

The potency of wild mango *Mangifera magnifica* as a new source of antidiabetic agents with concurrent antioxidant activity

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Abstract. Fitmawati, Roza RM, Emrizal, Juliantari E, Almurdani M. 2022. The potency of wild mango *Mangifera magnifica* as a new source of antidiabetic agents with concurrent antioxidant activity. *Biodiversitas* 23: 5159-5164. Diabetes mellitus has entered the top 10 causes of death, following a significant percentage increase of 70% since 2000. Researchers have been working on a new practical design of α -glucosidase inhibitor from plant resources that can be used as a therapeutic agent for diabetes mellitus. By inhibiting α -glucosidase, the digestion of carbohydrates slows down, which helps prevent hyperglycemia. In our preliminary study, *M. magnifica* is a neglected wild mango shown to have high levels of antioxidant activity. We conducted a study on the wild mango species *M. magnifica* as an α -glucosidase enzyme inhibitor. Antioxidant activities were carried out by the method of radical reduction 1,1-diphenyl-2-picrylhydrazyl (DPPH). Total phenolic content (TPC) was calculated by the Folin-Ciocalteu method and total flavonoid content (TFC) was calculated by colorimetric method. The antidiabetic activity was carried out by in vitro α -glucosidase biochemical test. The methanol extract and ethyl acetate fraction have high antioxidant activity and the strongest inhibitory α -glucosidase activity. *M. magnifica* leaves are a new source of antihyperglycemic agents with concurrent antioxidant activity. The research results will provide new information to support conservation efforts whose status is already rare while maintaining and improving the quality of value and diversity.

Keywords: Antioxidant, antidiabetic, ethnomedicinal plants, Neglected and Underutilized Species (NUS), wild mango

INTRODUCTION

Mangifera magnifica Kochummen is a species of wild mango whose distribution is broad, but its condition is still neglected and underutilized species, and not cultivated. The quality of the fruit in terms of taste and size is still low compared to cultivated mangoes (*M. indica*), making this species of mango less attractive. It is feared that there will be a risk of extinction. This neglected wild mango species have high acidity, a strong essential aroma, and a sharp sap. This particular characteristic shows this plant's potential as a therapeutic agent with very high antioxidant ability (Fitmawati et al. 2021).

Investigation of antioxidant profiles (gallic acid and quercetin) reported that *M. magnifica* had a high antioxidant activity with an inhibitory concentration of 50% (IC₅₀) 2.40 ppm (Fitmawati et al. 2020a). Further research after obtaining metabolite data is preclinical testing using test animals, including testing of *M. magnifica* leaves with the highest phagocytosis value as an immunostimulant agent (Fitmawati et al. 2020b). Toxicity tests on rat kidneys and liver showed damage of less than 25% (Fitmawati et al. 2018). Based on previous findings, *M. magnifica* has been proven to be a potential drug candidate. *Mangifera* known for its drupe fruit is also known for its antidiabetic potential (Wauthoz et al. 2007). The mangiferin compound from *Mangifera* fruits can slow α -glucosidase metabolism and be used as a hypoglycemic

agent (Sekar et al. 2019). Mangiferin possesses significant antidiabetic, antihyperlipidemic, and antiatherogenic properties (Muruganandan et al. 2005).

Diabetes mellitus is a metabolic disease that causes high blood sugar because of abnormal rates of carbohydrate, protein, lipid, and electrolysis metabolism (Shim et al. 2019; Riyaphan et al. 2021). The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), under half a billion people are living with diabetes worldwide, which is predicted to increase by 25% in 2030 and 51% in 2045 (Saeedi et al. 2019). Diabetes has entered the top 10 causes of death, following a significant percentage increase of 70% since 2000 (WHO 2020). Therefore, there is an urgent need to identify effective drugs to treat this disease.

Hyperglycemia, or elevated blood sugar, is a common effect of uncontrolled diabetes and can cause damage to the body's systems (Kharroubi & Darwish 2015; Wu et al. 2020). Researchers have been working on a new practical design of α -glucosidase inhibitors from plant resources (Zahratunnisa et al. 2017; Dewijanti et al. 2020; Ramadhan et al. 2022) that can be used as a therapeutic agent for metabolic suppression disorders such as diabetes mellitus (Halim et al. 2021; Liu et al. 2021). Alpha-glucosidase catalyzes starch and disaccharides to glucose (Ningsih et al. 2020; Rahman et al. 2021). By inhibiting α -glucosidase, the digestion of carbohydrates slows down, which helps prevent hyperglycemia (El-Shafey et al. 2020).

