Jurnal Fitofarmaka Indonesia, 2020; 7(3) 20-25
http://jurnal.farmasi.umi.ac.id/index.php/fitofarmakaindo/index

Potency of *Cinnamomum burmannii* as Antioxidant and α Glucosidase Inhibitor and Their Relation to Trans-Cinamaldehyde and Coumarin Contents

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Article info
History
Submission: 28-05-2020
Review: 30-05-2020
Accepted: 13-07-2020

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DOI: 10.33096/jffi.v7i3.639

Keywords:
Cinnamomum burmannii; polyphenol; cinamaldehyde; coumarin; antioxidant

Abstract

Cinnamon (Cinnamomum spp) is one of important export commodity for Indonesia. With annual production capacity about 103.594 tons, Indonesia is one of main cinnamon's exporter especially to United States. Recently the utilization of cinnamon is developed, where not only use as spices but also use in pharmaceutical and cosmetic industries. The development of cinnamon's use of course might lead to the market growth. But on the other side arise an issue about coumarin content, where Cinnamomum burmannii issued to have higher content of this hepatotoxic compound than Cinnamomum verum or Cinnamomum zeylanicum. This research result showed that, although coumarin content of Indonesian Cinnamomum burmannii is higher than Cinnamomum zeylanicum but the difference is not too significant. C. burmannii collected from Gunung. Mas, West Java has coumarin content of 0.0030 % which is slightly higher than C. zeylanicum (0.0017 %). This research result also shown that antioxidant activity and α glucosidase inhibition activity is related to polyphenol and flavonoid content.

I. Introduction

Cinnamon (*Cinnamomum* spp) is one of the oldest herbs that are widely used in the food, pharmaceutical and cosmetics industries. The part that is widely used is the inner bark. In the United States and European markets, two varieties of cinnamon are known, namely Ceylon and Cassia (Blahova & Svobodova, 2012). Ceylon cinnamon is also known as "true cinnamon" and comes from *Cinnamomum verum* J.S. Presl. (synonym *Cinnamomum zeylanicum* Nees) which is an indigenous plant of Sri Lanka and Southern India (Paranagama *et al*, 2001). While Cassia cinnamon comes from several countries, one of which is Chinese cassia (*Cinnamomum cassia* Blume, synonym *Cinnamomum aromaticum* Nees), cultivated mainly in Southern China, Burma (Myanmar) and Vietnam. While Indonesian cinnamon, which grows and is cultivated in Indonesia is *Cinnamomum burmannii* Blume, mainly originating from Sumatra (Chen *et al*, 2014).

With an area of cinnamon plantation (*Cinnamomum burmannii*) about 135,000 hectares spread across 19 Provinces, where the largest area is in West Sumatra and Jambi (80%), and the annual production capacity of around 103,594 tons, Indonesia is one of the main producers and exporters of cinnamon in the world (Ferry, 2013). Since some of the results of the study mentioned that *Cinnamomum burmannii* has a high coumarin content (2.15 g / kg, Wang *et al*, 2013), Indonesian cinnamon is slightly more difficult to enter European market, which applies strict rules to limit the tolerance of coumarin content. European Food Safety Authority (EFSA) provides a limit on coumarin Tolerable Daily Intake (TDI) or tolerance of daily consumption of 0.1 mg / kg body weight (Scientific Opinion of the Panel on Food Additives, 2008; Blahova & Svobodova, 2012) or if assumed the average body weight is 70 kg, so the total daily intake (TDI) tolerated is 7 mg coumarin per day. . With this EFSA rule, cinnamon from Sri Lanka (*Cinnamomum zeylanicum*) with much lower coumarin content (0.017 g / kg, Wang *et al*, 2013) is more easily accepted by the European market. However, because Ceylon cinnamon is more expensive and has less strong aroma, for industrial use with cinnamon as a scented material, cinnamon from Indonesia remains preferred, especially in the United States. Coumarin is a group of compounds containing the framework of 1.2 benzopyrone. This compound is found in several plants, including many types of vegetables, herbs, fruits and medicinal plants. Generally, the content of this compound, in edible plants, is at a safe level for consumption (Wang *et al,* 2013).

