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Research Article

Inhibitory Effect of Ethanol Extract of Cherry Mistletoe Leaves (*Dendrophthoe pentandra* (L.) Miq) on Xanthine Oxidase Enzyme

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ABSTRACT

One plant that can be used as an alternative treatment for hyperuricemia is the cherry plant. The usefulness of these plants is due to the secondary metabolite compounds that can inhibit the enzyme xanthine oxidase. Cherry mistletoe is thought to have the same flavonoids, saponins, alkaloids, terpenoids, and tannins as the cherry plant, which can act as inhibitors. The aim of the study was to determine the inhibitory effect of an ethanol extract of cherry mistletoe leaves on the xanthine oxidase enzyme. This study was conducted as an in vitro experimental study. Cherry mistletoe leaves were extracted with 96% ethanol. The extract was done with phytochemical screening, followed by an inhibition test on the xanthine oxidase enzyme using a spectrophotometer at a wavelength of 400 nm. Allopurinol was a positive control. The ethanol extract of cherry mistletoe leaves contains flavonoids, saponins, alkaloids, terpenoids, and tannins. The IC_{50} value of the ethanol extract of cherry mistletoe leaves was 23.44 mg/L. The ethanol extract of cherry mistletoe leaves has an inhibitory effect on the xanthine oxidase enzyme with moderate activity. Accordingly, the cherry mistletoe leaf extract can be considered as an alternative inhibitor of the xanthine oxidase enzyme in the control of hyperuricemia.

INTRODUCTION

Uric acid levels above 7.0 mg/dL in men and more than 6.0 mg/dL in women are referred to as hyperuricemia (Joosten *et al.*, 2020). The occurrence of hyperuricemia is caused by excessive production or decreased renal and/or gastrointestinal excretion of uric acid or both (Danve *et al.*, 2021). An enzyme called xanthine oxidase catalyzes the conversion of hypoxanthine to xanthine and xanthine to uric acid (Dari *et al.*, 2022). If overactive, this enzyme can cause pathologic excess uric acid production (Serrano *et al.*, 2020).

The most commonly prescribed first-line treatment for hyperuricemia is allopurinol, a xanthine oxidase inhibitor that increases uric acid excretion and renal secretion (Alghamdi *et al.*, 2020; Murdoch *et al.*, 2021). According to the findings of a study done in 2022 by Tien *et al.*, allopurinol is a uric acid-lowering medication that has the best short- and long-term effects and is effective in protecting the kidneys, but allopurinol also has side effects including diarrhea, nausea, vomiting, peripheral neuritis, intestinal nephritis, liver toxicity, and aplastic anemia (Tien *et al.*, 2022; Walid *et al.*, 2023).

Another option that can be used to heal diseases is through herbal medicine. Indonesia's biodiversity is one of the features of our country. Many plants have various potentials and benefits, including for health; therefore, it is necessary to identify and investigate the potential of plants that can be used as a treatment (Yulian, 2014). One of the plants that can be used as an alternative treatment for hyperuricemia is the cherry plant (*Muntingia calabura* L.). The

usefulness of cherry plants in overcoming hyperuricemia is due to the content of secondary metabolite compounds that have the ability to inhibit the enzyme xanthine oxidase (Sinulingga *et al*., 2023). This has been proven through phytochemical screening conducted by Anisa *et al*. in 2022, which showed the presence of flavonoids, saponins, alkaloids, terpenoids, and tannins in the ethanol extract of cherry leaves (Anisa *et al*., 2022).

In 2021, Yanti *et al*. conducted an in vivo study on rats to compare the inhibitory effect on uric acid levels between rats given cherry fruit peel infusion and rats given allopurinol. The results showed that infusion of cherry fruit peel had an inhibitory effect on uric acid levels that was almost the same as allopurinol, with a percentage reduction of 55% and 59%, respectively (Yanti *et al.*, 2021). The same results were also shown in Walid *et al*.'s research in 2023, which proved that an ethanol extract of green cherry fruit has anti-hyperuricemia activity characterized by a decrease in uric acid of 30.1%, which was only slightly different from the percentage reduction of allopurinol (45.7%) (Walid *et al.*, 2023).

