




RESEARCH ARTICLE

REVISED **Phytochemical screening and antioxidant profiling of Sumatran wild mangoes (*Mangifera* spp.): a potential source for medicine antidegenerative effects [version 3; peer review: 2 approved]**

Previously titled: Antioxidant (gallic acid and quercetin) profile of Sumatran wild mangoes (*Mangifera* spp.): a potential source for antidegenerative medicine

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Abstract

Background: New findings on the potential of wild mangoes from the island of Sumatra as a source of antioxidant helps their conservation effort as it introduces their useful compounds to the public. This study aims to analyze the antioxidant profile and quantification of gallic acid and quercetin content from leaves and bark of Sumatran wild mangoes. Exploration and analysis of phytochemical constituents from 11 Sumatran wild mangoes was performed.

Methods: Antioxidant activity of wild mangoes was analysed with 1,1-diphenyl-2-picryl hydroxyl (DPPH), and determination of quercetin and gallic acid content was performed by high performance liquid chromatography (HPLC) method. Total flavonoid and phenolic analysis was also performed. Curve fitting analysis used a linear regression approach.

Results: The highest level of antioxidant activity, phenolic compound and flavonoid compound was found in the leaves and bark of *Mangifera* sp1. (MBS), the bark of *M. foetida*₃ (var. batu) and leaves of *M. torquenda*, and the bark and leaves of *M. sumatrana*, respectively. The content of gallic acid in leaves ranged from 5.23-35.48 mg/g dry weight. Quercetin content of wild mangoes leaves ranged from 0.76 to 1.16 mg/g dry weight with the lowest value in *M. foetida*₂ (var. manis) and the highest in *M. laurina*.



Conclusion: The results obtained are expected to be useful in supporting the development of drugs that have antidegenerative effects.



Keywords

antioxidant, gallic acid, quercetin, Sumatran, wild mango

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REVISED Amendments from Version 2

There is a word added to the title "Phytochemical Screening" and changes to the conclusion of mango leaves as an immunomodulatory agent are not included. The term of "antidegenerative drugs" has been changed to be an "antidegenerative effects".

Any further responses from the reviewers can be found at the end of the article

Introduction

Sumatran wild mangoes have the potential to be used as an herbal medicine and are found in the Sumatra rainforests. However, they are threatened with extinction due to rapid and massive deforestation, and due to this species lower economic market value and low consumption by humans, there is little interest in their cultivation¹. This could lead to an increase in the number of endangered species in the Sumatran rainforest. In nature, these species are ecologically valuable as the primary food for primates and other wildlife.

There are eight wild mango species found in Sumatra: *Mangifera quadrifida*, *M. torquenda*, *M. magnifica*, *M. grifithii*, *M. kemanga*, *M. sumatrana*, *Mangifera* sp1. (MBS) and *Mangifera* sp2. (MH)^{2,3}. The conservation of wild mango types will not be effective if the benefits of these plants are unknown, while their unique characteristics show that these plants have the potential to be therapeutic agents with high antioxidant ability⁴. Consequently, studying their ecological role and finding their potential biomedicine compounds is the best way to aid wild mango conservation.

These wild mangoes are acidic and have a strong turpentine aroma, rough fibers and strong odor, showing that these mangoes are an antioxidant source as reported by Fitwawati *et al.*⁴. Grundhofer *et al.*⁵ Explains that mango is a rich source of many phytochemical compounds. Main compounds such as phenolic and flavonoid can be obtained from various parts such as fruit, kernel, leaves, and bark^{6,7}. Mohan *et al.*⁸ mentioned that mango leaves and bark contains phenolic were very high which were responsible for various pharmaceutical activities, as antioxidant. Antioxidants are vital to resolve some types of degenerative diseases, improving immunity and responding to external attacks, such as bacteria, viruses, fungi, and various disease-causing germs. They may even be used to manage chronic diseases, such as cancer. In the study by Taing *et al.*⁹, skin and flesh extracts of mangoes (*M. indica*) had the remarkable action of inhibiting proliferation of breast and colon cancer cells¹⁰.

Previous studies show that mango skin (*M. indica*) possess flavonol O- and xanthone C-glycosides¹¹, gallotannins and benzophenone derivatives¹². Mango seeds contained bioactive components such as phenolics, carotenoids and ascorbic acid¹³, carbohydrates (58–80%), proteins (6–13%), essential amino

acids and lipids (6–16%)¹⁴. The polyphenol component of mango extract is phenolic acid (gallic acid) and flavonoids (quercetin)¹⁵. These compounds are found in the edible fruits and have been shown to have great potential for protecting the body from oxidative stress-associated damages^{16,17}.

