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Research Article

Antioxidant Potential, Anti-Diabetes, and Toxicity of Aceh Cinnamon Extract (*Cinnamomum burmannii*)

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Abstract
Cinnamon ums often used empirically to overcome diabetes. This study aims to assess the effectiveness of Aceh cinnamon extract as an antioxidant and antidiabetic *in vitro* and to evaluate the toxicity of the extract. Cinnamons, obtained from coffee plantations in Aceh, were macerated with 96% ethanol for extraction. The extract phytochemical content was determined qualitatively, semiquantitatively (GC-MS), and quantitatively. The toxicity level was measured by an acute toxicity test based on the OECD and the BSLT assay. Antioxidant and anti-diabetes testing was determined *in vitro* by the DPPH inhibition method and α-glucosidase inhibition. The results showed that cinnamon extract contains alkaloids, flavonoids, polyphenols, tannins, quinones, saponins, and triterpenoid compounds. The total amount of phenol, flavonoid, and tannin extract levels were 66.34 mg GAE/gr, 80.52 mg QE/gr, and 566.33 mg AT/gr. The IC_{50} extract value against DPPH and α-glucosidase enzymes were 16.07 µg/mL and 123.52 µg/mL. LD_{50} ≥15 gr/ kg BW and LC_{50} extract was 350.57 ppm. Aceh cinnamon extract is categorized as a non-toxic ingredient, strong antioxidant activity, and moderate antidiabetics.
Keywords: Acute toxicity, Cinnamon, Shrimp larvae, α-glucosidase

Potensi antioksidan, Anti-Diabetes dan toksisitas Ekstrak Kayu Manis Aceh (*Cinnamomum burmannii*)

Abstrak
Kayu manis merupakan salah satu tumbuhan yang sering digunakan masyarakat secara empiris untuk mengatasi diabetes. Penelitian ini bertujuan menilai efektifitas ekstrak kayu manis Aceh sebagai antioksidan dan antidiabetes secara *in vitro* serta menilai toksisitas ekstrak. Sejumlah kayu manis yang diperoleh dari perkebunan kopi di Aceh di maserasi dengan etanol 96% sehingga diperoleh ekstrak kayu manis. Ekstrak dianalisis fitokimia secara kualitatif, semikuantitatif (GC-MS) dan kuantitatif. Toksisitas ekstrak dinilai dengan uji toksisitas akut berdasarkan OECD dan uji BSLT. Pengujian antioksidan dan antidiabetes ditentukan secara *in vitro* dengan metode inhibisi DPPH dan inhibisi α-glukosidase. Hasil penelitian menunjukkan bahwa ekstrak kayu manis mengandung senyawa alkaloid, flavonoid, polifenol, tanin, kuinon, saponin, dan triterpenoid. Kadar fenol, flavonoid dan tanin total ekstrak adalah 66,34 mg GAE/ gr, 80,52 mg QE/ gr dan 566.33 mg AT/gr. Nilai IC_{50} ekstrak terhadap DPPH dan enzim α-glukosidase berturut-turut adalah 16,07 µg/mL dan 123,52 µg/mL. Nilai LD_{50} ≥15 gr/kgBB dan LC_{50} ekstrak adalah 350,57 ppm. Ekstrak kayu manis Aceh dikategorikan sebagai bahan yang tidak toksik, memiliki aktivitas antioksidan yang kuat, dan antidiabetes yang sedang.
Kata Kunci: Toksisitas akut, Kayu manis, Larva udang, α-glukosidase