There have been many circulating drugs that are marketed as effective α -glucosidase inhibitors, but these drugs have side effects such as flatulence, diarrhea, and even liver disorders (IDFGDG 2014). Medicinal plants are rich in resources and secondary metabolites used in various treatments such as Diabetes (Almurdani et al. 2020). The therapeutic potential of alkaloid compounds can inhibit α -glucosidase (Zafar et al. 2016).

This finding is very interesting that mangiferin, a polyphenol present in mango fruit, exhibits hypoglycemic potential. Here, we conducted a study on the wild mango species *M. magnifica* as an α -glucosidase enzyme inhibitor. The results of this study became the first step in the development of wild mangoes as raw materials for standardized herbal medicines and phytopharmaca. The research results will provide new information to the community to support conservation efforts whose status is already rare while maintaining and improving the quality of value and diversity.

MATERIALS AND METHODS

Chemical reagent

Organic solvents (N-hexane, dichloromethane, ethyl acetate and methanol solution from Merck, Germany. 1,1-difenil-2- picrylhydrazyl (DPPH), ascorbic acid, gallic acid, quercetin, Folin-Ciocalteu, NaNO₂, Na₂CO₃, NaOH, CuCl₂, AlCl₃, Aqua DM, 10 mM, neocuproine (Nc), K₂S₂O₈, α - glucosidase enzyme, *p*-nitrofenil- α -D-glucopyranoside (*p*-NPG) from sigma aldrich Chemical Co, Singapore, acarbose from Bayer, Indonesia.

Collection and extraction of *Mangifera magnifica*

Sample of *M. magnifica* wild mango was collected from Sultan Syarif Hasyim Forest Park, Siak Regency, Riau Province, Indonesia. Wild mango leaves were dried in an oven at 40°C. Dried *M. magnifica* leaves (100 g) were ground into powder and then macerated with methanol for 3 x 24 hours and were ultrasonicated for 1 hour, then the maceration results were filtered. The maceration process was repeated 6 times. The obtained macerate was then concentrated using a rotary evaporator at a temperature of 50°C. Methanol extract was fractionated with n-hexane (1:1) and continued with ethyl acetate (1:1). The n-hexane and ethyl acetate fractions were each concentrated with a rotary evaporator at a temperature of 50°C to obtain a thick extract of n-hexane and a thick extract of ethyl acetate.

Antioxidant activity test

The antioxidant activity test of extracts of methanol, ethyl acetate and n-hexane fraction was carried out by the method of radical reduction 1,1-diphenyl-2-picrylhydrazyl (DPPH) (Molyneux 2004; Zhang et al. 2006).

Samples with a final concentration were diluted in 96 well clear polystyrene microplates. A total of 50 μ L of the sample was added with 80 μ L of DPPH 100 μ g /mL then incubated in a dark place for 30 minutes. Furthermore, the absorbance of each mixture was measured with a microplate reader (Berthold, Germany) with a wavelength

of 520 nm. The inhibitory concentration of 50% (IC₅₀) value is calculated using the regression equation $Y=ax + b$ obtained from plotting the percent inhibition value Vs in concentration. The activity of radical bounding was measured as a decrease in DPPH absorbance by the presence of a microplate reader and data processing. Positive control was used as a comparison for ascorbic acid gradient at a concentration of 50 μ g / mL.

The % Inhibition value is calculated by the following formula:

$$\% \text{ Inhibition} = \frac{(\text{Abs. of blank}) - (\text{Abs. of samples})}{(\text{Abs. of blank})} \times 100$$

Where, Abs of blank is the absorbance of the DPPH radical solution without the sample while Abs of samples is the absorbance of the sample with the DPPH radical solution.

Determination of Total Phenolic Content (TPC)

Determination of the total phenolic content was carried out by using the Folin-Ciocalteu method (Zhang et al. 2006; Bhanuz et al. 2017; Yu 2018) with gallic acid as the standard (Almurdani et al. 2020). Folin-Ciocalteu is a colorimetric process based on reactions of electron transfer between the Folin-Ciocalteu reagent and the phenolic compounds. Each 100 μ L of *M. magnifica* sample, gallic acid, and black was mixed with 50 μ L of Folin-Ciocalteu reagent 0.25 N in a 96-well microplate. Five minutes later, the sample was added with 100 μ L Na₂CO₃ 7.5% (w/v). The mixture was incubated for 30 minutes in the dark at room temperature. A microplate reader measured the absorbance value at a wavelength of 765 nm. The total phenolic content is expressed as milligrams of equivalent gallic acid per gram of dry matter of sample (mg GAE/g) through the calibration curve gallic acid. Linearity range of calibration curve was 10 -50 μ g/mL ($y = 0.016x + 0.0081$, $r = 0.992$).

