The Effect of Antioxidant activity, Total Phenols and Total Flavonoids on Arginase Inhibitory Activity on Plants of Genus Sterculia

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ABSTRACT
Background: The genus of Sterculia has the main compound of phenol and flavonoids. The secondary metabolites which have an arginase inhibitory activities were phenol and flavonoids. The aim of this study was to investigate the arginase inhibitory activity from genus Sterculia. The Plant of Sterculia: Sterculia rubiginosa Zoll. ex Miq., Sterculia comosa (Wall) Roxb., Sterculia parkinsonii F. Muell, Sterculia macrophylla Vent, Sterculia stipulata Korth. The simplisia were leaves and woods. Materials and Methods: The simplisia were extracted with n-hexane, ethyl acetate and methanol. The ethyl acetate and methanol extract determined the arginase inhibitory activity. The active extracts as an arginase inhibitory, determined the total flavonoids, total phenols and antioxidant activity, and the chemical content. Sterculia comosa (Wall) Roxb., Sterculia macrophylla Vent, Sterculia stipulata Korth., have arginase inhibitory activity. Results: The ethyl acetate extracts of Sterculia stipulata leaves is an active extract. The methanol extract which have an arginase inhibitory activity were Sterculia comosa (Wall) Roxb. wood and leaves, Sterculia macrophylla Vent, wood and leaves, Sterculia stipulata Korth., wood, and leaves. The methanol extract of Sterculia comosa (Wall) Roxb. Woods has the highest content of total phenols, antioxidant activity, and arginase inhibitory activity. The methanol extract of Sterculia macrophylla Vent, has the highest content of total flavonoids, but this extract as an arginase inhibitory activity more lower than Sterculia comosa. The active extract as an arginase inhibitory activity was methanol extract of Sterculia comosa (Wall) Roxb. Conclusion: The total phenols were more contributed for the response of the arginase inhibitory activity much more than antioxidant activity and total flavonoids.

Key words: Arginase, Antioxidant, Enzyme, Flavonoids, Phenols, Sterculia.

INTRODUCTION
The genus of Sterculia was included in the subfamily of Sterculioideae, the family of Malvaceae and right now becomes the family of Sterculiaeae.¹ Sterculia consists of 200 species. The stem, wood, leaves, fruit, and roots of the Sterculia have been used traditional medicine in many countries to treat various diseases, including digestive diseases, diabetes, respiratory diseases, and skin diseases. In addition, the genus Sterculia has been studied and has activities as antimicrobial, anti-inflammatory, antioxidant and anticancer² cytotoxic and immunomodulatory activities,³ anti-nociceptive and anti-inflammatory,⁴ sedative⁵ antibacterial⁶ and anti-TB.⁷ The genus Sterculia contains of compounds flavonoids and their derivatives, terpenoids mostly as triterpenoids, coumarins, alkaloids and other groups such as phenolic acid, phenyl propanoid, fatty acids, sugar and some steroids.⁸ The literature study confirms that the main content of the genus Sterculia was flavonoids which include flavones, C-glycoside flavones, flavonols, flavan, isoflavones, isoflavan and anthocyanins. Other phenolic compounds such as phenolic acid, propanoid phenyl, coumarin, lignans and lignin.⁹ Indonesia has plants of genus Sterculia: Sterculia macrophylla Vent. was found in Sumatra, Maluku and Papua. Sterculia rubiginosa Zoll. ex Miq. was found in Sumatra. Sterculia parkinsonii F. Muell. was found in Papua. Sterculia stipulata Korth and also sterculia comosa. Arginase was an enzyme responsible for converting L-arginine to L-ornithine and urea. The substrat was L-arginine. This substrat used for Arginase and nitric oxide synthase (NOS), they use same substrat, so arginase competes with NOS for arginine.¹⁰¹¹ Nitric oxide (NO) production has been correlated to arginase activity in vessels, such as in physiological and pathological conditions on hypertension,¹² diabetes,¹³,¹⁴ erectile dysfunction,¹⁵ atherosclerosis,¹⁶,¹⁷ and endothelial disfunction.¹⁸ Some secondary metabolites have arginase inhibitory activity such as phenol and flavonoids.¹⁹ It was interesting to find the relationship between total phenols, total flavonoids and antioxidant activity with the inhibitory enzyme arginase on Sterculia.

