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Utilization of Kersen Leaves as Antihyperuricemia

Nita Parisa[1*], Aprilia Paskah Samosir [2], Fatmawati[3], Rachmat Hidayat[4], Marlyani Tamara[2], Karina Nurul Fahira[2], Alfiyah Munawwaroh Abdullah[2], Rischka Salsabila Maulini[2], Rohaya[2]

[1]Department of Pharmacology, Faculty of Medicine, Sriwijaya University, Palembang, Indonesia
[2]Medical Education Study Program, Faculty of Medicine, Sriwijaya University, Palembang, Indonesia
[3]Department of Biochemical, Faculty of Medicine, Sriwijaya University, Palembang, Indonesia
[4]Department of Biology, Faculty of Medicine, Sriwijaya University, Palembang, Indonesia
E-mail: nitaparisa@unsri.ac.id

ABSTRACT

Kersen (*Muntingia calabura*), a tropical plant originating from Latin America, is a wild plant that has many benefits. Kersen contains flavonoid compounds, tannins, triterpenes, saponins, alkaloids that are useful as anti-inflammatory, anti-tumor, and anti-uric acid. Hyperuricemia is a metabolic disease characterized by high levels of uric acid in the blood which precipitates uric acid crystals in the kidneys and joints. Most patients with hyperuricemia do not require medical therapy, but lifestyle modifications can be made such as regular eating, adequate exercise, and avoiding foods and drinks high in protein and purines. This study aims to investigate the benefits of Kersen Leaf as an anti-uric acid. The method used in this study is a literature study based on library sources excavated through national and international sites such as Google, Google Scholar, and PubMed.

Keywords: jamaican cherry leaf, muntingia calabura, hyperuricemia, uric acid, xanthine oxidase

1. Introduction

Hyperuricemia is a condition characterized by increased levels of uric acid in the blood.[1] Hyperuricemia is said to be normal if levels reach the limit of 6.8 mg/dl. Hyperuricemia was defined as a serum urate concentration >7 mg/dl in men and >6 mg/dl in women. Allopurinol is a drug that can be used to help lower uric acid levels by inhibiting the action of the xanthine oxidase enzyme. Xantine oxidase enzyme works by converting hypoxanthine to xanthine and finally forming uric acid. However, most patients with hyperuricemia do not require medical therapy. Because gout drugs have the potential for side effects greater than the benefits of treatment. Therefore, the treatment of gout is more recommended by making lifestyle modifications and the use of natural materials. Indonesia has extensive tropical forest land that can be used as ingredients for traditional medicine, one of which is cherry. Cherry fruit is a source of antioxidants, because it has a fairly high vitamin C content, which is around 80.5 mg. Cherry fruit also contains flavonoids, phenols, niacin and beta-carotene which function as antioxidants. Flavonoids work in the same way as gout drugs, such as allupurinol. Flavonoids have compounds that can inhibit Xanthin Oxidase.[2] Based on this description, in addition to modifying lifestyle, cherry leaves can be used as an antihyperuricemia.

2. Method

The research method used is a literature study based on library sources excavated through national and international sites in the form of Google, Google Scholar, and PubMed. A literature search was carried out using related keywords such as jamaican cherry leaf, muntingia calabura, hyperuricemia, uric acid, xanthine oxidase, etc.

3. Discussion

3.1. Kersen Leaves

3.1.1. What is Kersen Leaves?

Kersen which is also called Jamaican Cherry has a scientific name in the form of *Muntingia* calabura. This plant is known by other names such as siam kerukup (Malaysia), jamaican cherry (English), talok (Java), and cherry (Kalimantan).[3]

Including in family *Elaeocarpaceace*, Jamaican cherry is tropical plants originating from Latin America.[4] Kersen contains flavonoid compounds, tannins, triterpenes, saponins, alkaloids which show antioxidant activity. Kersen plant parts which are known to have many benefits include the fruit and leaves. The known benefits of cherry leaves include anti-inflammatory, anti-tumor, and anti-uric acid.[5] Kersen leaf extract contains known tannins beneficial as antibacterial from protein complexes and binds to bacterial cell walls to inhibit bacterial growth or enzyme activity, besides that cherry leaves also contain saponin compounds. A study conducted by Ilkafah (2018) on patients with gout arthritis, explained that cherry leaves can reduce uric acid levels in the blood and the pain felt in gout sufferers.[3] In another study conducted by Ulfah A, et al (2015) on mice given a high-purine diet, explained that the ethanol extract of cherry fruit can reduce uric acid levels in the blood. This is supported by the research of Dezmonda RC, et al (2016) which showed that cherry leaf extract can reduce blood uric acid levels in mice given a high-purine diet and each graded dose has a comparable effectiveness in lowering uric acid levels.[6]