1. Introduction

Indonesia is the third largest mega-biodiversity country in the world. It should be a power and motivation for the discovering and developing of new drugs from natural origin. Spices are one of the natural wealth of Indonesian forests which are valuable commodities. Besides being used as a seasoning for cooking, spices are also used as supplements to maintain immunity, cosmetics, and overcome various health problems. Furthermore, spices have also been used in many herbal decoctions. They are part of the traditional medicine system in Indonesia, which has been passed down orally and written forseveral generations.[1] Cinnamon (*Cinnamomum burmannii*) is one of the most commonly utilized spices. Various studies have reported the properties of cinnamon such as antihyperglycemic, anti-cholesterol, antihypertensive, antimicrobial, and anti-inflammatory.[2] The study associated the therapeutic effect of cinnamon with its phytochemical content. Some studies report that cinnamon contains alkaloids, flavonoids, polyphenols, tannins, quinones, saponins, and triterpenoids.[3] Identification of compounds by chromatography techniques shows that eugenol and cinnamaldehydes compounds are metabolites that act most as intermediaries to the biological effects of cinnamon.[2,3]

Cinnamon grows at an altitude of up to 2,000 meters above sea level (m.dpl). However, the growing process will be better in areas with an altitude of 500 – 1,500 m.dpl, an average temperature of 25 ºC (18-27 ºC), and a humidity of 70-90 ºC.[4] Aceh, one of the largest cinnamon-producing regions in Indonesia, has the potential to develop the use of this plant as medicinal raw material if it issupported by safety and efficacy data.[5] The availability of this data can increase the classification of medicinal plants from herbal medicine to standardized herbal medicine and even phytopharmaceuticals.[6] One of the areas that produce cinnamon in Aceh is Simpang Teritit, Bener Meriah. This area uses an intercropping planting system by planting cinnamon alongside coffee plants. Natural characteristics in Bener Meriah which is a plateau with an altitude of 1000-2000 m.dpl, air temperature ranges from 20-23 ºC with air humidity of 77-91% is an ideal condition for cinnamon herbs. The content of these plant metabolites must be evaluated to get information about their phytochemical characteristics.

The plant's preparation conditions as medicine and environmental conditions can affect the type and metabolites level produced by plants, therefore affecting safety and efficacy.[7] Environmental conditions trigger the adaptation process resulting in different secondary metabolites to survive.[7] Differences in the content of metabolites affect the therapeutic effect.

People often use medicinal plants independently to cope with chronic diseases, including diabetes mellitus (DM).[8] Riskesdas 2018 data shows an increase in the prevalence of DM disease from 6.9% in 2013 to 8.5% in 2018. The data also showed that about 9% of patients with DM did not continue treatment. One of the reasons people stopped the treatment is because they consume traditional medicine.[9] This condition increases the interest of researchers to prove that traditional medicine carried out by the community has efficacy and is also safe as DM treatment. *In vitro* assay can be selected to conduct a preliminary screening of the efficacy of medicinal plants. One of the tests is the α-glucosidase enzyme inhibition test.[10] The data obtained can be an initial reference for continuing efficacy trials to pre-clinical trials using experimental animals and clinical trials. All these data are needed as evidence so that drugs can be used as treatment. In addition to efficacy tests, safety tests also need to be carried out. There are several toxicity test options, one of which is a test using shrimp larvae called the brine shrimp lethality test (BSLT). This test is cheap, easy, and simple to determine the safety of the test substance.[11]

DM is also associated with a state of oxidative stress. Administration of compounds with antioxidant activity can inhibit oxidative damage, thereby minimizing cell damage. One example is flavonoids which are found in many plants.

This is the earliest research to provide toxicity data and evidence of anti-diabetic efficacy *in vitro* against cinnamon extracts in Aceh. Several studies have reported the anti-diabetic activity of cinnamon extract. However, the activity value still varies depending on the source of the plant. In addition, the cinnamon cultivation system and the growing conditions in Aceh may produce secondary metabolites that are different from other studies, so we are interested in conducting this research in proving toxicity, antioxidant activity, and *in vitro* α-glucosidase activity in Aceh cinnamon.

2. Method

This is an experimental study *in vitro* using cinnamon ethanol extract and *in vivo* with Rattus norvegicus and shrimp larvae to test for acute toxicity of the extract.