Research has been conducted on the cherry mistletoe plant based on in vitro research on cherry plants that shows an inhibiting impact on the xanthine oxidase enzyme. Although it is known as a nuisance plant that is parasitic to its host plant, mistletoe has the same bioactivity substance as its host plant. This is due to the very high level of dependence of mistletoe on the plants it parasitizes (Haryanta, 2023). Mistletoe can connect to the xylem with the help of haustorium, allowing the transfer of nutrients, carbon, minerals, and water; therefore, cherry mistletoe plants (*Dendrophthoe pentandra* (L.) Miq) can have the same secondary metabolite content as cherry plants (Kong *et al*., 2023; Sinulingga *et al.*, 2023).

METHODS

This research is a pure experimental study with cherry mistletoe leaves (*Dendrophthoe pentandra* (L.) Miq) as samples, which were picked from trees in Sukarami Village, Palembang City, South Sumatra. The research was conducted in September to December 2023 and took place at the Laboratory of Medical Basic Chemistry, Faculty of Medicine, Universitas Sriwijaya. This research has received ethical approval from Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Sriwijaya (Protocol No. 318-2023).

Tools and Materials

The tools prepared were a micropipette (Bio-Rad, USA), blender (Philips, Indonesia), camera (Apple, California), analytical balance (Shimadzu, Japan), volume pipette (Pyrex, Indonesia), volumetric flask (Pyrex, Indonesia), separatory funnel (Pyrex, Indonesia), measuring cup (Pyrex, Indonesia), test tube (Pyrex, Indonesia), tissue, Erlenmeyer flask (Pyrex, Indonesia), oven (Memmert, Germany), maceration container, simplicia container, sieve, scissors, stainless steel spoon, sonde, spatula, filter paper, stirring rod, label paper, and UV-visible spectrophotometry (Shimadzu, Japan).

The solvent used in the study was a 96% ethanol solvent (Merck, Germany). The solution materials used in the phytochemical test were concentrated sulfuric acid (Merck, Germany), HCl solution (Merck, Germany), Mayer reagent, Dragendorff reagent, bismuth (III) nitrate, potassium iodide (Merck, Germany), nitric acid (Merck, Germany), $FeCl_3$ solution, magnesium powder (Merck, Germany), and mercury (II) chloride (Merck, Germany). The solution materials used in the xanthine oxidase enzyme inhibition test were xanthine oxidase (Sigma, Singapore), xanthine substrate (Sigma, Singapore), dimethylsulfoxide (DMSO) (Merck, Germany), distilled water, potassium dihydrogen phosphate (Merck, Germany), allopurinol (Kimia Farma, Indonesia), and 1 N sodium hydroxide (Merck, Germany).

Cherry Mistletoe Leaves Extraction

The cherry mistletoe leaves were washed first and then dried in the sun and aerated without direct sunlight. Next, the cherry mistletoe leaves were mashed. By macerating 400g of cherry mistletoe leaves simplicia in 96% ethanol for three days, the material was extracted. After that, the extract was run through filter paper and allowed to dry for three days at 50°C in an oven to produce a thick extract.

Phytochemical Test

Flavonoid identification was done by adding Mg powder and 2 ml of 2N HCl to 2 ml of the extract solution (Diba *et al*., 2019). Flavonoid compounds showed a purple-to-orange-red color (Raharjo, 2022; Sinulingga *et al*., 2020). Saponin identification was done by adding distilled water and, after that, a ten-second vertical shaking. The test result was positive if there was a stable foam as high as 1–10cm for several minutes. Alkaloid identification was done by adding 3 ml of the extract solution to 1 ml of 2N HCl and 6 ml of distilled water. Then, it was

divided into three in a separate tube. The appearance of a white to yellowish precipitate in the Mayer reagent tube, an orange-red precipitate in the Dragendorff reagent, and a brown precipitate in the Wagner reagent indicated the existence of alkaloid content (Diba *et al*., 2019).