Gallic acid (3,4,5-trihydroxybenzoic acid) is a major polyphenolic compound present in mangoes¹⁸. Phenolic compounds are vital in the immune system response to chronic degenerative diseases, such as anti-aging, anti-inflammatory, antidiabetic and antiproliferative activities, and have a cardioprotective effect, including reduction the side effects of chemotherapeutics¹⁹. Quercetin (3,3',4',5,7-pentahydroxyflavone) is one of the most abundant flavonoid-derived food compounds and is present in various mangos (e.g. *M. indica*)²⁰. Flavonoid structure contains a double bond in the C ring and a 4-oxo group, which enhances its potent antioxidant activity²¹. Flavonoids have been scientifically proven to be anti-allergic, anti-inflammatory, anti-cancer²², antimicrobial²³ and antiviral²⁴. Quercetin generally exists in edible plants and is mostly used in the production of traditional medicine to relieve some type of diseases^{25–27}.

Previous research related to the antioxidant potential of wild mango species from Sumatra had been carried out qualitatively by Fitwawati *et al.*⁴. Yet, this research topic needs the support of quantitative data and detailed metabolite content in order to clarify the antioxidant compound of wild mangos that have high potential to be a source of antidegenerative drugs. To the best of our knowledge, quantitative analysis of the antioxidants in wild mangos has not yet been reported. Therefore, this study aimed to analyze the antioxidant compound (gallic acid and quercetin) of wild mangos from Sumatra, Indonesia in order to preserve its existence in nature. The results obtained are expected to be advantageous in the effort of discovering types that contain highly phenolic and flavonoid compounds, which will support antidegenerative drug development for public health. The finding of medicinal compounds in wild mangos may make stakeholders pay attention to cultivation and restoration, so their population in nature will be conserved.

Methods

Equipment and materials

Equipment. Preparative-plate glass for thin layer chromatography, Whatman filter-paper, vacuum rotary evaporator, ultraviolet lamps 254 and 366, UV-Visible spectrophotometer (GENESYS 10S UV-VIS), High Performance Liquid Chromatography (HPLC; Shimadzu LC 20AD), cuvette, micropipette. **Materials:** stem bark and leaves of wild mango from Sumatra, distilled water (Batrac), ethanol (Batrac; as solvent), silica gel GF254 (Batrac; for isolation), and ethyl-acetate (Batrac; as solvent).

Plant preparation and extraction of wild mangoes

The wild mango samples were collected from several provinces in Sumatra Island, such as Riau, Jambi and South Sumatera, as depicted in Figure 1. Wild mango bark was dried in an oven at 40°C, while the leaves were freeze-dried. Dried bark and