2.1. Tools

The tools used in this research were a blender (Philips), micropipettes (Socorex), rotary evaporator (Heidolph), UV-Vis spectrophotometer (shimadzu UV mini-1240 UV-Vis Spectrophotometer), GC-MS (Shimadzu GCMS-QP2010 Ultra).

2.2. Materials

The chemicals used were the enzyme α glucosidase (Sigma-aldrich, USA), the substrate P-nitrophenyl-α-D-glucopyranose (PNPG) (Sigma-aldrich, USA), Tween 80, dimethylsulfoxide (DMSO) (Sigma-aldrich, USA), acarbose (Glucobay), distilled water, 70% ethanol, quercetin (Merck, Germany), tannic acid (Merck, Germany).

2.3. Methods

2.3.1. Cinnamon extraction

A total of 500 gr of cinnamon bark was harvested from a plantation in Simpang Teritit, Bener Meriah. It was dried without direct exposure to sunlight and crushed into a fine powder. The fine powder was macerated in 96% ethanol with a ratio of extract and solvent of 1:10 for 12 hours with twice remacerations. Maserate was processed into a viscous extract using a pressurized rotary evaporator. The extract was then measured yield, water content, and ash content, phytochemical analysis qualitatively (based on standards in Materia Medika Indonesia (Ministry of Health RI, 1995),[12] semiquantitative with GC-MS as well as the quantitative examination of total phenol, flavonoids, and tannin levels.

2.3.2. Acute toxicity test

Extract safety data were examined according to the OECD (Organization for Economic Cooperation and Development) Guidelines for Testing of Chemicals Section 4, Health Effects, 1981.[13] Five rats were fasted overnight, then given an extract orally at 15 g/kg BW. Clinical assessment and counting of the number of deaths were carried out at 1, 2, and 4 hours after administration of the extract. Observations continued for up to 14 days. All rats were decapitated and macroscopic examination was carried out on the last observation day. Abnormalities in the internal organs are recorded and examined microscopically when encountered.

2.3.3. Toxicity test with BSLT

The toxicity test method with BSLT follows the method of Meyer et al.[11] In short, the eggs of shrimp larvae (Artemia salina) were hatched in seawater. Testing using nauplii (mature shrimp larva). 20 mg of extract was dissolved in 1 ml of Tween 80 to becomes a stock solution of 2000 ppm. Furthermore, the solution concentration was manufactured using seawater, so a solution with a serial concentration of 10-1000 ppm was obtained. Each test performs twice by examining the number of dead larvae after 24 hours. The percentage of mortality and lethal concentration (LC_{50}) was determined based on the formula:

$$\text{Percent of death (\%)} = \frac{(\text{Total naupii} - \text{alive naupii}) \times 100\%}{\text{Total naupii}}$$

The number of dead larvae described the toxicity of the extract with a probit regression analysis program.

Table 1. LC_{50} of cinnamon extract

Cinnamon extract	Response (amount of dead larvae)															LC50 (ppm)
	Control			50 ppm			100 ppm			500 ppm			1000 ppm			
	0	0	0	0	1	0	3	2	1	8	7	7	10	10	10	**350.57**

2.3.4. Antioxidant activity test

DPPH radical scavenger activity was carried out in Kikuzaki et al.[14] 50 µL test samples with various concentrations coupled with 1.0 mL DPPH 0.4 mM, and 3,950 mL ethanol. The mixture was then vortexed and left for 30 minutes. The solution was measured for absorbance at a wavelength of 517 nm against the blank (consisting of 50 µL of extract and 4,950 mL of ethanol). Control absorbance measurements of 1.0 mL DPPH and 4.0 mL ethanol were also carried out. As a comparison, Vitamin C was used, which was known as an antioxidant. IC_{50} values were assessed based on the regression curve and the formula:

$$\text{Percent (\%) radical capture} = ((Ao - A1) / Ao)) \times 100\%$$

Ao is the control absorbance (does not contain the test extract) and A1 is the absorbance in the presence of a test sample or comparison compound.

