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The solvents influence in the continuous extraction to antioxidant and α-glucosidase inhibition of *Cinnamomum burmannii* bark

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Abstract

The proanthocyanidins, the polyphenolic compounds from *Cinnamomum burmannii* (Lauraceae), have been known for their insulin-like effects. The different use of solvents and extraction methods would influence the bioactive phytochemicals. This research examined the solvents used in the continuous extraction method to provide a higher yield of bioactive extracts. The use of ethanol only compared to the gradual polarity of n-hexane, ethyl acetate, and ethanol in the soxhletation to the standardized dried cinnamon bark. The extracts were then analyzed for their total phenolic content, antioxidant, and α-glucosidase inhibition. The extracts contained essential oils, tannins and flavonoids, triterpenoids, coumarins, and glycosides. The ethanolic solvent provides a higher yield and total phenolic content compared to other extracts. The ethanolic extracts phenolic content was highest, and its IC_{50} DPPH antioxidant activity was no significant difference from rutin. The IC_{50} α-glucosidase inhibition of most extracts was lower than acarbose, thus classified as vital to moderate activity. The correlation analysis preceded a negative result of total phenolic content to α-glucosidase inhibition activities. These results supported the beneficial use of *C. burmannii* bark ethanol extract as α-glucosidase inhibitor and oxidative stress relieving in diabetes dietary supplements.

1. Introduction

Type 2 Diabetes Mellitus (T2DM), a chronic endocrine metabolic disease, has dramatically increased in world statistics for the last decade (International Diabetes Federation (IDF), 2021). The main therapeutic goal for T2DM patients' therapy is to maintain blood glucose at a normal level to prevent complications. This may be achieved by diet and lifestyle adjustments to the use of synthetic and natural medicine. This effort may improve the capacity production of pancreatic islet cells and insulin qualities. Among plants, the Cinnamons have been known for positive results in clinical improvement of glycemic control (Megadama, 2015).

The Cinnamomum genus has approximately 250 species, with different types and varieties. They spread across Southeast Asia, China, and Australia. They contain phytochemicals that are beneficial for human life. Cinnamon's phytochemicals are used as spices in food, beverages, cosmetics industries, and traditional and modern medicine. Among the species, *Cinnamomum burmannii is* mainly found in Sumatra and Java islands in Indonesia (Sangal, 2011). Prior research has found the water extract of *C. burmanii* phenolics content and observed their antioxidant and α-glucosidase inhibitor activities (Ervina *et al.*, 2019). These findings support the use of Cinnamon in preventing oxidative stress in diabetes insulin resistance pathogenesis and complications (Khan *et al.*, 2015; Kanwugu *et al.*, 2022). Moreover, Cinnamon's phytochemicals showed α-glucosidase inhibition activity similar to acarbose, thus promising for T2DM therapy.

The extraction method and the solvents influenced the extract's phytochemical and pharmacological properties. The polar solvents are frequently used to extract phenolic compounds from plants. Moreover, continuous extraction with ethanol is suitable for heat-stable phenolic compounds. Thus, this research examined the solvents used in continuous extraction (soxhletation) with ethanol only to gradient solvent extraction with n-hexane, ethyl acetate, and ethanol on

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C. burmannii bark. The extracts were then evaluated on their phytochemicals, total phenolic content (TPC), *in vitro* DPPH (2,2-diphenyl-1-pycrylhydrazil) antioxidant activity (AA), and *α*-glucosidase inhibition (*α*GI). This work aimed to obtain a more efficient extraction method for the Cinnamomum (higher yield and activities) bark than the previous water extract (Ervina *et al*., 2019).

2. Materials and methods

2.1 Materials

A local representative provided the bark for medicinal plants (Materia Medica Batu, Indonesia). The solvents and reagents are obtained from local suppliers.

2.2 Sample preparation and continuous extraction

The bark was prepared as described by Ervina *et al*. (2019) and standardized its quality parameters according to the monograph (Ministry of Health Republic of Indonesia, 2008). The continuous extractions were divided into two parts, which were ethanolic and gradual polarity of n-hexane, ethyl acetate, to ethanol soxhletation. Both were carried out until the dripped filtrate from the siphon was colorless (90°C, approximately 4 hrs for each solvent). The extract was evaporated on the rotary vacuum evaporator until viscous or dry extracts. The four final extracts were coded as T (total extract) for the ethanolic-only method, meanwhile EH (n-hexane extract), EA (ethyl acetate extract), and EE (ethanolic extract) for the latter products. All obtained extracts were examined for their identity, physical characteristics (color, odor), and water content.