MATERIALS AND METHODS
Materials
The Sterculia genus used were: macrophylla Vent, Sterculia stipulata, Sterculia parkinsonii, Sterculia comosa and Sterculia rubiginosa. The part of the plant from Sterculia used were leaves and woods. The Plants collected from Botanical Garden of Bogor, Indonesia and determined in Botany Herbarium Research Institute, Cibinong, West Java. The solvents used were n-hexane, ethyl acetate and methanol from local suppliers. Nor-NOHA (N ω-hydroxy-L-arginine) standard (Cayman, USA). Arginase enzymes (Sigma, Singapore), maleic acid (Sigma, Singapore). DMSO (Dimethyl sulfoxide) (Merck, Germany) and L-arginine (Sigma, Singapore). Ethyl acetate pro-analysis (Merck, Germany).
methanol pro analysis (Merck, Germany), n-hexane pro analysis (Merck, Germany), manganese sulfate (Sigma, Singapore). Urea assay kits (Quantichrom® Bioassay, United States), DPPH (2,2-Diphenyl-1-picrylhydrazyl) (Merck, Germany), the chemical reagents for identification of the compound and determining the content phenols total and flavonoids total.

**Extraction**

The powder from woods and leaves of *Sterculia* plants (20 g) were extracted by using a solvent continuously with n-hexane, ethyl acetate and methanol. The ratio between powder and solvent was 1:10. Each extract was concentrated with a rotary evaporator at 50 °C, then continued using a waterbath at 50 °C. Ethyl acetate and methanol extracts were tested for their activity as an arginase inhibitor.

**Arginase inhibitor activity**

The method for determined the arginase inhibitor activity used the procedure from the Kit and has been slightly modified. This procedure has also been carried out in previous studies. In the preliminary research, the concentration of the extracts in the well was made 100 µg/ml. The extract (50 mg) was added with 400 µl DMSO to dissolve, added with aquabidestillata to 5 ml (stock 1). This solution was taken 1 ml and diluted with aquabidestillata to 2 ml (stock 2). From the stock 2, 90 µl was taken and diluted with aquabidestillata to 1 ml (stock 3). This solution (stock 3) would be tested for arginase inhibitory activity. Ten (10) µl extract solution (stock 3) were added to the well, 15 ml enzyme (1 U/ml), added 25 µl of L-arginine (570 mM) solution and shake for 5 sec. Incubated at 37 °C for 30 min. After incubation added with 100 µl urea kits A and B (1:1), shake for 5 s. Incubate for 1 h at room temperature. The absorbance was read at 430 nm. The concentration extract for this activity was 100 µg/ml in well. The nor-NOHA as a positive control was performed under the same conditions and determined the IC₅₀.

**Antioxidant activity**

The Antioxidant activity used the DPPH method from Bobo garcia (2015) with microplate as an instrument. For the antioxidant activity, the concentration of extracts were used 100 µg/ml. The extract (50 mg) was added with 400 µl DMSO to dissolve, added with Na₂CO₃ 7.5% to prepare the mixture added 80 µl of Na₂CO₃ 7.5%. The incubation was carried out for 2 h in a dark place at room temperature. The absorbance was read at 517 nm. The absorbance results was read at 517 nm. The absorbance was read at 430 nm. The absorbance results was read at 517 nm. The absorbance results was read at 517 nm.

The determination of total flavonoids content used the method from Farasat (2014) with microplate as an instrument. The concentration of the extract in the well was 100 µg/ml. Twenty (20) µl extracts in methanol (1200 µg/ml) were added in the well, 20 µl aluminum chloride 10%, Added 20 µl potassium acetate 1 M and 180 µl distilled water. The mixture was incubated for 30 min at room temperature. The absorbance was read at 415 nm. The standard curve was used quercetine (3; 6; 9; 12; 18; 24 µg/ml). Total flavonoids was calculated as quercetine equivalent (mg/g) dry extract (mg QE/g extract).

**Biochemical screening and TLC chromatogram**

The chemical compounds in the active extracts were determined by the method of Harborne and Indonesian pharmacopoeia. The content of the chemical compounds: tannins, alkaloids, flavonoids, phenols, saponins and anthraquinones. The active extracts were determined the profile of TLC chromatogram.