2.3.5. Antidiabetic activity test

The antidiabetic activity was determined based on the inhibition of α-glucosidase activity referring to the Sancheti method.[15] Briefly made extract concentrations of 50-1000 µg/mL. In the microplate, the α-glucosidase solution was mixed with the sample solution, phosphate buffer, 4-nitrophenyl-D-glucopyranoside as substrate. The absorbance of the solution was measured with an ELISA reader at 410 nm. The percent inhibition of α -glucosidase was calculated by the formula:

$$\text{\% inhibition} = [1-(\text{ABS sample}/ \text{ABS control})] \times 100$$

The IC50 value was determined based on the regression equation obtained from data fitting with plots of percent α -glucosidase inhibition to acarbose concentration.

2.3.6. Statistical Analysis

The analysis was carried out in duplicate. Data are presented as mean ± SD and data analysis is descriptive and categorical based on parameters.

3. Result

The Cinnamon ethanol extract obtained was a thick reddish-brown extract. The characterization of the cinnamon extract obtained was 1.028% extract water content with 4.23% ash content. Phytochemical analysis of cinnamon ethanol extract contains alkaloids, flavonoids, polyphenols, tannins, quinones, saponins, and triterpenoids. Quantitative analysis of total phenol, flavonoid and tannin levels from the cinnamon extract was obtained using a standard curve using quercetin and gallic acid standards. The total phenol content was 66.34 mg GAE/gr, the total flavonoids content was 80.52 mg QE/gr, and total tannin extract was 566.33 mg AT/gr.

The content of cinnamon extract

Table 2. % Inhibition to DPPH and IC_{50} of cinnamon extract

Concentration (µg/mL)	Absorbance		% inhibition		IC50 (µg/mL)	
	Vit C	Cinnamon	Vit C	Cinnamon	Vit C	Cinnamon
2	0,071	0,095	35,45	13,64		
4	0,064	0,09	41,82	18,18		
6	0,063	0,086	42,73	21,82	8,32	16,07
8	0,056	0,078	49,09	29,09		
10	0,05	0,072	54,55	34,55		