The test material was dissolved in chloroform for the phytochemical screening of terpenoids and steroids. Anhydrous acetic acid (0.5 ml) was then added. Additionally, 2 mL of sulfuric acid were introduced via the tube wall. The creation of brownish or violet rings around the edge of the solution indicated the presence of triterpenoids, whereas the solution turned greenish when steroids were present. Terpenoids were identified using the Salkowski test, and the presence of steroids was identified by the solution's turning greenish in color (Subandrate *et al.*, 2019). The tannin phytochemical screening was carried out by reacting to 1 ml of the extract solution with 10% $FeCl_3$. The appearance of a dark blue or blackish green tint suggested the presence of tannins (Diba *et al*., 2019).

Xanthine Oxidase Inhibition Test

After dissolving xanthine (Sigma X0626) in a NaOH solution and bringing the pH down to 7.5, a 0.15 mM xanthine solution was created. Using a potassium phosphate buffer (pH 7.5), xanthine oxidase (Sigma X4376) was diluted to a final concentration of 0.2 U/mL. Cherry mistletoe leaves ethanol extract was utilized at concentrations of 12.5 mg/L, 25 mg/L, 50 mg/L, 75 mg/L, and 100 mg/L. A positive control for the xanthine oxidase inhibition test was allopurinol (Suwandi and Perdana, 2017).

Ingredients for the xanthine oxidase inhibition assay were 100µL of sample, 100µL of enzyme solution, 100µL of distilled water, and 300µL of potassium phosphate buffer (pH 7.5). For fifteen minutes, the test solution was incubated at 37°C. The test solution was then mixed with 200µL of a 0.15 mM xanthine substrate solution, and it was incubated for 30 minutes at 37°C. To terminate the reaction, 200 µL of 0.5 M HCl was added (Suwandi and Perdana, 2017).

At 400 nm in wavelength, absorbance values were determined with a UV-Vis spectrophotometer. By comparing the absorbance of the uric acid generated in the test solution with the absorbance of the negative and positive controls, the xanthine oxidase inhibitory activity was determined. The inhibition value was calculated by the formula [(AControl-ASample)/AControl] x 100. To assess the inhibition of cherry mistletoe leaves (*Dendrophthoe pentandra* (L.) Miq), the IC_{50} value was calculated. The IC_{50} calculation is based on the linear equation y = ax + b, so that the IC_{50} value = (50-b)/a (Putri and Rissyelly, 2016).

RESULTS AND DISCUSSION

This study used cherry mistletoe leaves that were picked from trees in Sukarami Village, Palembang City, South Sumatra, in September-December 2023. Fresh leaves were washed first, dried in the sun, and aerated without direct sunlight for seven days. After drying, weighing was carried out to determine the weight of the initial material and obtained a dry weight of 400 grams. The dried cherry mistletoe leaves were then pulverized with a blender.

About 400 grams of simplicia powder were extracted by the maceration method. The maceration process was repeated twice using 96% ethanol as the solvent. In the first maceration, 96% ethanol was used in 1.5 L. Meanwhile, in the second maceration, 96% ethanol was used in 0.5 L. Simplicia and solvent were mixed in a dark glass bottle and closed until airtight. The extraction was carried out for three days. After that, filter paper was used to filter the extract, and it was dried for three days at 50°C in an oven to produce a thick extract. A yield value of 5.2% was attained with a total of 20.8 grams of thick extract.

Secondary Metabolites

To determine the secondary metabolite compounds in the ethanol extract of cherry mistletoe leaves, phytochemical screening was conducted. The results of phytochemical screening showed that flavonoids, saponins, alkaloids, terpenoids, and tannins were present in the ethanol extract of cherry mistletoe leaves (Table 1).

It is known that the ethanol extract of cherry mistletoe leaves has flavonoid, as confirmed by the onset of an orange-red color. This occurs due to the interaction between the hydroxyl groups in flavonoids and Mg^{2+} ions (Masriani and Budi, 2017). Flavonoids can be attracted by ethanol, which is a polar solvent, because of its similarity in nature. This was also shown in the phytochemical analysis of *Salsola cyclophylla* conducted by Mohammed *et al*. in 2021, which detected the presence of flavonoids in aqueous ethanol extract (Mohammed *et al.*, 2021).