Determination Total Flavonoid Content (TFC)

Determination of the total flavonoid content of extracts was carried out by using the colorimetric method of aluminum chloride (Bhanuz et al. 2017) with quercetin as standard (Almurdani et al. 2020). Each of 50 μ L sample of *M. magnifica*, quercetin and blank was mixed with 10 μ L 5% NaNO₂ (w/v), 10 μ L AlCl₃ 10% (w/v) in 96 micoplate wells. Five minutes later, 100 mL of 1 M NaOH was added. The mixture was added with 30 mL of distilled water and incubated for 30 minutes in a dark place at room temperature. The absorbance of the mixture was measured at a wavelength of 510 nm by a microplate reader. The total content of flavonoids is expressed as milligrams of equivalent quarcetin per gram of dry matter of the sample (mg QE/g). Linearity range of calibration curve was 10 -50 μ g/mL ($y = 0.0162x + 0.0755$, $r = 0.999$).

In vitro α -glucosidase inhibitor activity test

In vitro α -glucosidase inhibitor activity test of methanol extract, ethyl acetate, and n-hexane fraction was carried out according to the method of Almurdani study (Almurdani et

al. 2020). 10 μL DMSO was added with 65 μL phosphate buffer (pH 6.8), 25 μL p-NPG 20, and 25 μL of the α -glucosidase enzyme (0.2 U/mL) were prepared (blank) in a 96-well microplate. 10 μL of samples with various concentrations were added with 65 μL of phosphate buffer (pH 6.8), 25 μL of p-NPG 20, and 25 μL of the α -glucosidase enzyme (0.2 U/mL) were prepared (Samples) in the same 96 well microplates with blanks. Then each mixture was incubated for 30 minutes at 37°C. After that, 100 μL of 0.1 M Na_2CO_3 solution was added, and the absorbance was measured at a wavelength of 405 nm with a microplate reader (Berthold, Germany). Acarbose as a positive control was also tested using the same method as the sample. Percent inhibition can be calculated using formula 2. The IC_{50} value is calculated using the regression equation $Y=ax +b$ obtained from plotting the percent inhibition value Vs in concentration. Based on its IC_{50} value, antioxidant activity of certain sample can be classified into 5 groups; $\text{IC}_{50} < 10 \mu\text{g/ml}$ = very strongly active, $10\text{-}50 \mu\text{g/ml}$ = strongly active; $50\text{-}100 \mu\text{g/ml}$ = moderately active; $100\text{-}250 \mu\text{g/ml}$ = weakly active, $> 250 \mu\text{g/ml}$ = inactive (Phongpaichit et al. 2008).

$$\% \text{ Inhibition} = \frac{(\text{Abs. of blank}) - (\text{Abs. of samples})}{(\text{Abs. of blank})} \times 100$$

RESULTS AND DISCUSSION

Antioxidant activity

To assess the radical scavenging activity of *Mangifera magnifica* Kochummen leaves extracts and fractions, we have used DPPH radical scavenging test (Blios 1958; Yao et al. 2020) with positive control vitamin C (ascorbic acid). The positive control used in this study was used as a comparison in calculating the value of the antioxidant activity. When the IC_{50} value of the sample is equal to or close to the IC_{50} value positive control, it can be assumed that the sample has the potential to be strong antioxidants. The antioxidant activity of leaves samples was different even though they were from the same material. This depends on the ability of the solvent used to dissolve phenolic compounds. The antioxidant activity of extracts and pure compounds from *M. magnifica* leaves against DPPH radicals can be seen in Table 1.

Based on the results of the quantitatively antioxidant activity test, ethyl acetate fraction had the highest value of IC_{50} compared to the other IC_{50} value sample. The methanol extract and ethyl acetate fraction had a high antioxidant activity with IC_{50} values of 17,824 and 38,772 $\mu\text{g/mL}$. The antioxidant activity was higher in the polar extract than in the non-polar fraction, but the activity obtained was lower than that of ascorbic acid as a positive control. The n-hexane fraction did not show antioxidant activity with an IC_{50} value greater than 250 $\mu\text{g/ml}$ (598.342 $\mu\text{g/ml}$). This has shown that solvents with high polarity show high activity, and also due to differences in the content of phenolic compounds.