Several other countries in Asia continue to improve the quality and quantity of cinnamon exports and become a competitor to Indonesia. These countries are: China, Vietnam and Sri Lanka. With an average global cinnamon import requirement of around 100,000 tons per year, the emergence of other exporting countries will automatically reduce the need for imports from Indonesia. The United States is the largest importer followed by India, the United Arab Emirates, Mexico, the Netherlands, Middle Eastern Countries, Singapore, South Korea, Brazil and Japan. On the other hand, cinnamon bark which was originally only used as a spice and raw material for essential oils, later developed as a pharmaceutical raw material (herbal medicine), and cosmetics, especially for perfume. The development demand of Cinnamon is related to the demand for preservative free cosmetics, which is aimed at reducing risk of allergies due to the utilization of synthetic preservatives such as methyl parabens (Nabavi *et al,* 2015) With the development of the use of cinnamon, the level of need will increase. This can be seen from the increase in exports by 9% and domestic demand increased by 81.08% (Ferry, 2013).

In connection with the competition in the cinnamon bark trade, it is very necessary to study the diversity of cinnamon in Indonesia. The study was focused on some important parameters, those are content of cinnamaldehyde, polyphenols, trans-cinnamaldehyde, and coumarin in *Cinnamomum burmannii* and their relation to antioxsidan and α glucosidase inhibition activities of ethanol extracts of cinnamon bark taken from some difference regions. *Cinnamomum burmannii* bark used is taken from five different regions in Indonesia, namely Aceh, Bau-bau, Berastagi, Jambi, and Gunung Mas, West Java.

II. Research Method

II.1 Materials

Cinnamomum burmannii bark is taken from several regions, namely Aceh, Berastagi (North Sumatra), Jambi, Bau-Bau (Southeast Sulawesi), Gunung (Gn) Mas, Puncak, Kab. Bogor (West Java).

II.2 Extraction

Extraction was carried out by maceration method using 96% ethanol solvent. Weighed a total of 100 grams of cinnamon bark from each region then put it in a glass container and then added 96% ethanol solvent. The immersion is allowed to stand for 24 hours, while stirring at each specified time interval, then filtered. Repeat three times, or until the extracted liquid looks clear.

II.3 Analysis of Polyphenols

Analysis of total polyphenol content was performed using the Folin-Ciocalteu Spectrophotometry method (Singleton *et al,* 1965).

II.4 Determination of trans-cinamaldehyde and coumarin levels

Determination of trans-cinamaldehyde and coumarin levels was carried out using Shimadzu LC-20 AD HPLC, with column C 18 (25 Cm), flow rate of 1 ml / min, the mobile phase of acetonitrile: water (5: 1) and UV / Vis detectors for trans - cinamaldehyde with a wavelength of 283 nm, while coumarin at a wavelength of 254 nm.

II.5 Determination of antioxidant activity

In vitro measurement of antioxidant activity was carried out by neutralizing or reducing free radicals using DPPH (1,1-diphenyl-2 picrilhydrazyl). Measurement of free radical reduction is carried out using spectrophotometry at a wavelength of 517 nm. (Yen and Duh, 1994).