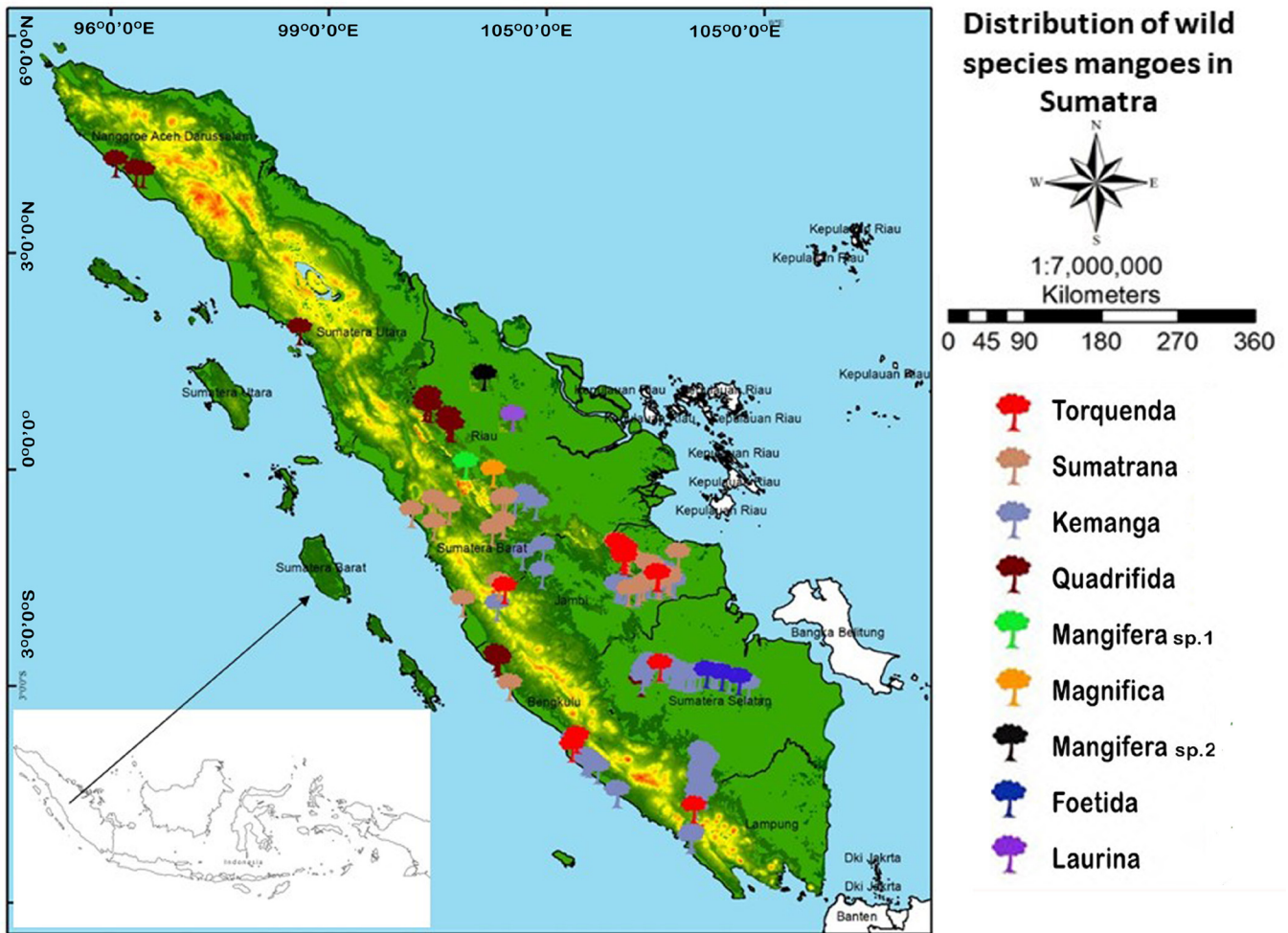


Figure 1. Distribution of the wild mango sources involved in this study.

leaves were ground by a blender and ~100 g of the resulting powder was macerated with 200 ml ethanol until it was submerged, and was then soaked for a day. All macerate was collected and evaporated with a rotary vacuum evaporator at 50°C to obtain a solid-liquid extract.

Quantification of antioxidant content

Antioxidant activity analysis was assessed with the DPPH(2,2-diphenyl-1-picryl-hydrazyl-hydrate) method²⁸. Briefly, approximately 2 mg of the dried sample was dissolved in 2 mL of methanol until the concentration reached 1000 mg/mL. Then, in a plate consisting of rows A-H (each row consisted of 12 wells), 100 mL of sample was added to each well in row A. Then, a total of 50 mL methanol was added to each well for rows B to F. 50 mL was taken from row A and then added to the row B; the same volume taken from row B and added to row C; the same procedure was done to row F. 50 mL was taken from row F and discarded. The following concentrations were obtained through this process: 1000 (row A), 500 (B), 250 (C), 125 (D), 62.5 (E), and 31.25 (F) g/mL. Row G to H were filled with 50 mL of methanol, only wells 1-6 of row H were filled.

Furthermore, for DPPH test, additional methanol of 80 mL (concentration of 80 mg/mL) is added to the rows A to G, and then incubated for 30 minutes. Radical bounding was measured by the decrease in DPPH absorbance using a microplate reader at a wavelength of 517 nm. A positive control was used as a comparison (ascorbic acid, 50 µg/mL).

The antioxidant activity is presented as inhibition percentage of IC₅₀, which was calculated by the formula below²⁹:

$$\%Inhibition = \left(\frac{A_0 - A_i}{A_0} \right) \times 100\% \tag{1}$$

where A₀ is the absorbance without sample and A_i is the absorbance of the tested sample.

Quantification of total flavonoid content

Analysis of total flavonoid content was carried out using the method of Xu and Chang³⁰. Quercetin solution was firstly dissolved into five concentrations (20, 40, 60, 80 and 100µg/ml) for a standard curve. Subsequently, ~100 µl of quercetin (blank)

sample was mixed together with 50 NaNO₂ 5% and 50 µl AlCl₃·6H₂O (aluminum chloride hexahydrate) 10% and 50 µl NaOH 1 M were added to a 96 well clear polystyrene microplate. The mixture was incubated in a dark place at room temperature for 30 minutes. After that, the mixture was assessed using a microplate reader at a wavelength of 510 nm. Total flavonoid content is determined by following equation:

$$M = \frac{bD_p V}{m_t} \left(\frac{m_{total}}{m_{dry}} \right) \quad (2)$$

where b and D_p are regression coefficient and dilution factor, respectively, V is extracted volume of the sample, and m_t is extracted mass. Note that the mango sample is in dried form and mass of 100 gr, so that m_{total} refers to total mass of extracted sample and m_{dry} indicates sample dry mass.

Quantification of total phenolic content

Analysis of total phenolic contents from dried samples of 100 gr was performed using the method of Folin-Ciocalteu from Musa *et al.*³¹. Gallic acid solution was initially dissolved into five concentrations (20, 40, 60, 80, and 100 µg/ml) for the standard curve. About 100 µl of hydrolysis and non-hydrolysis of gallic acid as reference sample was then mixed with 50 µl of Folin-Ciocalteu reagent 0.25 in a 96 well clear polystyrene microplate. Next, 50 µl Na₂CO₃ 7.5% was added to each well. The mixture was subsequently incubated in a dark place at room temperature for 30 minutes and was read using a microplate reader at a wavelength of 765 nm. Total content of phenolic is calculated by the same equation used for determining flavonoid content as in Equation 2.