**Statistical analysis**

The multiple linear regression was used as a statistical analysis to find the relationship between antioxidant activity, total phenols and total flavonoids on arginase inhibitory activity. The total phenols, total flavonoids and antioxidant activity as independent variable, and dependent variable was arginase inhibitory activity.

**RESULTS AND DISCUSSION**

**Arginase activity**

Methanol extract was an active extract from plants in the genus *Sterculia*. This active extract in wood and leaves. The results showed in table 1 and table 2. The IC₅₀ for nor-NOHA as a positive control was 3.773 µg/ml. The result showed on table 2 and figure 1.

**Antioxidant activity**

The DPPH was method to determined the antioxidant activity. Quercetine was used as a positive control, the IC₅₀ of quercetine was 5.63 µg/ml. The result of antioxidant activity showed on table 1 and figure 2.

**Determination of total flavonoids and total phenols**

The determination of total flavonoids used the method from Quercetine as a standard. The result of linear regression was $\gamma = 0.0198x - 0.0215$ ($R^2 = 0.9964$). *Sterculia macrophylla* leaves extract had the highest of total flavonoids. The total flavonoids was 67.74 mg QE/gram. The determination of total phenol was used gallic acid as standard. The linear regression was: $\gamma = 0.026x + 0.3373$ ($R^2 = 0.996$). The highest phenol content was *Sterculia comosa* wood extract. The value was 709.39 mg GAE/gram. The result showed on table 2 and figure 2.

**Phytochemical screening**

The active extract as an arginase inhibitor was determined the chemical constituents. The results showed on table 6. The Chromatogram Profile of Active Extracts showed on table 7.

**Statistical analysis**

The multiple linear regression used for statistical analysis to find the effect of antioxidant activity, total phenols and total flavonoids to arginase inhibitory activity. The Significance value 0.000 (*P<0.05) it was meant that Ho was rejected. It can be said that total phenol, total flavonoids and antioxidant activity have an affect to the arginase inhibitory activity. The value of beta coefficient for total phenol was 0.891; the value of beta coefficient for total flavonoids was -0.053, it can be concluded that the total phenols more contributed
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**Figure 1**: The arginase inhibitor activity of nor-NOHA.

\[ y = 5.4539x + 28.378 \]
\[ R^2 = 0.9997 \]

**Figure 2**: Antioxidant activity of quercetine.

\[ y = 8.0154x + 4.863 \]
\[ R^2 = 0.998 \]

**Table 1**: Arginase inhibitor activity of methanol extracts.

| Extract (100 µg/ml) | Average Inhibition (%) | Sd  | kv  |
|---------------------|------------------------|-----|-----|
| Leaves              |                        |     |     |
| Sterculia comosa    | 61.66                  | 7.07| 11.46|
| Sterculia macrophylla | 32.61              | 5.56| 17.07|
| Sterculia parkinsonii | -92.75             | 13.71| -14.78|
| Sterculia rubiginosa | -121.80              | 5.89| -4.83|
| Sterculia stipulata | 14.47                 | 2.07| 14.30|
| Woods               |                        |     |     |
| Sterculia comosa    | 84.25                  | 10.34| 12.28|
| Sterculia macrophylla | 92.54             | 5.90| 6.38|
| Sterculia parkinsonii | -66.71            | 11.41| -17.11|
| Sterculia rubiginosa | -222.17             | 17.33| -7.80|
| Sterculia stipulata | 17.80                 | 3.00| 16.84|
| Nor-NOHA (IC₅₀)     | 3.733 µg/ml           | R²=0.9997|

**Table 2**: Arginase inhibitor activity of ethyl acetate extracts.

| Extract (100 µg/mL) | Average Inhibition (%) | Sd  | kv  |
|---------------------|------------------------|-----|-----|
| Leaves              |                        |     |     |
| Sterculia comosa    | -35.57                 | 6.63| -18.64|
| Sterculia macrophylla | -93.36            | 12.61| -13.51|
| Sterculia parkinsonii | -93.16            | 14.06| -15.10|
| Sterculia rubiginosa | -76.56               | 14.81| -19.34|
| Sterculia stipulata | -51.03                | 5.75| -11.27|
| Woods               |                        |     |     |
| Sterculia comosa    | -12.54                 | 0.05| -0.42|
| Sterculia macrophylla | -8.31              | 1.35| -16.24|
| Sterculia parkinsonii | -64.90             | 11.48| -17.69|
| Sterculia rubiginosa | -2.96                | 0.55| -18.50|
| Sterculia stipulata | 19.19                 | 1.25| 6.49|
| Nor-NOHA (IC₅₀)     | 3.733 µg/ml           | R²=0.9997|
Table 3: Antioxidant activity of methanol extracts.