2.3 Determination of total polyphenolic content

The total phenolic content (TPC) of extracts was determined with Folin Ciocalteau (FC) method based on Ervina *et al*. (2019). The 0.02 mL extracts or gallic acid (GA), mix thoroughly with 10% FC reagents (0.1 mL) and Na_2CO_3 7.5% (0.08 mL). The microplate was incubated in a dark condition for 1 hr at room temperature. The absorbance was measured with a multiscan GO Microplate Reader UV/Vis Spectrophotometer at 765 nm. The calibration curves of gallic acid concentrations (12.5-500 µg /mL) to absorbance were used for TPC calculated content. The TPC was presented as milligram gallic acid equivalent per gram sample (µg GAE/ g sample). In this method, we added rutin (R) as the reference standard.

2.4 Determination of α-glucosidase inhibition

The *α*-glucosidase activity inhibition (*α*GI) was determined according to Ervina *et al*. (2019), which is described as follows. The optimum concentration of the enzyme activities was established through a preliminary test. The amount (0.02 mL) of various α-glucosidase (from *Saccharomyces cerevisiae*, Sigma) concentration of 1-5 U/mL was mixed with 0.13 mL 67 mM phosphate buffer, pH 6.8 for 1 min. The mixture was pre-incubated at 37°C for 15 min, following 0.02 mL of 5 mM pNPG (*p*-nitrophenyl-*α*-D-glucopyranoside, Sigma) substrate. The mixture was incubated at 37°C for 15 mins then. The reaction was stopped by adding 0.08 mL of 0.1 M sodium carbonate. The absorbance was measured at 405 nm (multiscan GO *Microplate Reader UV/Vis Spectrophotometer*). The absorbance was plotted to the linearity of enzyme concentration to the absorbance curve. The optimum enzyme concentration was chosen at 3 U/mL. This concentration was applied in the further *α*-GI determination. The IC_{50} of the samples and acarbose were obtained by each sample's concentration versus % α-glucosidase inhibition.

2.5 In vitro antioxidant activity assay

The DPPH scavenging method was performed according to Ervina *et al*. (2019). The antioxidant activity is expressed as IC_{50}. Rutin and gallic acid were used as the reference standard.

2.6 Statistical analysis

The results are presented as mean and standard deviation values from the triplicate experiments. The significant difference and the correlation among data were obtained using one-way ANOVA (p-value < 0.05) with SPSS version 24 software.

3. Results and discussion

T2DM is a metabolic disease directly related to insulin quality and production. Moreover, radicals and oxidative stress have recently played a role in diabetes pathogenesis. Some processes are increasing production of free radicals, which are glucose autoxidation, disproportions on cellular oxidation or reduction, reducing antioxidant defenses, increasing some prooxidants, and interaction of advanced glycation end products (AGEs) with AGE receptors. Furthermore, diabetes complications are assumed to be caused by oxidative stress (Kanwugu *et al*., 2022)

Cinnamon has been used as a supplement in managing T2DM therapy. Though their coumarins contents arose attention since their hepatotoxicity side effect on human health. The *Cinnamomum zeylanicum* and *C. burmannii* are considered safer than *Cinnamomum cassia* since their higher coumarin content in the latter species. The antidiabetic mechanism of cinnamon was proposed as glucose transporter-4 (GLUT -4) receptor synthesis and translocation. It acted as an

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insulin receptor in the auto-, and de-phosphorylation, or via pyruvate kinase (PK) and phosphoenolpyruvate carboxykinase (PEPCK) in modulating hepatic glucose metabolism. It may also alter the expression of PPAR (γ) and inhibit intestinal glucosidases. In animal models, the cinnamon reduced fasting, postprandial plasma glucose, and HbA1c. Furthermore, the aqueous or powder form of *C. cassia* has been tested in clinical trials. The improvement in glycemic control was seen in patients who take Cinnamon only, in those with pre-diabetes and high pre-treatment HbA1c (Megadama, 2015). Anderson *et al.* (2016) found that aqueous extracts of *C. cassia* have insulin-like effects by increasing glucose uptake into adipocytes. Previous results also obtained that the water extract of *C. burmannii* was comparable to the acarbose reference (Ervina *et al.*, 2019). Thus, this research aimed to improve the efficiency of the extraction method. The continuous extraction (soxhletation) with a different sequence of solvents was applied, which were ethanol only compared to polar gradient solvents from n-hexane, ethyl acetate, and ethanol regarding its yield contents and AA to *α*-GI activities.

The quality sample of the dried cinnamon was established and compared to the national standard. The results showed the model's character and quality complied with the cinnamon characteristic standard and sequential to reported by Ervina *et al.* (2016). The pharmacognosy standardized qualities of *C. burmannii* bark are presented in Table 1.