Quantification of quercetin and gallic acid content by HPLC

Mango extract was dissolved in ethanol (100 g/100 mL). Quercetin and gallic acid standards purchased from Sigma-Aldrich. These standard compounds were each prepared in several concentrations of 100, 50, 25, and 12.5 µg/ml. Each standard compound was mixed with 20 µL and eluted for 20 minutes through elution gradient method (with water/methanol = 0-100 and UV detector with wavelengths of 360 and 370 nm) to obtain a standard chromatogram. Chromatographic analysis was performed using an analytical scale (4.6 x 150mm) Shimadzu ODS C18 HPLC column with a particle size of 0.5 µm (flow rate 0.75 mL/min). The sample was then filtered using a 0.45 µm filter (13mm PTFE) and analyzed according to the HPLC method of quercetin and gallic acid. The level of quercetin and gallic acid contained in each sample was calculated from regression plot of $Y = a \ln X + b$. This plot is described the ratio of the sample concentration to the standard chromatogram of the quercetin and gallic acid standard.

Data analysis

The content of gallic acid and quercetin in the sample is indicated by the change of the solution color in DPPH test which indicated antioxidant activity³². This change was read by a microplate (Berthold, Germany) using the software of MikroWin 2000 version 4.3x. Furthermore, a linear regression curve is performed to obtained quantification of gallic acid and quercetin content from each sample.

Results

Antioxidant content

Antioxidant values in this study were determined using the DPPH method. This method is a simple, easy, fast and sensitive method. Only a small amount of natural material is used to evaluate antioxidant activity, so it is widely used to test the ability of compounds that act as electron donors³². The principle of this measurement is the presence of stable free radicals, namely DPPH mixed with antioxidant compounds that have the ability to donate hydrogen so that free radicals are neutralized³³. Measurement of antioxidant activity using UV-vis spectrophotometry is used so that the value of free radical will be known, expressed by the value of IC₅₀ (inhibitory concentration). Table 1 contains the antioxidant activity of eight wild mango species.

Antioxidant compounds will generally react to DPPH radicals through mechanism of donation of hydrogen atoms which causes the discoloration from purple to yellow³². In this study, the strongest levels of antioxidant activity in wild mangos was found in *Mangifera* sp1. (MBS) leaves and bark extract with IC₅₀ value of 0.88 ppm and 33.24 ppm, respectively. Antioxidant compounds at a moderate level were discovered in the extract of

Table 1. IC₅₀ of wild mango species from Sumatran, Indonesia, using the DPPH (1,1- diphenyl-2-picryl hydrazyl) method.

| Species | | IC ₅₀ value (ppm) |
|---------------------------------------|--------|------------------------------|
| <i>Mangifera foetida</i> (var. limus) | Bark | 60.52 |
| | Leaves | 196.24 |
| <i>Mangifera foetida</i> (var. manis) | Bark | 117.62 |
| | Leaves | 195.12 |
| <i>Mangifera foetida</i> (var. batu) | Bark | 34.22 |
| | Leaves | 119.66 |
| <i>Mangifera kemanga</i> | Bark | 7.034 |
| | Leaves | 152.23 |
| <i>Mangifera sumatrana</i> | Bark | 10.57 |
| | Leaves | 8.70 |
| <i>Mangifera laurina</i> | Bark | 22.51 |
| | Leaves | 18.25 |
| <i>Mangifera</i> sp1. (MBS) | Bark | 33.24 |
| | Leaves | 0.88 |
| <i>Mangifera</i> sp2. (MH) | Bark | 45.48 |
| | Leaves | 2.40 |
| <i>Mangifera quadrifida</i> | Bark | 28.44 |
| | Leaves | 26.26 |
| <i>Mangifera torquenda</i> | Bark | 66.87 |
| | Leaves | 47.62 |
| <i>Mangifera magnifica</i> | Bark | 41.75 |
| | Leaves | 6.76 |

*Mangifera foetida*₁ (var. limus) leaves (IC₅₀ value of 196.24 ppm) and *Mangifera foetida*₂ (var. manis) bark (IC₅₀ value of 117.62 ppm).

Phenolic and flavonoid content

The phenolic and flavonoid compounds were quantified in the mangos using the method of Folin-Ciocalteu from Musa *et al.*³¹ and the method of Xu and Chang³⁰, respectively. Total phenolic content was represented in milligrams (mg) of gallic acid, which was equivalent to per gram of the dry weight of mango leaves (mg GAE/g) (Table 2). Total flavonoid content was represented in milligrams (mg) of quercetin, which was equivalent to per gram of the dry weight of mango leaves dry weight (mg of QE/g).

Gallic acid and quercetin content

Spectrum chromatogram of standard solutions and chromatograms of each species at wavelengths of 360 and 370 nm were used. Specific quantitative tests of gallic acid and quercetin on the leaves of wild mangos from Sumatra using HPLC showed that the plant leaves were positive for both bioactive compounds. The plot of standard calibration for quercetin and gallic acid is shown in Figure 2 and the results are summarized in Table 3.