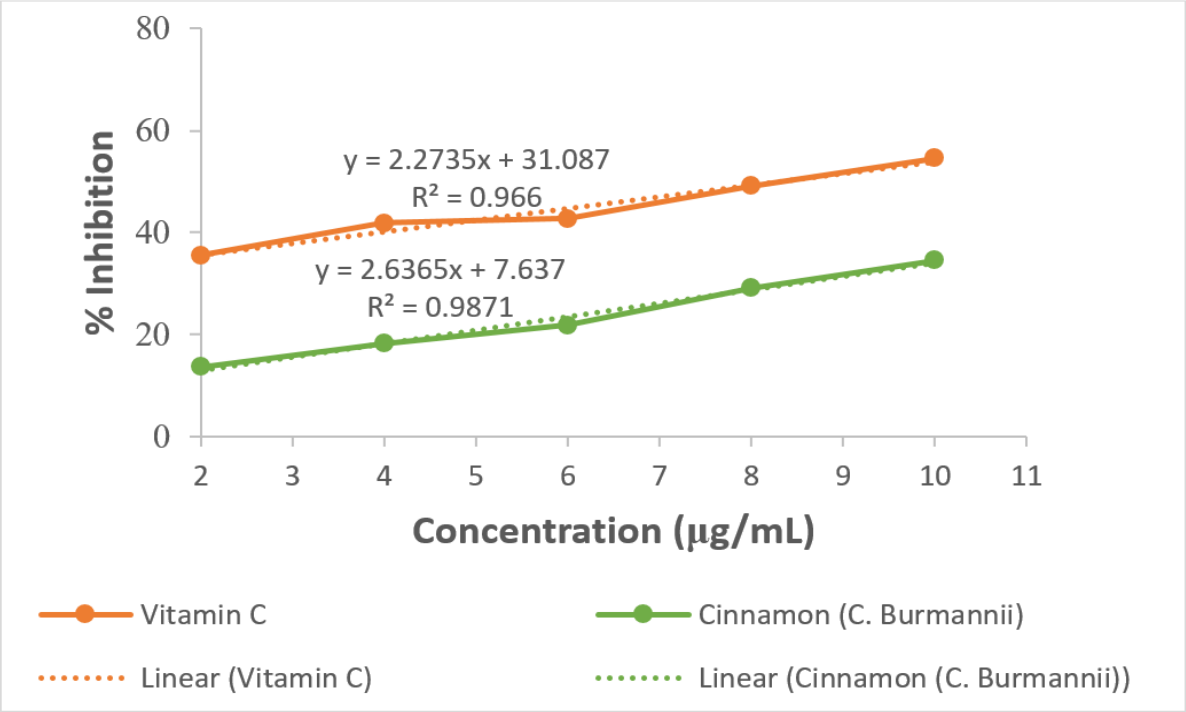

Figure 1. Calibration curve of vitamin C and cinnamon extract

with GC-MS was found that cinnamon extract contained 2-furan carboxy aldehyde 5-(hydroxymethyl), coumarin, 2,3-dihydro-3,5-dihydroxy-6-methyl-4H-piran-4-one, 2-amino-5-guanidino-pentanoic acid, cinnamyl alcohol, glycerin, -furol, N-Acetyl-d,l-norleusenin, cinnamaldehyde, d-Glycero-d-galacto-heptose, 1,5-anhydro-d- talitol, 3,4-altrosan, imidazole, 2-hydroxy-4-methyl, and hydro coumarin.

3.1. Acute toxicity test of the extract

This study proves that after administration of a dose of cinnamon extract 15 g/kg BW rats did not find death in rats. Observation of the organs after the autopsy also did not reveal any abnormalities. Based on these data, it showed that the administration of a single preparation orally in white rats at a dose of 15 g/kg BW does not cause death, and this was following the criteria for practically non-toxic in the classification of the degree of toxicity of the test preparation.

3.2. Toxicity test with BSLT

The results of the toxicity test using BSLT were determined based on the number of dead shrimp larvae at various extract concentrations (Table 1). The LC_{50} value was obtained through probit analysis of the data and it was found that the LC_{50} value of cinnamon was 350.57 ppm.

3.3. The antioxidant activity of cinnamon extract

The percentage of extract inhibition

Table 3. Absorbance and IC_{50} to α-glucosidase of cinnamon extract

Concentration (µg/mL)	Absorbance		IC_{50} (µg/mL)	
	Abs	% inhibition	Acarbose	Cinnamon
0	0,94	0	0.207	123.523
25	0,796	15.25		
50	0,635	32,34		
100	0,504	46,38		
250	0,312	66.81		
500	0.219	76,67		