The phytochemical screening of the extract was conducted with the TLC method (mobile phase toluene: ethyl acetate 7: 3) and sprayed with specific spotting reagents (Ervina *et al.*, 2019). The results observed polyphenol, tannin and flavonoids, essential oils, saponins, quinone, triterpenoids, glycosides, and coumarin in the extracts. The TLC of T and EE showed differences in their chromatogram pattern. The EE content was less and simple than ET. The cinnamaldehyde's purple spot at retention factor (Rf) 0.87 was presented on all extracts. These findings were consistent with previous research and added content information of glycoside, coumarin, and cinnamaldehyde which did not observe in Cinnamon's water extract (Ervina *et al.*, 2019). Moreover, the phenolics and flavonoid compounds were observed as brighter fluorescence spots with $AlCl_3$ spray reagent, on the initial line at the plate of T, EA and EE. This highlighted the polarity of the compound with one or more aromatic rings or hydroxyl groups, which binds stronger on the silica gel polar stationary phase. The previous finding was also observed in the polyphenolics proanthocyanidin and quercetin from the Cinnamon's water extract. Both have antioxidant and inhibited α-glucosidase. These findings were consistent with previous research (Ervina *et al.*, 2016; Ervina *et al.*, 2019) and added content information on glycoside and coumarin in *C. burmannii* (Ervina *et al.*, 2019).

The quality of extracts was determined in Table 1. The yield of the extracts was in a range from 1.17±0.14% to 24.88±0.89% (Table 2). The yield of n-hexane extract was the lowest quantity of non-polar extracted substances. This included volatile oil and the nonpolar compound of the bark. The best yield was produced by ethanolic extract (T). This explains the T as the total extract, which contained most of Cinnamon's contents. The EE was Cinnamon's polar fractions, which were separated from non- and semi-polar substances in the prior solvents used. The statistical analysis showed a significant difference in the ethanolic extract (T) yields

Table 1. Pharmacognosy quality parameters of dried and *C. burmannii* extract.

Parameter	Dried bark			
Identity	*Cinnamomum burmanii* bark			
Appearance	roll shape with a length of 15-22 cm, typical appearance and specific odour of cinnamon, reddish-brown colour			
Ethanol soluble extractive content (%)	27.02±0.42			
Water-soluble extractive content (%)	9.95±0.32			
Total ash content (%)	4.50±0.19			
Drying shrinkage (%)	5.35±0.04			
	Extracts			
	T	EH	EA	EE
Identity	*Cinnamomum burmanii* extractum siccum	*Cinnamomum burmanii* extractum spissum	*Cinnamomum burmanii* extractum siccum	*Cinnamomum burmanii* extractum siccum
Appearance	Reddish-brown dried extract, cinnamon typical smell.	Yellowish-brown viscous extract, cinnamon typically aroma.	A reddish-brown dried extract, cinnamon commonly smell.	A reddish-brown dried extract, cinnamon commonly smell.
Drying shrinkage	7.02±0.08%	-	-	6.69±0.14%

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Table 2. The yields percentage, total phenolic content, DPPH scavenging activity, and α-GI of *C. burmannii* extracts.

Extract or reference compound	Yield (%)	TPC (µg GAE equivalent/mg sample)	IC_{50} (µg/mL)	
			AA	α-GI
T	24.88±0.89^{d}	328.54±6.45^{c}	16.80±0.37^{b}	0.42±0.01^{a}
EH	1.17±0.15^{a}	151.11±8.15^{a}	5812.36±287.06^{c}	10.33±0.32^{b}
EA	3.05±0.09^{b}	243.79±4.64^{e}	20.83±0.17^{b}	0.97±0.05^{a}
EE	22.71±0.96^{c}	292.65±17.73^{b}	17.29±0.40^{b}	0.42±0.01^{a}
R	--	369.62±9.80^{d}	15.60±0.92^{b}	--
GA	--	--	4.47±0.94^{a}	--
A	--	--	--	104.40±1.30^{c}

Values are presented as mean±SD. Values with different superscripts within the same column are statistically significantly different at α = 0.05.

compared to others (EH, EA and EE). This result highlighted the ethanol use as solvent for general extractions. The influence of different solvents used in soxhletation moreover was shown by Murugan and Parimelazhagan (2014) and Yang *et al*. (2012). On the contrary found the ethanol produced least yield compared to methanol, ethyl acetate, and n-hexane on the *Osbeckia parvifolia* soxhletation. The difference on the time and the extraction soxhletation method, made difference result compared to this finding. While Yang *et al*. (2012) found that ethanol was more effective to extract phenolics and flavonoid contents than the supercritical CO_2. The variety of the plant used may also influence the results. They pointed out that the soxhletation produced a higher yield than maceration. Adding to the findings, ethanol has an advantage and health safety issues compared to methanol solvent. Ethanol is more selective compared to water. It extracted less inert compounds (proteins and carbohydrates were less soluble in ethanol).