II.6 Determination of inhibitory activity against α glucosidase

In vitro antidiabetic activity testing was carried out using the α-glucosidase enzyme inhibitory method (Saijyo *et. al*, 2008). 1 mg of the α-glucosidase enzyme is dissolved in 1 mL phosphate buffer (pH 7). Then 12 µL of the enzyme solution was diluted in 30 mL phosphate buffer before being used for testing. 250 µL 20 mM p-nitrophenyl-α-D-glucopyranoside, plus 475 µL 100 mM phosphate buffer and 25 µL of sample solution in 1% DMSO are mixed and homogenized. After homogeneous solution, incubated for 5 minutes at 37 ^{o}C, then 25 µL of sample solution in 1% DMSO is mixed and homogenized. 250 l of α-glucosidase solution was added, incubation was continued for 25 minutes. The reaction was stopped by adding 1 mL of 0.2 M Na_2CO_3. The remaining amount of p-nitrophenyl-α-D-glucopyranoside was measured at a wavelength of 400 nm. The percentage of inhibition is calculated by the equation:

$$\% \text{ Inhibition} = [(C-S)/C] \times 100 \quad (1)$$

Where C = control – blank; S = S1 - S0

Control shows absorbance with the addition of enzymes without samples, Blank shows absorption without the addition of enzymes and samples, S1 shows absorbance with the addition of samples and enzymes, S0 shows absorbance by adding samples without enzymes. The IC_{50} (Inhibition Concentration 50) value is an antidiabetic concentration (ppm) which can inhibit 50% of the α-glucosidase enzyme. IC_{50} value is obtained from the intersection of the line between 50% resistance to the concentration axis, then entered into the equation Y = a + bX where, Y = 50 and the X value indicates IC_{50}.

III. Result and Discussion

III.1 Extraction

The yield of contraction varies with a fairly wide range. Extraction results from *Cinnamomum burmannii* bark obtained from the Bau-bau area

gave the lowest yield (14.63%) and the highest yield from *Cinnamomum burmannii* obtained from the Berastagi area (28.31%) (Table 1). These results cannot conclude that only differences in growth location cause differences in the amount of extract obtained. Differences in plant age, differences in climate in which plants grow, and how to harvest can be other influential factors (Blahova & Svobodova, 2012 (1)), where in this study, these factors are not controlled. On average, the yield of extractions from several samples of cinnamon bark is almost the same as the results reported by Wardatun *et al* (2017), where by maceration method with 96% ethanol solvent it was reported that the yield was 20.860%.

Table 1. Yields of cinnamon extract

No	Origin of sample	Sample weight (gr)	extract weight (gr)	Yield (%)
1	Aceh	100	18.92	18.92
2	Jambi	100	15.70	15.70
3	Berastagi	100	28.31	28.31
4	Bau-Bau	100	14.63	14.63
5	Gn... Mas	100	24.39	24.39

Data from polyphenol analysis from *Cinnamomum burmannii* bark taken from several regions in Indonesia (Table 2), shows that *Cinnamomum burmannii* bark taken from Gn. Mas tea plantations in the Puncak District area of Bogor, West Java has the highest polyphenol content (17 , 96%), followed by cinnamon bark obtained from Berastagi, North Sumatra (16.77%). The high content of polyphenols in *Cinnamomum burmannii* originating from Gn. Mas and Berastagi may be influenced by the location of growing of plants, where Gn. Mas and Berastagi are both highlands with relatively cool temperatures. While the polyphenol content for *Cinnamomum burmannii* bark originating from the Baubau and Jambi regions were 8.71% and 6.35%, respectively. The content of polyphenols from these two regions is in the range of *Cinnamomum cassia* polyphenol content as reported by Yang *et al* (2012) which is between 6.313 - 9.534 g / 100 g dry weight.

Table 2. Polyphenols content of cinnamon bark

Origin of sample	Polyphenol content (%)	Water content (%)
Gn. Mas, West Java	17,96	8.12
Baubau, Sulawesi	8,71	8.71
Berastagi, North Sumatera	16,77	8.49
Jambi	6,35	10.22