Table 1. Secondary metabolite compounds of cherry mistletoe leaves

Compounds	Ethanol Extract
Flavonoids	+
Saponins	+
Alkaloids	+
Terpenoids	+
Tannins	+

The presence of flavonoid content is one of the reasons that the ethanol extract of cherry mistletoe leaves has the ability to inhibit the enzyme xanthine oxidase. Flavonoids themselves, especially quercetin, have been widely known through various in vitro studies to be significant xanthine oxidase inhibitors. Puff and colleagues revealed that quercetin works to inhibit the xanthine oxidase enzyme by binding to the molybdenum active site. This binding results in Van der Waals interactions between the conjugated ring structure of quercetin and the active site residues of phenylalanine, as well as polar interactions between the hydroxy of quercetin and the polar residues of the active site (Cao *et al*., 2014).

Referring to the results of the study, it is known that the ethanol extract of cherry mistletoe leaves has saponin, which is confirmed by the emergence of stable foam as high as 1 cm for ten minutes due to the decreased surface tension of water. The presence of fat-soluble aglycones in saponins and water-soluble sugar chains is behind this phenomenon (Kregiel *et al.*, 2017). The polarity of saponins allows ethanol, an organic solvent, to extract them. The success of ethanol was also experienced by Min Yang *et al.* when analyzing the phytochemistry of *Raphanus sativus* extract (Yang *et al*., 2021).

A study conducted by Fan Xu *et al*. regarding the inhibition of saponins from the stems of *Homonoia riparia* (IC_{50} = 11.16 nmol/mL) against xanthine oxidase showed a better value than allopurinol (IC_{50} = 11.84 nmol/mL) which is the main drug to treat hyperuricemia; therefore, it can be said that saponins have the potential to be a significant xanthine oxidase inhibitor (Xu *et al.*, 2014).

The ethanol extract of cherry mistletoe leaves has alkaloids, which are confirmed by positive results when mixed with Dragendorff, Mayer, and Wagner reagents. Alkaloids are naturally occurring special metabolites whose chemical structure is composed of nitrogen as a characteristic element. Nitrogen is known to have free electron pairs, so it has a negative charge and has reactive properties towards metal ions. The generation of an orange-red precipitate in the test with the Dragendorff reagent is caused by the interaction between alkaloids and tetraiodobismuthate (III) ions. In experiments with Mayer's reagent, a yellowish precipitate arises caused by the interaction between alkaloids and tetraiodomercurate (II) ions, so that complex compounds are formed, which then precipitate. The emergence of brown precipitates in testing with Wagner's reagent is caused by the interaction between alkaloids and iodine ions (Masriani and Budi, 2017).

Thenmozhi *et al*. examined the anti-inflammatory activity of alkaloid extracts from *Vitex trifolia* leaves in inhibiting xanthine oxidase, and the results showed an inhibition percentage above 70.22%. Thus, alkaloid extract can be a safe and promising natural medicine (Bhambhani *et al.*, 2021; Thenmozhi *et al.*, 2023).

It is known that the ethanol extracts cherry mistletoe leaves have a terpenoid in the form of steroids, which is confirmed by the onset of a greenish color. This occurs due to the formation of conjugated double bonds due to oxidation reactions in steroids, which are shown through changing colors. To identify steroids through phytochemical tests, chloroform, anhydrous acetic acid, and sulfuric acid need to be added to the test tube. Chloroform acts to make steroids soluble in the sample, while sulfuric acid serves to release water in steroids so that ions are formed that cause color reactions (Subandrate *et al.*, 2019).

Ethanol has been widely used as a solvent in the maceration method to identify steroid compounds. Cherry mistletoe leaves, which contain many organic compounds, including steroids, can be drawn from ethanol because of its nature as a universal solvent. This is in line with the research of Hidayah *et al*., that examined getih-getihan leaves to isolate and identify steroid compounds (Hidayah *et al*., 2016).

The ethanol extract of cherry mistletoe leaves has tannins, as confirmed by the onset of a blue-black color. This occurs due to the interaction between the content of hydroxyl groups in tannins and iron ions that form complex compounds (Masriani and Budi, 2017). Tannins are solid polyphenolic compounds with a high molecular weight that have functional groups in the form of hydroxyl so that they can form stable bonds in different molecules (Fraga-Corral *et al*., 2020). Tannins, as secondary metabolite compounds, can be dissolved in polar solutions; thus, ethanol is able to attract these compounds in the extraction method by maceration (Besharati *et al*., 2022).