The TPC with FC method was examined for all extracts, and rutin as gallic acid equivalent (Table 2). The TPC of the samples ranged from 151.11±8.15; to 328.54±6.45; while rutin of 369.62±9.80 µg GAE/mg samples; in which all showed significant different statistics groups. These results were higher than the previous Cinnamon water extract (Ervina *et al*., 2019). The ethanolic extracted most of plant's contents. Akomolafe *et al*. (2014) observed that tannic and gallic acid suppressed ROS generation, lipid peroxidation, and oxidative stress in kidney tissues and exhibited the nephroprotective effect. Gallic acid is produced by tannic acid oxidizing or dilute sulphuric acid hydrolyzing. The statistical analysis of TPC obtained no significant difference between ethanolic extract. It showed that ethanolic solvent (T) was more efficient in extracting polyphenolic compounds and no significant difference in the use of gradient polar solvent. According to Huang *et al*. (2002), most phenolic compounds are hydrophilic. They are more soluble in the solvent with high index polarity, such as ethanol.

The DPPH free radical is a common chemical used in antioxidant screening for scavenging activity. The antioxidant activity of extracts was concentration-dependent (Table 2). The statistical analysis showed no significant difference between ethanolic, ethyl acetate extracts, gallic acid, and rutin. This result indicated that Cinnamon extracts have antioxidant potency compared to both reference compounds. The latter substances are glycoside flavonoids and polyphenolic compounds. The lowest activity of DPPH scavenging was observed on n-hexane extract, which was supposed to correlate to the low potency of Cinnamon essential oils as electron or proton donors. This result was also supported by the TLC autographic of the extracts and sequence to the previous conclusion (Ervina *et al*., 2016). The proanthocyanidins, another cinnamon's contents, are naturally occurring compounds widely found in fruits, vegetables, nuts, seeds, flowers, and the bark. The molecular structure describes it as polyphenolic compounds, oligomers, or polymers of polyhydroxy-flavan-3-ol units, which is consisting of (+)-catechin and (−)-epicatechin (Figure 1). This compound has antioxidant activity and acts moreover as an inhibitor against some cancer cell line growth (Lin *et al*., 2016).

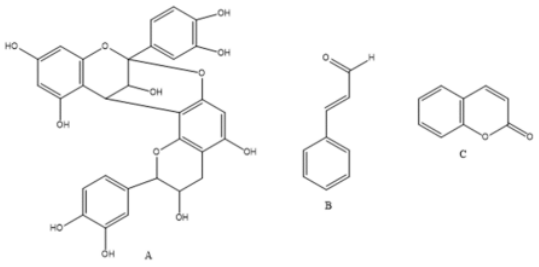

Figure 1. Some of Cinnamomum's phytochemicals contents (A) type A proanthocyanidin with flavan-3-ol monomers, (B) cinnamaldehyde, (C) coumarin.

The *α*-glucosidase inhibition measurement was based on the Ervina *et al*. (2019) method. A preliminary test to optimize the enzyme α-glucosidase condition has been done. The data showed a linear correlation to some extent between enzyme concentrations and the catalysis

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activity of the α-glucosidase enzyme. The chosen level of the enzyme was 3 U/mL since it showed in the middle step the exponential rate of the enzyme. Table 2 shows the IC_{50}'s extract comparable to the acarbose. The IC_{50} was in the range of 0.42±0.01 to 10.33±0.32; while acarbose was 104.40±1.30 µg/mL. The IC_{50} α-GI of the extract was 10 – 300 higher than acarbose as an oral antidiabetic reference drug (Figure 2). The IC_{50} α-GI of total and ethanolic extracts was similar to the rounding calculation result. ANOVA analysis showed significant differences among all extracts and references, except for ethanolic extracts. The IC_{50} α-GI indicates no difference between continuous ethanolic and gradual use of polar solvent on soxhletation to the potency of the cinnamon extract as α-glucosidase inhibitor agents. Salehi *et al.* (2013) determined that *C. zeylanicum* methanol extract was stronger than acarbose, and so did Shihabudeen *et al*. (2011).