III.2 Trans-cinnamaldehyde and coumarin

Two important compounds that are worthy of being used as signaling compounds of the chemical content of cinnamon bark are cinnamaldehyde or rather Trans-cinnamaldehyde (TCA) and coumarin. TCA is a flavonoid compound which in addition to being a flavor compound (aroma) is also an active compound whose existence is associated with cinnamon activity as an antioxidant and antidiabetic. While coumarin is a compound that also affects the aroma of cinnamon and acts as an antibacterial, it is also a compound that is known to have toxic or hepatotoxic properties. Therefore, good quality cinnamon is expected to have a high TCA content and low coumarin. The TCA content of the ethanol extract of cinnamon bark extracted from several regions varied between 1.758% (Berastagi) to 10.115% (Gn. Mas, Bogor Regency) (Table 3). These results are consistent with the results reported by Wardatun *et al* (2017), where it was reported that cinnamon bark obtained from the market in Bogor region had a cinnamaldehyde content of 124,143 mg / g (12.4%) and a TCA of 151,362 mg / g (15.1%).

The content of coumarin in *Cinnamomum burmannii* taken from several regions in Indonesia varies between 0.03% to 1.698%. These results are in accordance with Jayatilaka *et al* (1995) where from the results of his study stated that cassia cinnamon contains up to about 1% coumarin. These results also show that the coumarin content of *Cinnamomum burmannii* known as Indonesian cinnamon is not all high as reported by Wang *et al* (2013) Even the coumarin content of *C. burmannii* obtained from Gn. Mas (0.0030%) is only slightly higher than the average *Ceylon cinnamon* content (0.0017%).

Table 3. TCA and coumarin content

Origin of sample	TCA content (% B/V)	Coumarin content (% B/V)
Gn. Mas, West Java	10,115	0,003
Baubau, Sulawesi	3,951	1,658
Berastagi, North Sumatera	1,758	0,020
Jambi	5,353	1,698
Aceh	10,174	0,058

III.3 Antioxidant Activity

Based on IC_{50} values (Table 4), it appears that cinnamon bark extracts originating from the Gn. Mas, West Java has a very strong antioxidant activity (IC_{50} = 1.273 ppm), even stronger than vitamin C as a positive control (IC_{50} = 3.634 ppm). The IC_{50} values of other regional samples are still inferior compared to positive controls. High antioxidant activity of *Cinnamomum burmannii* bark extracted from Gn. Mas, in the Puncak area of Bogor Regency, West Java, shows a direct relationship between polyphenol content and antioxidant activity, where the total polyphenol content of *Cinnamomum burmannii* originates from Gn. Mas is the highest compared to that obtained from other regions. *C. burmannii* bark from Gn. Mas and from Aceh, also had the highest TCA content, namely 10.115% and 10.174%, respectively. This also shows the relationship between the content of flavonoid compounds with antioxidant activity.

Table 4. IC_{50} value

No	Origin of sample	IC_{50} (ppm)
1	Gn Mas, West Java	1,273
2	Jambi	7,269
3	Bau-bau	11,717
4	Aceh	6,639
5	Berastagi	11,586
6	Vitamin C (control +)	3,634

Other studies conducted by Devi *et al* (2007), and Chakraborty and Das (2010), reported that *Cinnamomum tamala* leaf extracts have inhibitory activities of superoxide and hydroxyl radicals due to the presence of polyphenol content in the extract. In addition, *Cinnamomum tamala* leaf extract also showed potential as an antioxidant in in vivo experiments using white Wistar rats that were previously induced with streptozotosin so that it became hyperglycemia. The anti-oxidant activity of *Cinnamomum tamala* leaf extract was also evidenced by the results of research from Palanisamy *et al* (2011). Where in the study using 50% alcohol extract it was seen that *Cinnamomum tamala* leaf extract had strong anti-hyperglycemic and anti-oxidant activity in rats that were previously induced with streptozotocin.