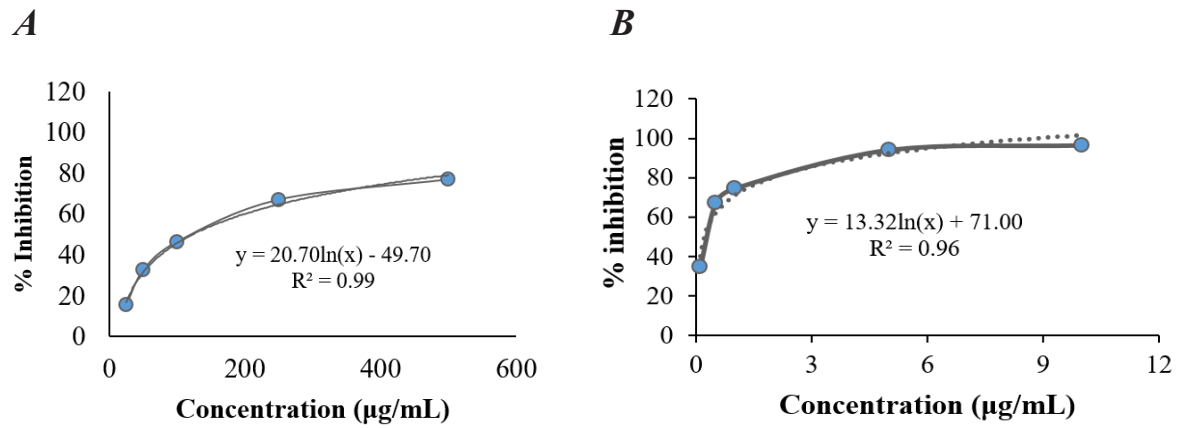

Figure 2. Calibration curve of cinnamon extract (A) dan acarbose (B)

data can be seen in Table 2. The antioxidant activity of cinnamon extract obtained from the IC_{50} value of the extract in inhibiting DPPH was 16.07 µg/mL with a comparison of vitamin C whose IC_{50} was 8.32 µg/mL. (Figure 1) Based on the results of the antioxidant test of cinnamon extract using the DPPH method *in vitro*, it was shown that cinnamon extract showed strong antioxidant abilities.

3.4. The antidiabetic activity with α-glucosidase inhibition

The antidiabetic activity was carried out *in vitro* by assessing the IC_{50} of the extract in inhibiting the α-glucosidase enzyme. The absorbance values of cinnamon and acarbose are shown in Table 3. Figure 2 shows the calibration curve to obtain the regression equation in determining the IC_{50} of cinnamon extract.

Based on the absorbance value and IC_{50} value calculation, the IC_{50} value of cinnamon extract was 123.52 µg/mL. These results were obtained by comparing with acarbose standard which has an IC_{50} of 0.21 µg/mL.

4. Discussion

This study conducted an acute toxicity test as a preliminary safety test and an *in vitro* test to assess the antioxidant and antidiabetic activity of cinnamon extract (*Cinnamomum burmannii*). Cinnamon is widely used as a spice and traditional medicine to treat various health problems.[3] The content of secondary metabolites in cinnamon is specific according to where it grows. The content of metabolites in plants is highly dependent on intrinsic and extrinsic factors, including genes, structure, and the number of precursors of secondary metabolite biosynthesis.[7] Differences in phytochemical content are due to differences in exposure to light, temperature, humidity, pH, nutrient content in the soil, radiation, and altitude in the plant's growing area.16 In this study, the cinnamon extract contained alkaloids, flavonoids, polyphenols, tannins, quinones, saponins, and triterpenoids. This finding was in line with various other studies.[17]

This study proved that cinnamon extract contains abundant phenolic compounds in the form of flavonoids and tannins. Various studies have proven that cinnamon contains many flavonoids. Ervina et al[17] reported that cinnamon contains high polyphenols and other researchers isolated the active ingredients in cinnamon extract and found that cinnamon contains cinnamaldehyde, linalool, caffeic acid, coumarin, and benzoic acid compounds.[18] Semiquantitative analysis with GC-MS found that the most compounds found in Aceh cinnamon extract were 2-furan carboxy aldehyde 5-(hydroxymethyl), coumarin, and cinnamaldehyde.

In this study, the IC50 value of cinnamon extract in inhibiting DPPH was calculated to determine the antioxidant activity of this compound. Based on the regression equation, it was found that the IC_{50} of cinnamon in inhibiting DPPH was 16.07 µg/mL. This concentration value was classified as a compound that has strong antioxidant activity. Other studies have proven that cinnamon has strong antioxidant activity.[8,17] Research has shown a correlation between levels of

flavonoid and tannin metabolites in plants and their antioxidant activity. In this study, cinnamon contains high levels of flavonoids and tannins, so these compounds might mediate the effect.