Total phenolic (TPC) and flavonoid content (TFC)

The highest total phenolic content (TPC) was the ethyl acetate fraction of *M. magnifica* leaves compared with methanol extracts and n-hexane fraction with a value of $209.861 \pm 0.127 \text{ mg GAE/g dry sample}$. Likewise, the highest total flavonoid content (TFC) was ethyl fraction extract from *M. magnifica* leaves with a value $255.041 \pm 0.730 \text{ mg QE/g dry sample}$ (Table 2). The TFC value of *M. magnifica* extract was higher than that of TPC. These two values cannot be distinguished because they both have different methods and standards, where TPC uses gallic acid as standard while flavonoids use quercetin. The use of methanol as a solvent for plant extraction is known to be able to extract more active compounds and has a higher total phenolic content than other solvents (Abdelwahab et al. 2011).

Inhibitor activity of α -glucosidase in vitro

The inhibitory activity of the α -glucosidase enzyme in vitro extracts and pure compounds from *M. magnifica* leaves can be seen in Table 3. The strongest inhibitory activity was obtained from the ethyl acetate fraction (IC_{50} 137.312 $\mu\text{g/mL}$) but still lower than the positive control acarbose (IC_{50} 102.004 $\mu\text{g/mL}$). The type of solvent used affects the bioactive content, so it can cause differences in the biological activity of *M. magnifica*. The solvent with optimal polarity for the extraction of α -glucosidase inhibitory active compounds from plants is difficult to predict and is thought to depend on the species or sample (Chai et al. 2015; Dirir et al. 2022).

Table 1. Antioxidant activity of extracts and pure compounds of *Mangifera magnifica* leaves against DPPH radicals

Sample	IC_{50} ($\mu\text{g/mL}$)
n-Hexane fraction	598.342 ± 18.121
Methanol extract	38.772 ± 3.754
Ethyl Acetate fraction	17.824 ± 1.292
Ascorbic acid	9.006 ± 0.405

Table 2. Total phenolic and flavonoid content of *Mangifera magnifica* leaves

Sample	Total phenolic (mg GAE/g dry sample)	Total flavonoid (mg QE/g dry sample)
Ethyl Acetate fraction	209.861 ± 0.127	255.041 ± 0.730
Methanol extract	161.260 ± 0.127	210.117 ± 1.232
n-Hexane fraction	52.864 ± 0.063	49.158 ± 0.464

Table 3. In vitro α -glucosidase enzyme inhibitors extracts and pure compounds from *Mangifera magnifica* leaves

Sample	IC_{50} ($\mu\text{g/mL}$)
n-Hexane fraction	>1000
Methanol extract	194.065 ± 12.674
Ethyl Acetate fraction	137.312 ± 12.329
Acarbose	102.004 ± 10.347

Discussion

We are conducting a study to find an alternative for treating diabetes from plant species that are not noticed by the public, namely wild mango. This study aims to explore the potential and benefits of wild mangoes so that their conservation is effective and long-lasting. The results of this study serve as the first stone in the development of wild mangoes as raw materials for standardized herbal medicines for diabetes through its potential to inhibit the enzyme α -glucosidase.

Mangifera magnifica is still neglected and underutilized mango and not cultivated. Wild mangoes are still widely available in nature but have not been appropriately utilized because the fruit is not pleasant (sour) to eat. From the results of this study, we found new potential in one species of wild mango, namely *M. magnifica* leaf, as an inhibitor of the α -glucosidase enzyme for people with diabetes. The IC_{50} value in the wild type α -glucosidase test of *M. magnifica* is almost equivalent to that of the mango (*M. indica*). Alpha-glucosidase is the enzyme responsible for the hydrolysis of long-chain complex carbohydrates into simple-chain glucose molecules to facilitate their transport inside the cells (Sekar et al. 2019; Barber et al. 2021). Alpha-glucosidase catalyzes starch and disaccharides to glucose. By inhibiting α -glucosidase, the digestion of carbohydrates slows down, which helps prevent hyperglycemia (Ningsih et al. 2020). The attention of scientists has turned to the prospection and evaluation of antioxidant agents for the prevention and treatment of several diseases such as diabetes.

Flavonoids are a large group of natural antioxidant substances containing variable phenolic structures and are mostly found in fruits, vegetables, nuts, tea, and herbs (Ong & Khoo 2000; Vinayagam & Xu 2015). Phenolics are one of the important groups of active compounds in wild mangoes that contribute to antioxidant activity (Fitmawati et al. 2020a). In addition, sugar compounds are also thought to act as antioxidants because the stabilization of free radical activity by antioxidants is caused by their ability to donate hydrogen (Akowuah et al. 2005).