III.4 α glucosidase inhibitory activity

Several studies have shown that the administration of cinnamon extract (*Cinnamomum* spp) has great potential as an antihyperglycemia, antibacterial, and antioxidant. Ziegenfuss *et al*, (2006), reported that consumption of 500 mg / day of water extract from cinnamon for 12 weeks provided a significant improvement in fasting blood sugar levels, systolic blood pressure and reduced the risk of cardiovascular disease. Based on research conducted by Kim *et al*, (2006) using mice as test animals, research results were obtained which showed that extracts from *Cinnamomum cassiae* bark can reduce blood sugar levels from test animals that were previously made hyperglycemia. In that study, there was an increase in the decrease in blood sugar levels from test animals given cinnamon extract at various doses of 50, 100, 150, and 200 mg / kg body weight. In addition, there is also another study conducted by Rekha *et al* (2010), who reported that extracts from *Cinnamomum zeylanicum* at a dose of 200 mg / kg body weight were able to reduce blood sugar and blood lipid levels of test animals that were previously induced with streptozotosin to become diabetes. A similar study using *Cinnamomum zeylanicum* bark extract was conducted by Hassan *et al* (2012), which showed antidiabetic and hypolipidemic activity of cinnamon water extracts in rats that were previously diabetic by inducing streptozotocin. In this study the dose of water extract of cinnamon bark given orally to rats was 200 mg / kg body weight for 15 days. Lipid profile improved with a significant decrease in total cholesterol, triglycerides, LDL-cholesterol and VLDL-cholesterol respectively by 12.5; 23.86; 14.96 and 20%. In this study in addition to parameters of blood sugar levels also observed changes in lipid profile. This is conducted because people with diabetes generally also suffer from hyperlipidemia or blood cholesterol levels above normal, known as diabetic hyperlipidemia. Hyperlipidemia in people with DM is generally associated with high levels of triglycerides and low levels of HDL-cholesterol.

Based on the IC_{50} value of the antidiabetic test results of ethanol extract of cinnamon bark from 5 regions in Indonesia from low to high values respectively as follows: Gn. Mas, Bogor Regency (111,168 ppm); Aceh (158,515 ppm); Bau-bau (236,100 ppm); Berastagi (549,017) and Jambi (895,798 ppm) (Table 5). From the IC_{50} value it can be concluded that the ethanol extract of cinnamon bark originating from Gn. Mas, Bogor, followed by those from Aceh, had better inhibition compared to other regions. This shows an association between TCA content and α glucosidase inhibitory activity, where cinnamon bark from Gn. Mas and Aceh have higher TCA content compared to those from other regions. Sarjono *et al* (2010), showed that at a concentration of 50 ppm, the inhibitory activity of cinnamon bark was 45.31% with an IC_{50} value of 55.02 ppm. Gunawan, and Suhendra, (2013), reported research results of cinnamon decreased postprandial blood glucose levels, the average postprandial blood glucose level 30 minutes of people who consumed rice pudding with cinnamon which was 121.33 mg / dL was very significantly different from those who consumed rice pudding without cinnamon at 130.13 mg / dL with $p < 0.01$. Blood glucose levels after consuming rice pudding with cinnamon are lower than after consuming rice pudding without cinnamon. While the results of research Hananti *et al*, (2012), who tested the

antidiabetic activity of ethanol extract of cinnamon bark orally on Swiss Webster male white mice using glucose tolerance method showed the results of a decrease in blood glucose levels. The decrease in blood glucose levels is the best shown by the dose group 2 with a dose of 100 mg / kg BW with a percentage of 21.32%. From the ANOVA data and LSD test at 30.60, 90, and 120 minutes, the dose 2 group gave the best antidiabetic results compared to the dose 1 and dose 3 groups.

IV. Conclusion

From the results of this study it can be concluded that the antioxidant activity of the ethanol extract of *Cinnamomum burmannii* bark is determined by the amount of polyphenol and plavonoid content. From the results of this study it was also seen that the content of coumarin compounds in *Cinnamomum burmannii* which grew in several regions in Indonesia was not too high. *Cinnamomum burmannii* bark taken from the Gn. Mas, West Java has a coumarin content of 0.0030%, this content is only slightly greater than the coumarin content of Ceylon cinnamon (0.017 g / kg or equal to 0.0017%) known as "true Cinnamon" and marketed at much higher price.

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