Previous study was conducted on the phytochemical test of cherry mistletoe leaves. One of them is the research of Sinulingga *et al*. in 2020. The results showed that the water-ethanol fraction of cherry mistletoe leaves contained flavonoids, saponins, steroids, tannins, and alkaloids (Sinulingga *et al*., 2020). The similarity of the results obtained between that research and this study is due to the similar methods and solvents used. In addition, it was proven through this study that the content of compounds possessed by mistletoe leaves depends on the host because in cherry mistletoe leaves, compounds similar to cherry leaves were obtained, which had previously been found by Widjaya *et al.* in 2019 and Anisa *et al*. in 2022 (Anisa *et al.*, 2022; Widjaya *et al*., 2019).

Xanthine Oxidase Inhibition

An in vitro xanthine oxidase enzyme inhibition test was conducted to assess the inhibitory ability of an ethanol extract of cherry mistletoe leaves. The IC_{50} of the ethanol extract of cherry mistletoe leaves was 23.44 mg/L, with a linear regression equation of y = 0.49x + 38.46. The same test was also carried out on allopurinol and obtained an IC_{50} value of 3.72 mg/L (good strength) with a linear regression equation of y = 1.279x + 45.24. The ethanol extract of cherry mistletoe leaves has the ability to inhibit the xanthine oxidase enzyme with moderate strength (IC_{50}=10.50 mg/L). The IC_{50} is the concentration value required to inhibit the enzyme activity by 50%. These results indicate that the greater the concentration of the ethanol extract of cherry mistletoe leaves, the greater the inhibited enzyme activity (Thenmozhi *et al.*, 2023).

A study conducted by Sinulingga *et al*. in 2022 related to the inhibitory effect of the ethyl acetate extract of cherry mistletoe leaves on the xanthine oxidase enzyme obtained the results that the extract can inhibit enzyme activity expressed through an IC_{50} value of 9.86 mg/L (Sinulingga *et al*., 2023). The ability of cherry mistletoe leaves to inhibit the xanthine oxidase enzyme is derived from its host plant, cherry. This is supported by the findings of a study conducted by Efendi and Trisnawati in 2022, which showed an IC_{50} value of 1.17 mg/L for cherry leaves extract (Efendi and Trisnawati, 2022). In addition, an in vivo study conducted by Safrida and Sabri in 2019 stated that an ethanol extract of cherry bark at a dose of 300 mg/kg had the same inhibitory effect on serum uric acid levels as rats receiving allopurinol (Safrida and Sabri, 2019). Walid *et al*. also tested the anti-hyperuricemia activity of green cherry fruit extract in Wistar strain white male rats and found that the greater the dose of cherry fruit extract, the greater the percentage of uric acid reduction (Walid *et al.*, 2023).

The IC_{50} value not only determines whether or not there is an inhibitory effect but can also determine the amount of inhibitory activity of an extract. The categorization range can be seen in Table 2. Based on this, the ethanol extract of cherry mistletoe leaves is classified as having moderate activity, while allopurinol is classified as having good activity (Indrayanto *et al.*, 2021).

Table 2. IC_{50} categorization range

IC_{50}	Sample Activity
<10mg/L	Good
10–50mg/L	Moderate
50–100mg/L	Low
>100mg/L	Not active

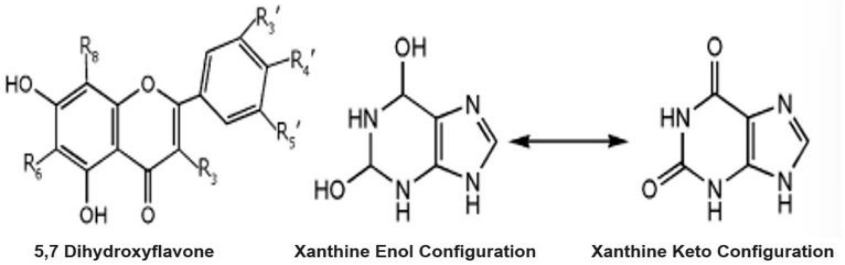


Figure 1. Structural similarity of 5,7-diydroxyflavon with xanthine enol.