Wild mango is rich in phenolic compounds, including flavonoids. Investigation of antioxidant profiles (quercetin) reported that wild Sumatran mango (*Mangifera* spp.) with the highest level of antioxidant activity in wild mango was found in *M. magnifica* (Fitmawati et al. 2020a). This finding was supported by a study that flavonoids have been reported as antidiabetic agents, such as quercetin (Cushnie & Lamb 2005; Bule et al. 2019; Eid et al. 2020; Singh et al. 2020). Some literature states that compounds inhibiting α -glucosidase activity belong to this group (phenolic compounds) (Kwon et al. 2008; Shobana et al. 2009; Praparatana et al. 2022) and most dietary flavonoids provided various medical activities, including antidiabetic agents (Al-Ishaq et al. 2019). Phenolic compounds and flavonoids are known as antioxidants and many other important bioactive agents that benefit human health and cure and prevent various diseases (Ahmed et al. 2016; Tungmunnithum et al. 2018; Ahmed et al. 2020). A flavonoid with two catechol groups presenting an IC_{50} much lower than the one found for the most widely

prescribed α -glucosidase inhibitor, acarbose. The present work suggests that several of the studied flavonoids have the potential to be used as alternatives for reducing post-prandial hyperglycemia (PPHG) (Proenca et al. 2017).

In vitro antidiabetic properties of mango, the extract has also been examined by determining the inhibition of α -glucosidase activity from mango (*M. indica*) peel extract that the inhibitory potential of α -glucosidase was much higher than α -amylase (Gondi & Prasada 2015). Antioxidant test and α -glucosidase inhibitory activity of seed kernel extract and fraction show a strong DPPH radical scavenging and α -glucosidase inhibitory capacity (Yang et al. 2020). The 95% ethanol extracts from two different kinds of mango seed kernel, namely, Kaew and Choke-Anan, both had a good α -glucosidase inhibitory activity with IC_{50} values of $163:19 \pm 2:33$ and $113:51 \pm 5:85$ $\mu\text{g/ml}$ (Namngam & Pinsiroadom 2017). Other research showed that the methanol extract of mango seed kernel could significantly inhibit the activity of α -glucosidase. Although it was used for centuries as a traditional folk prescription in China (Ironi et al. 2014). Evidently, mangiferin from *M. indica* fruits slows down glucose metabolism thereby could be used as a possible hypoglycemic agent owing to its inhibitory enzyme properties. Mangiferin showed better alpha-glucosidase inhibitory activity (Sekar et al. 2019). Various studies on the effectiveness of cultivated mango (*M. indica*) as an antidiabetic drug. The effectiveness of cultivated mangoes as antidiabetic through the inhibition of the α -glucosidase enzyme can also be replaced by wild mango species, namely *M. magnifica*.

The ethyl acetate fraction has an inhibitory value of the α -glucosidase enzyme, which is almost close to acarbose. Although acarbose is a promising therapeutic option for diabetics (Li et al. 2022), in the long term, like any other therapeutic drug, it has some setbacks that cannot be ignored (Altay 2022). Continuous intake of acarbose has been shown to exhibit side effects such as abdominal distension, flatulence, diarrhea, etc. (Schnell et al. 2016; Gupta et al. 2021; Chiasson et al. 2022) From the findings of this study, *M. magnifica* leaves have the potential and can be recommended as herbal plants to inhibit α -glucosidase enzymes for diabetic patients. In further studies, we will isolate and characterize compounds that can inhibit the α -glucosidase enzyme in *M. magnifica* leaf extract.

In summary, antioxidant and α -glucosidase inhibitory activities of the extract and fractions from wild mango leaves were first documented. In this study, we found that the leaves of *Mangifera magnifica* are rich in polar bioactive constituents, as evidenced by the high content of phytochemicals and strong bioactivity of the extract prepared with polar solvent. *M. magnifica* leaves are a promising source for antidiabetic and radical scavengers. Antioxidants derived from plants are very effective in preventing destructive processes caused by oxidative emphasize. Antioxidant activity tests made a great contribution to revealing the potential of Indonesia's original natural resources as a source of medicinal raw materials. The result gives a strong rationale for future

exploration of *M. magnifica* leaves as a new source of antihyperglycemic agents with concurrent antioxidant activity. The research results obtained provide new information to the community so that they can support conservation efforts whose status is already rare while maintaining and improving the quality of value and diversity.

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