This study found that α-glucosidase inhibition is supposed to be due to the higher total phenol content of ethanolic extracts compared to n-hexane and ethyl acetate extracts (Figure 2). The correlation analysis of TPC, AA, and α-GI exhibited negative (-0.873) results at a significance of α 0.01 level. This result was described in a 3D graph among the factors (Figure 3). The relationship among those three was also obtained by Ervina *et al*. (2019) and Miao *et al*. (2016), who found a correlation among Hawthorn fruit content of polyphenols and triterpenoids, protocatechuic acid and epicatechin to the α-glucosidase inhibition activity. Moreover, they observed the contribution of flavonoids, polyphenols, vanillic acid, gallic acid, catechin, and chlorogenic acid to its antioxidant activity. They also obtained the highest DPPH scavenge and ferric reducing power exhibited both in the deionized water extract. Some studies have shown that phytochemical compounds inhibit α-glucosidase, such as triterpenoid compounds (Lai *et al*., 2012), phenolics and flavonoids (Mugaranja and Kulal, 2020; Barber *et al*., 2021). Kim *et al*. (2016) proposed the role of dietary polyphenols in preventing and managing T2DM. Healthy polyphenols may improve glucose homeostasis in the small intestine by inhibiting α -amylase and α-glucosidase, inhibiting sodium-dependent glucose transporter 1 (SGLT1); thus, reducing digestion and intestinal glucose absorption of dietary carbohydrates in the muscle, adipocyte, stimulate pancreas insulin secretion and reduce hepatic glucose output in the liver. Polyphenols may also enhance insulin -dependent glucose uptake, activate 51-adenosine monophosphate-activated protein kinase (AMPK), modify the microbiome in the large intestine, and have anti-inflammatory effects. The mechanism of proanthocyanidin (PA) (Figure 1) binds islet cells was proposed by Jiao *et al.* (2013). They found anti-amyloidogenic PA by preventing human islet amyloid polypeptide (hIAPP) oligomers and aggregation. The misfolding of hIAPP was supposed to cause β-cell dysfunction in T2DM. Furthermore, the result revealed that Cinnamon's PA as a primary compound effectively inhibited hIAPP. The PA with trihydroxy-phenyl rings or gallate esters have a similar structure to (–)-epigallocatechin-3-gallate, which previously exerts an inhibitor of hIAPP amyloid formation.

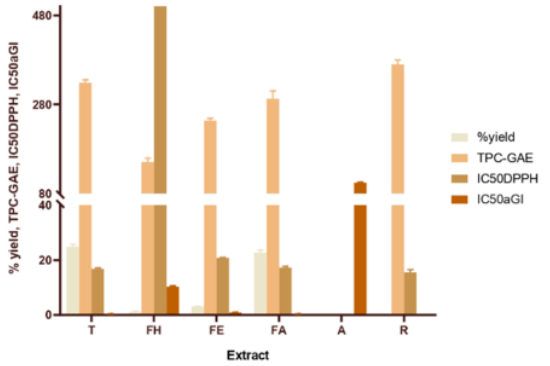

Figure 2. TPC, IC_{50} AA, and IC_{50} αGI of *C. burmannii* extracts and reference compounds. T= total extract, EH: n-hexane extract, EA: ethyl acetate extract, EE: ethanolic extract, R: rutin, GA: gallic acid, A: acarbose

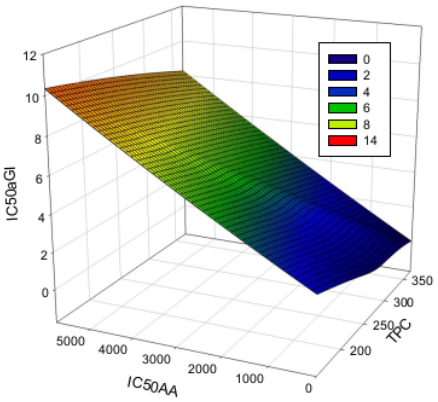

Figure 3. The 3D negative correlations among TPC to IC50 AA dan αGI of extracts. The axis represents TPC's (x), IC_{50}AA (y) and αGI (z)

4. Conclusion

The experiment showed that the ethanol solvent only with the soxhletation method produced a higher yield than the gradual polarity. The TPC of ethanolic extract was not significantly different from rutin. Moreover, the IC_{50} α-glucosidase inhibition of the ethanolic extracts was more potent than acarbose. A negative correlation resulted between the total phenolic content, antioxidant activity, and α-GI of the extracts. *Cinnamomum burmannii* provides benefits as α-glucosidase inhibitor

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and oxidative stress relieving in diabetes dietary supplements.

Conflict of interest

The authors declare no conflict of interest.

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