus roseus* shows antioxidant activity and significantly increases insulin secretion *in vitro* (Goboza *et al*. 2020). Magnoflorin compounds from *Mahonia aquifolium*, *Tinospora cardifolia*, and *Rhizoma coptidis* show antioxidant activity and inhibitory activity of the α-glucosidase enzyme and the PTP-1B (Protein tyrosine phosphatase 1B) enzyme (Okon *et al.* 2020). *In silico* studies show the role of alkaloid structural features in inhibition, including the presence of benzene rings forming π-π stacking, hydrogen atoms from hydroxyl groups and nitrogen atoms forming hydroxy bonds, carbonyl groups of piperidine rings, halogen atoms in alkaloids also forming halogen bonds (Zafar *et al*. 2016).

Phenolics and flavonoid compounds have been reported to have antidiabetic and antioxidant activity, such as protocatechic acid, a diphenol that is active as an antioxidant and antidiabetic (Famuyiwa *et al*. 2019), 8-hydroxyapigenin 7-O-β-D-glucopyranoside isolated from the extract of *Tetrastigma angustifolia* leaf methanol, which

Table 6: Antioxidant activity of *U. sclerophylla* twigs extract

Sample	Concentration (µg/mL)	Mean % DPPH scavenging ± SD	R^2	EC_{50} (µg/mL)
Quercetin	1	17.63 ± 1.7310		
	2	35.96 ± 2.8494	0.9938	
	3	50.06 ± 7.0280		2.9786
	4	68.59 ± 6.8984		
	5	79.44 ± 2.4677		
	20	36.51 ± 0.3590		
Twig methanol extract	25	41.89 ± 1.0220		
	30	54.25 ± 1.4166	0.9843	28.76
	35	59.82 ± 0.7950		
	40	67.41 ± 2.1097		
	20	17.66 ± 0.5587		
Twig ethyl acetate extract	30	23.43 ± 1.7557		
	40	30.53 ± 0.7541		
	50	36.49 ± 0.7072	0.9961	68.13
	60	43.33 ± 1.2423		
	80	59.42 ± 1.0583		
	40	19.15 ± 4.2478		
Twig dichloromethane extract	80	38.00 ± 0.5297		
	120	55.20 ± 0.5657	0.9893	114.52
	160	68.16 ± 0.8136		
	200	79.89 ± 1.0019		
	50	44.30 ± 1.4611		
Twig n-hexane extract	60	46.79 ± 2.8944		
	70	52.75 ± 0.8270	0.9877	65.14
	80	55.93 ± 1.5271		
	90	60.17 ± 1.2046		

Data are mean ± SD or % ± SD for triplicate measurements

Table 7: Antioxidant activity of *U. sclerophylla* stems extract

Sample	Concentration (µg/mL)	Mean % DPPH scavenging ± SD	R^2	EC_{50} (µg/mL)
Quercetin	1	17.63 ± 1.7310		
	2	35.96 ± 2.8494		
	3	50.06 ± 7.0280	0.9938	2.9786
	4	68.59 ± 6.8984		
	5	79.44 ± 2.4677		
	10	18.67 ± 3.8869		
Stem methanol extract	20	38.54 ± 1.1798		
	30	57.89 ± 1.4329	0.9817	27.76
	40	71.12 ± 0.7843		
	50	81.51 ± 0.8494		
	20	21.12 ± 0.5311		
Stem ethyl acetate extract	30	28.90 ± 0.2452		
	40	35.92 ± 0.5398	0.9922	62.98
	50	42.25 ± 0.3786		
	60	47.00 ± 0.5889		
	50	17.59 ± 2.9922		
	100	27.74 ± 2.8347		
Stem dichloromethane extract	150	38.06 ± 0.6976	0.9975	220.20
	200	45.63 ± 0.9014		
	250	55.40 ± 0.6873		
	50	48.14 ± 0.7625		
Stem n-hexane extract	100	51.16 ± 0.6474		
	150	52.75 ± 1.0025	0.9890	84.98
	200	54.65 ± 0.9518		
	250	56.78 ± 0.2421		

Data are mean ± SD or % ± SD for triplicate measurements

had hypoglycemic effects on mice induced by streptozotocin and antioxidants (Junejo *et al*. 2020); the antioxidant compounds resveratrol, epicatechin, quercetin, gallic acid which have inhibitory activity against both the α-glucosidase enzyme and the DPP-4 enzyme (Praparatana *et al*. 2022); isoscutellarein, hypolaethin and kaempferol compounds which have antioxidant activity and inhibit the α-glucosidase enzyme and the DPP-4 enzyme (Sarian *et al*. 2017).

Apart from having antioxidant activity, flavonoids are also reported to have antidiabetic activity, so the flavonoid compounds contained in the extract have a role in helping to overcome diabetes (Kim *et al*. 2018; Sharma *et al*. 2019; Kumar *et al*. 2021). Diabetes complications can be reduced

with the help of antioxidants, which can be used as therapy or in combination with the treatment of diabetes. β-cell function can be maintained by antioxidants by addressing oxidative stress, thereby reducing diabetes-related complications and helping to restore insulin sensitivity (Suresh *et al*. 2021). Various studies have shown that antioxidants such as lycopene, retinol, tocopherol, ascorbic acid, carotene, lutein, and zeaxanthin, contained in various plants, offer an essential role in helping overcome diabetes complications (Ghasemi-Dehnoo *et al*. 2020).

The assay results of *U. sclerophylla* extract showed that there was inhibitory activity against diabetes-related enzyme such as α-glucosidase from *U. sclerophylla* extracts (Table 4). To further explore the mechanism of the antidiabetic activity of this species, it is necessary also to assay other diabetes-related targets such as dipeptidyl peptidase-4, sodium-glucose cotransporter type-2 (SGLT-2) and peroxisome proliferator-activated receptor γ (PPARγ). The twigs and stems of this plant also showed excellent antioxidant activity, supported by data on the phytochemical content of phenols and flavonoids (Table 2–3, 6–7). This further strengthened the potential of this plant to help treat diabetes mellitus because the role of antioxidants has been widely reported to help treat diabetes (Khan *et al*. 2020; Darenskaya *et al*. 2021; Suresh *et al*. 2021).

Conclusion

The twigs and stems of *U. sclerophylla* showed inhibitory activity against the α-glucosidase enzyme and had antioxidant activity, which underlies that the twigs and stems of this species have the potential to continue to be explored and developed in the treatment of diabetes mellitus, as is its traditional use as an antidiabetic.

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Author Contributions

All authors have contributed equally to this work and have permitted it to be published.

Conflicts of Interest

The authors declare that no conflict of interest or personal relationship can affect the research results written in this paper.

Data Availability

The author can provide access to the data upon reasonable request.

Ethics Approval

Outside the scope of this paper

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