Discussion

Antioxidants are a group of chemical compounds that have the function of suppressing cell damage, caused by free radicals, by giving electrons speedily and transforming the free radicals into stable forms, in order to prevent oxidative damage that cause ailments³⁴. The presence of antioxidants in plants is primarily as a protective compound from pest and disease, known as bioactive compounds. In this study, the quantitative phytochemical analysis was purposely conducted to determine the level of antioxidants and content of flavonoid and phenolic compounds, specifically gallic acid and quercetin. These analyses were performed using the DPPH method, and concentration of gallic acid and quercetin were analyzed using HPLC.

Based on the results of total antioxidant values of wild mangoes using DPPH assay, it was revealed that *Mangifera* sp1. (MBS) is the highest antioxidant activity amongst other wild mangos (leaves, 0.88 ppm; bark, 33.24 ppm). According to Badarinath³⁵, antioxidants are expected to be very strong if the IC₅₀ value is smaller than 50, in the range of 50–100 ppm, yet it is weak when the IC₅₀ value ranges between 100–250 ppm and is inactive if the IC₅₀ is <250 ppm. The smaller the IC₅₀ value, the higher

Table 2. Total phenolic and flavonoid content of wild mango species from Sumatran, Indonesia.

| Species | | Total phenolic content (mg GAE/g) | Total flavonoid content (mg QE/g) |
|---|--------|-----------------------------------|-----------------------------------|
| <i>M. foetida</i> ₁ (var. limus) | Bark | 41.76 ± 0.29 | 63.93±0.39 |
| | Leaves | 24.64 ±0.14 | 57.29±0.26 |
| <i>M. foetida</i> ₂ (var. manis) | Bark | 75.36 ± 0.10 | 68.93±0.16 |
| | Leaves | 63.59±0.18 | 63.82±0.24 |
| <i>M. foetida</i> ₃ (var. batu) | Bark | 100.65 ± 1.94 | 94.34±0.24 |
| | Leaves | 70.83±0.36 | 92.50±0.41 |
| <i>M. kemanga</i> | Bark | 90.65 ± 0.59 | 87.46±0.35 |
| | Leaves | 20.08±0.18 | 48.55±1.55 |
| <i>M. Sumatrana</i> | Bark | 88.43 ± 1.82 | 98.69±0.89 |
| | Leaves | 65.72±0.23 | 107.50±3.93 |
| <i>M. laurina</i> | Bark | 44.10 ± 2.97 | 39.00±0.21 |
| | Leaves | 81.07±1.40 | 95.36±0.41 |
| <i>M.sp</i> ₁ . (MBS) | Bark | 84.80 ± 6.60 | 68.30±0.44 |
| | Leaves | 69.63±0.27 | 81.55±3.92 |
| <i>M. sp</i> ₂ . (MH) | Bark | 93.01 ± 0.41 | 82.92±0.06 |
| | Leaves | 64.70±0.19 | 96.72±1.36 |
| <i>M. quadrifida</i> | Bark | 79.72 ±0.18 | 58.85±0.24 |
| | Leaves | 89.00±0.77 | 75.53±0.27 |
| <i>M. torquenda</i> | Bark | 76.30±0.18 | 85.10±0.21 |
| | Leaves | 92.48±0.14 | 66.65±0.35 |
| <i>M. magnifica</i> | Bark | 77,37±0.50 | 66.55±0.14 |
| | Leaves | 45.63±0.44 | 65.70±3.71 |

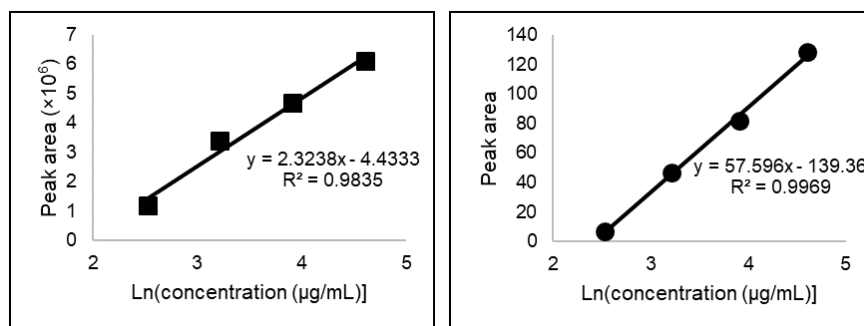


Figure 2. Plot of standard calibration of quercetin (left) and gallic acid (right).