| Extract (100 µg/ml) | The part of Plant | Antioxidant Activity (%) | sd  | kv  |
|--------------------|-------------------|--------------------------|-----|-----|
| Sterculia stipulata | Leaves            | 78.81                    | 1.26| 1.60|
| Sterculia macrophylla | Leaves           | 78.65                    | 2.69| 3.42|
| Sterculia stipulata | Woods             | 8.30                     | 0.38| 4.60|
| Sterculia macrophylla | Woods            | 77.20                    | 2.53| 3.28|
| Sterculia comosa | Woods             | 91.31                    | 1.67| 1.83|
| IC₅₀ Quercetine |                   | 5.63 µg / ml             |     |     |

Table 4: Total phenols content of methanol extract.

| Extract (100 µg/ml) | The Part of Plant | Total Phenols (mg GAE/g) | sd  | kv  |
|--------------------|-------------------|--------------------------|-----|-----|
| Sterculia stipulata | Leaves            | 141.62                   | 10.54| 7.44|
| Sterculia macrophylla | Leaves        | 316.29                   | 35.66| 11.27|
| Sterculia stipulata | Woods             | 50.00                    | 5.15 | 10.30|
| Sterculia macrophylla | Woods           | 515.00                   | 37.33| 7.25 |
| Sterculia comosa | Woods             | 709.39                   | 35.47| 5.00 |

Table 5: Total flavonoids content of methanol extract.

| Extract (100 µg/ml) | The Part of Plant | Total Flavonoids (mg QE/g) | sd  | kv  |
|--------------------|-------------------|---------------------------|-----|-----|
| Sterculia stipulata | Leaves            | 41.45                     | 5.84 | 14.08|
| Sterculia macrophylla | Leaves        | 67.74                     | 6.50 | 9.60 |
| Sterculia stipulata | Woods             | 27.99                     | 0.62 | 2.22 |
| Sterculia macrophylla | Woods           | 28.87                     | 4.24 | 14.69|
| Sterculia comosa | Woods             | 33.27                     | 3.74 | 11.24|

Table 6: Phytochemical screening of the methanol extract.

| Extract | Sterculia stipulata Leaves | Sterculia macrophylla Leaves | Sterculia comosa Woods | Sterculia macrophylla Woods | Sterculia stipulata Woods |
|---------|---------------------------|-------------------------------|------------------------|---------------------------|---------------------------|
| Terpenoids/steroids | Terpenoids + | Terpenoids + | Steroids + | Steroids (+) | Terpenoids + |
| Alkaloids | + | + | + | + | + |
| - Dragendorff | + | + | + | + | + |
| - Mayer | + | + | + | + | + |
| Tannins | + | + | + | + | + |
| - FeCl₃ | + | + | + | + | + |
| - Folin | + | + | + | + | + |
| - Gelatine | + | + | + | + | + |
| Flavonoids | + | + | + | + | + |
| Antraquinones | - | - | - | - | - |
| Saponins | + | + | + | + | + |

Note: + = presence, - = Absence

Table 7: The chromatogram profile of active extracts.