Antioxidants play an important role in protecting the body against free radical damage. Free radicals can be formed *in vivo* from a series of biochemical reactions in the body. In the DM state, an environment triggers the production of free radicals, thereby triggering oxidative stress. An imbalance between the concentration of pro-oxidants and endogenous antioxidants causes oxidative stress. The state of oxidative stress is the main pathway that causes the progression of disorders in DM, so it triggers complications in various organs, both microvascular and macrovascular. Hyperglycemia is a condition that can trigger an increase in the production of ROS (reactive oxygen species) and nitrogen species. The four classical pathways that play a role in the formation of ROS in hyperglycemic conditions are increased polyol pathway, increased AGE-RAGE formation, PKC-NFκB activation, and increased hexosamine pathway.[3,19]

Thus, antioxidant supplementation plays a role in preventing complications and protecting body tissues against further oxidative damage. According to Lee et al., non-enzymatic protection systems can be vitamin C, E, carotenoids, and polyphenols. The antioxidant role of these compounds can be through free radical quenchers, donating hydrogen atoms, free radical scavengers, and metal chelating agents. Based on this research, it was proven that cinnamon has strong antioxidant activity.

This extract also had antidiabetic activity although at moderate levels. The IC_{50} value of cinnamon in inhibiting the -glucosidase enzyme was 123.52 µg/mL. Various studies have also proven that cinnamon extract has antidiabetic activity.[20]

Ercan et al. demonstrated that the IC_{50} of cinnamon in inhibiting α-glucosidase is 1592 ± 17.58 µg/mL.[21] A study by Gulcin et al. comparing the IC_{50} of water and ethanol cinnamon extract reported that values of IC_{50} were 206.86 and 220.00 µg/mL, respectively.[22] Vijayakumar K et al. also reported IC_{50} values for cinnamon extract in water, ethanol, and methanol as 0.79 mg/mL, 0.62 mg/mL, and 0.77 mg/mL, respectively.[23] Despite the varying reported IC_{50} values by different researchers, all studies conclude that cinnamon extract has the potential as an anti-diabetic agent by inhibiting α-glucosidase enzyme activity in the gastrointestinal tract.

In the development of herbal medicines, in addition to efficacy considerations, it is imperative to assess the level of toxicity of these herbs. Good herbs are herbs that have good efficacy with low toxicity. In this study, the toxicity of the extract was assessed by the acute toxicity test and the BSLT method. This study proved that after the administration of a dose of 15 g/kg BW of cinnamon extract, there was no death in rats. In the conventional method, determining acute toxicity values for drugs, traditional medicines, and other materials uses the classification contained in the toxicity test guide. This result is in accordance with the research of Yesi Nursofia et al., where the toxicity category of cinnamon leaf extract (*Cinnamomum burmanii*) is classified as practically non-toxic because it has LD 15 gr/KgBW.

Cinnamon extract toxicity was also assessed by BSLT. The BSLT test is easy and relatively inexpensive. Many researchers use this test to assess the toxicity of their test materials. The LC_{50} value of cinnamon in this study was 350.57 ppm. This value was categorized as a substance that has low toxicity. This study shows that cinnamon extract is good to be developed as a herbal medicine because it has good efficacy as an antioxidant and anti-diabetic with low toxicity.

Some limitations need to be discussed in this study. Our results suggested that the activity of cinnamon extracts was potent antioxidants using DPPH methods. However, *in vitro* studies to prove the antioxidant activity of the extracts could be carried out to support this result.

5. Conclusion

Based on the data obtained from this study, it can be concluded that Aceh cinnamon extract (*Cinnamomum burmannii*) has LD_{50} > 15 g/kg BW. It was categorized as a practically non-toxic material, with strong antioxidant activity and moderate antidiabetic activity. Although the anti-diabetic effect of cinnamon extract through α-glucosidase inhibition is moderate, it should be continued with tests that support other antihyperglycemic mechanisms of action, so it is suggested that further research investigate the anti-diabetes using other assays and followed by *in vivo* studies using diabetes animal model.

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