Table 3. Quercetin and gallic acid content of wild mango leaves from Sumatran, Indonesia.

| Species | Peak area (a.u.) | | Retention time (min) | | Content (mg/g dry weight) | |
|---|------------------|-------------|----------------------|-------------|---------------------------|-------------|
| | Quercetin | Gallic acid | Quercetin | Gallic acid | Quercetin | Gallic acid |
| <i>M. foetida</i> ₁ (var. limus) | 51153 | 144789 | 14.97 | 10.24 | 0.76 | 13.89 |
| <i>M. foetida</i> ₂ (var. manis) | 138513 | 198816 | 15.64 | 10.49 | 0.79 | 35.48 |
| <i>M. foetida</i> ₃ (var. batu) | 137886 | 123830 | 15.71 | 10.26 | 0.79 | 9.65 |
| <i>M. kemanga</i> | 550164 | 98147 | 15.47 | 10.26 | 0.97 | 6.18 |
| <i>M. sumatrana</i> | 714087 | 88518 | 15.45 | 10.26 | 1.06 | 5.23 |
| <i>M. laurina</i> | 902079 | 122354 | 15.43 | 10.23 | 1.16 | 9.41 |
| <i>Mangifera</i> sp ₁ (MBS) | 96833 | 115273 | 15.56 | 10.23 | 0.78 | 8.32 |
| <i>Mangifera</i> sp ₂ (MH) | 227010 | 128227 | 15.51 | 10.23 | 0.83 | 10.42 |
| <i>M. quadrifida</i> | 230653 | 113892 | 15.49 | 10.26 | 0.83 | 8.12 |
| <i>M. torquenda</i> | 462008 | 114851 | 15.50 | 10.28 | 0.93 | 8.26 |
| <i>M. magnifica</i> | 243010 | 111497 | 15.48 | 10.26 | 0.83 | 7.79 |

the antioxidant activity. The antioxidants contained in mangos are essential for enhancing the immune system in the body, and are an immunomodulator agent³⁶, including analgesic³⁷, antimicrobial and antidiabetic properties³⁸. Fitmawati *et al.*³⁹ reported that powder ethanol extract of *Mangifera* sp1. (MBS) leaves are immunomodulatory agents with phagocytic activity at 69.67%. Ascorbic acid contained in the bark and leaves of mangos has great potential to heal chronic wounds and inflammation⁴⁰. Also, mangos are a particularly rich source of polyphenols, a diverse group of organic micronutrients found in plants, which exert specific health benefits.

The presence of gallic acid and quercetin from wild mangoes in this study shows that they have potential as antioxidants of phenolic and flavonoid groups. Generally the higher levels of phenolic and flavonoid compounds, the antioxidants values is also higher. Based on the results of this study antioxidants values are determined by total phenolic and flavonoid compounds, and not only their that contributing in antioxidants values. Research by Ou *et al.*⁴¹ did not find a linear relationship between total phenolic with antioxidants values. Antioxidants values are not

limited to phenolic or flavonoid compounds, so there is no simple relationship between total phenolic and flavonoid when comparing antioxidants values between plant extracts⁴². The highest phenolic compounds of wild mangos were in the bark of *M. foetida* (var. batu) and leaves of *M. torquenda* (100.65 mg/g and 92.48 mg/g, respectively). Whereas, the lowest phenolic compounds of wild mangos were in the bark of *M. foetida* (var. limus) and the leaves of *M. kemanga* (41.76 mg/g and 20.08 mg/g).

In a previous study on the bark, old leaves, and young leaves of Van Dyke cultivated mango in Brazil, gallic acid content was 0.24 g/kg, 0.43 g/kg, and 3.49 g/kg, respectively¹⁵. The results of the present study show that wild mangos have higher phenolic contents than cultivated mangoes, such as the Van Dyke mangos. With the abundant phenolic content, wild mangos from Sumatra have a potential source of natural antioxidant agents. Currently, herbal tea derived from mango leaves (*M. indica*) has been developed and scientifically proved to be a source of mangiferin and other phenolic contents^{43,44}. Therefore, phenolic contents found in wild mangos in this study may be expected to be further developed into healthcare products in the future.

The highest amount of flavonoid compounds were found in the bark and leaves of *M. sumatrana* (98.69 mg/g and 107.50 mg/g, respectively), and the lowest values were found in the bark of *M. laurina* and leaves of *M. kemanga* (39.00 mg/g and 48.55 mg/g, respectively). Barreto *et al.*¹⁵ reported that quercetin pentoside compounds in methanol extract of leaves of Van Dyke cultivated mangos from Brazil was 1.33 g/kg in old leaves and 4.93 g/kg in young leaves. In contrast, pentoside was undetectable in the bark¹⁵. However, the present study revealed that all bark of wild mangos assessed contained quercetin. Ali *et al.*⁴⁵ and Kim *et al.*¹⁸ also reported that cultivated mangoes (*M. indica*) mostly contain flavonoids, carotenoids, vitamin E and C, terpenoids and steroids.