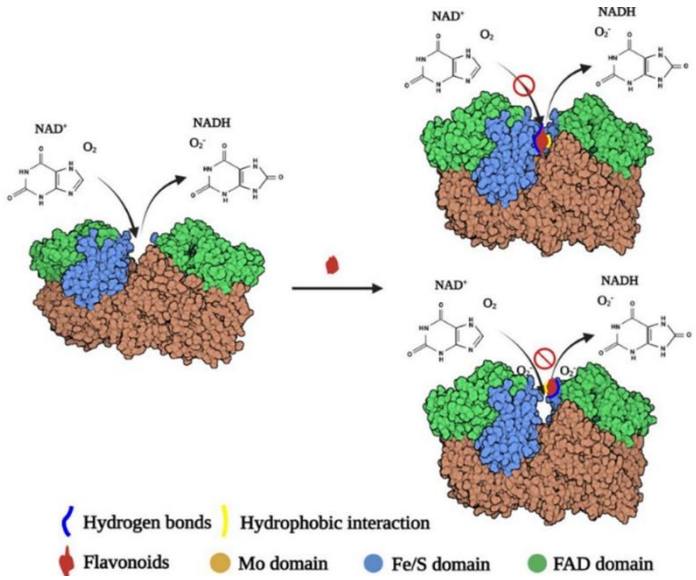


Figure 2. Flavonoid inhibition mechanism

This inhibition ability is due to the content of secondary metabolite compounds contained in the ethanol extract of cherry mistletoe leaves. Recently, flavonoids that have been used to treat many diseases, such as cardiovascular disease and cancer, have also been found to alleviate metabolic syndrome diseases related to hyperuricemia and uric acid. This has been proven in several in vitro studies (Pan *et al*., 2021). Mohos *et al*. tested the effect of flavonoid aglycones on xanthine catalyzed by xanthine oxidase and found that each of the flavonoids tested was able to inhibit uric acid formation. In addition, each flavonoid aglycone has a better inhibitory ability than allopurinol (Mohos *et al*., 2020). This is in line with the results of this study, which show that the IC_{50} value of allopurinol is 3.72 mg/L, while the ethanol extract of cherry mistletoe leaves is 23.44 mg/L. The lower IC_{50} value illustrates the level of inhibition ability that is getting stronger (Putri and Rissyelly, 2016). The structural similarity of 5,7-dihydroxyflavone with xanthine enol, as seen in Figure 1, shows the same binding site at the xanthine oxidase allosteric center. This is a supporting factor for flavonoids to be able to inhibit the xanthine oxidase enzyme (Lin *et al*., 2015).

Hydrogen bonds and hydrophobic contact forces are easily produced between flavonoids and xanthine oxidase. This is due to the fact that the majority of flavonoids have a large number of hydroxyl groups that readily form hydrogen bonds with the polar amino acid residues of xanthine oxidase, and the active region of xanthine oxidase has a large number of hydrophobic amino acid residues that readily bind to flavonoids through hydrophobic interactions. Flavonoids also inhibit the entry of

substrates or block the diffusion of oxygen ion radicals, which can cause rearrangements and changes in the confirmation of xanthine oxidase. The method by which flavonoids inhibit xanthine oxidase is summarized in Figure 2. Flavonoids bind to amino acid residues of xanthine oxidase, primarily through hydrogen bonds and hydrophobic interactions, entering the active region of the enzyme. This causes structural changes in the enzyme that ultimately prevent xanthine from occupying the active region of xanthine oxidase or prevent the diffusion of oxygen ion radicals, which lowers the activity of xanthine oxidase (Xue *et al.*, 2023).

CONCLUSIONS

According to research findings and a discussion of the xanthine oxidase enzyme inhibitory impact of cherry mistletoe leaves ethanol extract, flavonoids, alkaloids, tannins, saponins, and terpenoids are present in the extract that have an inhibitory effect on the xanthine oxidase enzyme with moderate activity.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in this research.

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