| No. | Mobile phase | Sterculia stipulata Woods (RF, UV365) | Sterculia stipulata Leaves (RF, UV365) | Sterculia macrophylla Leaves (RF, UV365) | Sterculia comosa Woods (RF, UV365) | Sterculia macrophylla Woods (RF, UV365) |
|-----|--------------|----------------------------------------|----------------------------------------|------------------------------------------|----------------------------------|------------------------------------------|
| 1   | Hexan: Ethyl acetate: Methanol (11:4:2) Stationary phase: Silica Gel GF₂₅₄ | 0.76 (red) | 0.76 (red) | 0.38 (blue) | 0.67 (black) spray with H₂SO₄, 10% becomes yellow 0.76 (red) | 0.45 (blue) | 0.76 (blue fluorescent) 0.91 (blue) |
| 2   | Ethyl acetate: Methanol (9:1) Stationary phase: Silica Gel GF₂₅₄ | 0.2 (blue) | 0.15 (blue) | 0.21 (black) spray with H₂SO₄, 10% becomes yellow 0.85 (red) | 0.76 (blue fluorescent) | 0.45 (light blue) | 0.76 (blue fluorescent) 0.89 (blue) |
| 3   | Ethyl acetate : Formic acid ( 8:3:0,1) Stationary phase: Silica Gel GF₂₅₄ | 0.64(light yellow) 0.73 (light yellow) | 0.64(light yellow) 0.73 (yellow) | 0.55 (blue) 0.69 (black) spray with H₂SO₄, 10% becomes yellow 0.76 (yellow) 0.91(red) | 0.55 (blue) | 0.64 (blue) | 0.91 (blue) |
for the arginase activity than total flavonoids and antioxidant activity. The VIF (Variance Inflance Factor) values showed for total phenols 2.338, total flavonoids 1.444 and for antioxidant 2.430, from the three independent variables showed that there was no multicollinearity. The multiple linear regression with 3 independent variables as follow: Y = 28.289 + 0.128 X \_1 - 0.497 X \_2 - 0.069 X \_3, X \_1 = independent variable (total phenols), X \_2 = independent variable (total flavonoids), X \_3 = independent variable (antioxidant activity).

Endothel dysfunction was related to arginase activity, one of the disease was hypertension. L-arginine is a substrate that used by NOS and arginase. Under physiological conditions NOS maintains the health of blood vessels by producing NO. Arginase produces ornithine, which would be metabolized to polyamine for tissue growth and proline for collagen. Under pathological stimulation with the presence of RhoA/ROCK, arginase activity would be increase so that it would deplete the substrate NOS, L-arginine. When NOS does not have enough substrate, it will become unbound and produce more superoxide (O\_2\(^{-}\)) than NO. Increased production of polyamines and proline can also cause pathological and vascular stiffness.\(^{23,24}\) Availability of NO will affect the regulation of vascular tone and maintenance of vascular integrity.\(^{2}\) The inhibition of arginase activities by phenol, flavonoids, among of them were chlorogenic acid, quercetin, epicatechin, wogonin, (2R, 4S)-4,5,6,7,8,8′-Hexamethoxylflavan, (2S), 7, dihydroxy-2′dimethoxyyl avanone, (2S)-5, 2,5′-Trihydroxy-7,8-dimethoxylavanone, naringenin, 7-Hydroxyxacinone, taxifolin, kaempferol, caffeic acid, Sauchinone, meso-Dihydroxyauric acid, apigenin, resveratrol, piceatannol, Guaiacian, Naringenin-5-O-β-D-glucopyrana, (2S) -5,5′-Dihydroxy-7,8 dimethoxylavanone-2′-O-β-D-glucopyranoside.\(^{23}\) Flavonoids such as luteolin, fisetin can inhibit the arginase enzyme.\(^{26}\) Our previous study showed that Sterculia macrophylla which has arginase activity also have high of antioxidant activity and total flavonoids.\(^{27}\) The woods of Sterculia more active than leaves. And the methanol extract more active than ethyl acetate extract for inhibit arginase. The recent study the stem bark of Caesalpinia turtosa have the arginase activity with the IC\(_50\) 11.58 µg/ml for methanol extract and 33.81 µg/ml for ethyl acetate extract.\(^{24}\) This result was same with our study. Sterculia contain phenol compounds and flavonoids as the abundant compound.\(^1\) Interesting to examine whether the arginase inhibitory activity of from the genus Sterculia was influenced by antioxidant activity, total phenol levels and total flavonoids. The analytical results by multilinear regression analysis showed that total phenol was more contributed for this activity than total flavonoids and antioxidant activity. Sterculia comosa and Sterculia macrophylla have a high inhibitory activity on arginase. It is need more research to know the chemical compound which was responsible for this activity.

CONCLUSION

The total phenols of the plant of Sterculia genus responsible for the arginase inhibitory activity. The most active plants was Sterculia comosa woods. Based on this study Sterculia comosa woods may be used for many diseases causes by endothelial dysfunction.

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CONFLICTS OF INTEREST

We declare that we have no conflicts of interest.

ABBREVIATIONS

S: Sterculia
TPTZ: 2,4,6-tripryridyl-s-triazine
FRAP: Ferric Reducing Antioxidant Power
AFS: Ammonium ferrous sulphate

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