Phenolic and flavonoid have many derivatives. Mangiferin was a phenolic compound that very high levels in mango leaves and bark⁸. Wauthoz *et al.*⁴⁶ reported that mango bark were contains protocatechic acid, catechin, mangiferin, alanine, glycine, γ -amino-butyric acid, kinic acid, shikimic acid, and the tetra cyclic triterpenoids cycloart-24-en-3 β ,26-diol,3-keto dammar-24(ES-en-2Os,26-diol,C-24) epimers of cycloart-25 en 3 β ,24,27-triol and cycloartan-3 β , 24,27-triol. The main flavonoids present in mango were quercetin and catechin⁴⁷. The presence of other phenolic and flavonoid compounds that affect the amount of gallic acid and quercetin in mango leaves and bark.

Based on the results of the HPLC chromatogram, the contents of the bioactive compounds of wild mangos showed that the content of gallic acid obtained from wild mangoes leaves ranged from 5.23-35.48 mg/g of dry weight, where the lowest content was in *M. sumatrana* and the highest was *M. foetida* (var. manis). According to Soong and Barlow⁴⁸, mango seed extract (*Mangifera indica* L.) contains gallic acid (23-838 mg/100 g of dry weight, equivalent to 0.23-8.38 mg/g). Rastraelli *et al.*⁴⁹ also stated that gallic acid content in mango bark is ~226.2 mg/100g of dry weight, 6.0 mg/100 g in seed kernel⁵⁰, and 6.9 mg/kg in mango pulp⁵¹. These results indicate that gallic acid content is higher in wild mango leaves (as seen in the present study) compared to other parts of the mango.

The study by Barreto *et al.*¹⁵ reported that gallic acid is the major secondary metabolite component in the flesh and seeds of mangoes (*M. indica*). Gallic acid is the most abundant molecule in 'Ataulfo' mango peel⁵². The flesh, seeds, and kernel of *M. indica* are sources of gallic acid, which is a bioactive compound with potential health-promoting activity⁵³.

Gallic acid has anticancer, anti-inflammatory, antimicrobial, and antimutagenic, including radical-scavenging, activities⁵⁴. It has also been shown to inhibit colon cancer cell (HCT-15) proliferation, inhibits platelet aggregation, calcium mobilization, and tyrosine protein phosphorylation in platelets²⁰, and inhibits inflammatory allergic reactions⁵⁵.

Quercetin plays a role in triggering fruit color development. Ajila and Prasada⁵⁶ stated that quercetin is the major flavonoid type in the ripe peel of mango. In the present study, *M. laurina* had the highest quercetin content, while the lowest was found

in *M. foetida*, (var. limus). Quercetin content of wild mangoes leaves ranged from 0.76 to 1.16 mg/g of dry weight. Berardini *et al.*¹¹ reported that quercetin content in mango peel was 65.3 mg/kg of dry matter, equivalent to 0.653 mg/g dry weight. Based on these data, wild mangos leaves have higher quercetin content (as found in the present study) than peel. High quercetin content is found in fruits and quercetin-3-glucoside is mainly found in leaves²⁰.

Quercetin has various medicinal benefits, including aiding treatment in brain disorders, renal injury, cardiovascular diseases, high blood pressure, cancer, bacterial activity, inflammation, diabetes mellitus, arthritis and asthma⁵⁷⁻⁵⁹. It decreases estrogen receptor cells of breast cancer, inhibits tyrosine kinase, arrestshuman leukemic T cell development⁶⁰, protects the liver from oxidative damages⁶¹, prevents cardiovascular disease, and exhibits antihistamine and anti-inflammatory effects associated with various forms of arthritis²⁰.

Fitmawati *et al.*³⁹ demonstrated that wild mangos leaves from Sumatra have immunostimulant activity and antioxidant compounds⁶², including therapeutic efficacy potential for the prevention of degenerative diseases. Wild mangos from Sumatra contain flavonoids in high amounts, hence these contents need to be further explored and maximized for medicinal usage, in order to support the availability of medicinal resources. The results of the antioxidant activity using the DPPH method as assessed in the present study, and the total content of flavonoids and phenolics exhibited the varied results for each species. Wild mango species that have the highest antioxidant content may not have the highest total levels of flavonoids and phenolics because each plant species has different levels and types of metabolites.

Conclusions

This study provided quantitative information about the presence of antioxidants, as well as the content of one of the main compounds from the flavonoid (quercetin) and phenolic (gallic acid) of wild mangos from Sumatra. The current investigation was undertaken to quantify the percentage of phytochemicals in the leaves and bark of wild mangos as an alternative raw material for medicine. The results obtained are expected to be useful in supporting the development of drugs that have anti-degenerative effects, as well as to support the conservation of wild mangos, which are rare while maintaining and improving their quality and diversity.

Data availability

Underlying data

Open Science Framework: Wild Mango Exploration in Sumatra for Potential Health Medicine, <https://doi.org/10.17605/OSF.IO/MP6KF>⁶³.

This project contains the following underlying data:

- Raw_Data_for_Gallic_Acid
- Raw_Data_for_Quercetin

Data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

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Kamal Rullah 

Kulliyah of Pharmacy, International Islamic University Malaysia, Kuantan, Malaysia

Recommendation

The manuscript by Fitmawati and co-workers describes the antioxidant profiling of Sumatran wild mangoes (*Mangifera spp.*). I noted that the manuscript had been revised from the previous submission. Overall, it is a more organized and constructed paper that reports the findings from a sound and interesting study. This manuscript showed a good similarity checker as well. Thus, the manuscript may be recommended for publication in F1000Research after some revision.

1. The author(s) need to revise the title of the manuscript. The term 'antidegenerative medicine' is uncommon in a scientific paper. There are no antidegenerative medicine and antidegenerative drug as well, but there is a term 'antidegenerative effect'. Hence, I suggest that the title should be '....Phytochemical Screening and Antioxidant Profiling of Sumatran Wild *Mangifera* Species.....'.
2. Why the author(s) decided that the compound gallic acid and quercetin are representing the phenolic and flavonoid compound, respectively? Based on the reference Barreto and co-worker (<https://doi.org/10.1021/jf800738r> and the author(s) have cited the paper), the major phenolic compound was mangiferin, a precise compound isolated from *Mangifera*. In my view, the mangiferin is a more noteworthy compound from *Mangifera* species. Moreover, there is no report on quercetin as the aglycone form (as the author(s) applied as a standard compound) in *Mangifera* species. Thus, I suggest the author(s) verify the qualitative component of both ethanolic extract, leaves, and bark, by using the Liquid chromatography-Mass Spectrometry (LC-MS). Check whether the standard compound exists in the desired ethanolic extract by mass spectrometry. This is necessary to ensure the selection of the specific standard compound.
3. The statistical data is missing. The author(s) should provide extensive statistical analysis in this manuscript, i.e. standard deviation (SD) is missing in Table 1, Table 2, and Table 3 as well. While presenting research data, the author(s) should be aware of using adequate statistical measures.
4. The validation of the analytical procedures of HPLC is missing, including accuracy, precision, specificity, etc.

5. The author(s) needs to improve the conclusion. The manuscript was not employed *Mangifera* species as an immunomodulatory agent.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medicinal Chemistry and Drug Discovery

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 04 May 2020

<https://doi.org/10.5256/f1000research.24692.r61846>

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Sarifah Nurjanah 

Department of Agriculture Engineering and Biosystem, Faculty of Agro-Industrial Technology, Padjadjaran University, Bandung, Indonesia

The authors describe in detail a new information on antioxidant profile of 11 Sumatran wild mangoes (*Mangifera* spp), including flavonoid and phenolic content as well as gallic acid and quercetin of its leaves and barks. The paper is well written. A few suggestions are made, however:

Introduction: Need information why antioxidant activity is determined on leaves and barks instead of

mango's peel, pulp and seed kernel.

Method :

1. There is no information about quercetin and gallic acid standard for HPLC analysis. Need to specify the origin of quercetin and gallic acid standards.
2. No information of HPLC column, please specify the column used.

Results and discussion :

1. The last sentence of paragraph 6 stated "Ailla and Prasada⁴⁶ stated that quercetin is the major flavonoid type in the peel of mango", since this paragraph talk about gallic acid not quercetin, so discussion about quercetin should be moved in the paragraph 8.
2. On paragraph 8 stated the lowest quercetin was found in *M foetida* (var Limus), actually as we can see from Table 3, it should be *M foetida*₂ (var. manis) and *M foetida*₃ (var. batu).
3. Total phenolic is represented by gallic acid content. Increasing phenolic content should increase the gallic acid, but the study didn't show this. Why this condition can appear? Does any others phenolic compound instead of gallic acid influence the total phenolic in mango barks and leaves?
4. Flavonoid content is represented by quercetin. Increasing flavonoid content should increase the quercetin, but the study didn't show this. Why this condition can appear? Does any others flavonoid compound instead of quercetin influence the flavonoid compound in mango barks and leaves?
5. IC₅₀ values indicate the antioxidant activity, the lower IC₅₀ value the higher antioxidant activity. In this study the antioxidant activity is represented by total phenolic and flavonoid content. Lowering IC₅₀ should increase total phenolic and flavonoid content, but the study didn't show this. Please discuss this phenomena.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Active compound of agriculture product

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 13 May 2020

Fitmawati Fitmawati, Universitas Riau, Pekanbaru, Indonesia

We would to thank the reviewer for their comments to our manuscript. In this new version, we have reviewed and modified text to improve the clarity and understanding manuscript. The main changes have been:

- 1). Introduction the reason for using leaves and bark to determine the antioxidant value of wild mangoes is added.
- 2). The method has already mentioned the origin of the standard quercetin and gallic acid and the HPLC column used.
- 3). In the results and discussion of data changes due to input errors in the previous article. It has been discussed that there are other compounds of flavonoid and phenolic derivatives in leaves and bark of wild mango that refer to the literature, thus affecting the amount of gallic acid and quercetin, as well as antioxidant values.

Competing Interests: No competing interests were disclosed.

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