3.1.2. Chemical Content

Kersen leaves contain flavonoid compounds, tannins, triterpenes, saponins, and polyphenols which show antioxidant activity. Research conducted by Noorhamdani in 2014 found that the anti-inflammatory and anti-inflammatory contents were in the form of flavonoids and saponins stimulate release endorphins and inhibit the transmission of pain impulses to the brain so that the pain will gradually decrease.[5]

a. Saponins

Saponins are glycosides that have aglycones in the form of steroids and triterpenoids. Saponins have various glycosyl groups attached to the C_3, but some saponins have two sugar chains attached to the C_3 and C_{17}. Saponins can also reduce uric acid levels, by decreasing the activity of the xanthine oxidase enzyme in serum and liver of hyperuricemic rats, and increasing urinary uric acid levels.

b. Flavonoids

Flavonoids are a group of naturally occurring substances found in fruits, vegetables, grains, root bark, stems, flowers, teas, and grapes with variable phenolic structures. With anti-oxidative, anti-inflammatory, anti-mutagenic, and anticarcinogenic properties, flavonoids are known as strong inhibitors of several enzymes including xanthine oxidase, cyclo-oxygenase, lipoxygenase and and saponins stimulate phosphoinositide 3-kinase. Flavonoid compounds can reduce uric acid levels through inhibition of the enzyme xanthine oxidase, an enzyme that acts as a catalyst in the oxidation process of hypoxanthine to xanthine and then to aric acid.

c. Alkaloids

Compounds metabolites secondary there is in the plant. One of compound secondary metabolites are alkaloids, their distribution in nature and their biological activity are very importand. The strong physiological effects and selectivity of alkaloid compounds cause these alkaloid compounds to be very useful in terms of medicine.

d. Tannins

Tannin is a secondary metabolite compound that is able to bind to proteins. Natural tannins dissolve in water and give color to water, the color of tannin solutions varies from light to dark or brown, because each tannin has a distinctive color depending on the source. Tannins can inhibit protein absorption.

3.1.3. Benefits

Kersen fruit is a source of antioxidants, because it has a fairly high vitamin C content, which is around 80.5 mg. Kersen fruit also contains flavonoids, phenols, niacin and beta-carotene which function as antioxidants. Antioxidants consisting of vitamin C, vitamin E, the mineral selenium, zinc, and copper, work by blocking oxidant stress from free radicals and repairing endothelial damage. Vitamin C is a 6-carbon chain that is not synthesized by humans due to the absence of the enzyme gulonolactone oxidase in the liver. Antioxidants can protect lipoproteins especially LDL and VLDL from oxidation reactions.[2]Flavonoids can be used as a drug for hyperuricemia by reducing uric acid concentrations. Flavonoids have compounds that can inhibit Xanthin Oxidase. This can be used as a reference that cherry leaves can allegedly be used as an alternative medicine for gout because they contain flavanoids.[2]

3.2. Hyperuricemia

3.2.1. Definition

Hyperuricemia is a condition characterized by increased levels of uric acid in the blood.[1] Hyperuricemia is said to be normal when levels reach a limit of 6.8 mg/dL. Symptoms of hyperuricemia can occur if it shows a value of more than 7 mg/dL.[7] In humans, normal uric acid levels are 2.6–5.7 mg/dL for premenopausal women and 3.5–7.0 mg/dL for men and postmenopausal women.[8] Hyperuricemia is defined as a serum urate concentration of >7 mg/dL in men and >6 mg/dL in women. Abnormal state of uric acid in children and adolescents when the concentration is 5.5 mg/dL.[9] Hyperuricemia It is primarily caused by disorders of purine metabolism and is closely associated with an increased risk of cardiovascular disease, kidney disease, diabetes, and obesity. Hyperuricemia is a major factor leading to long-term systemic inflammation in patients with gout.[10]

3.2.2. Etiology

Cases of hyperuricemia caused by two factors. First, excessive uric acid production. This is due to a diet rich in purines. Besides, an error occurred purine metabolism that causes deficiency *hypoxanthine phosphoribosyltransferase* (HPRT) and *synthesis phosphoribosylpyrophosphate* (PRPP) is excessive. Excessive production of uric acid also results from cell damage or turnover: lymphoproliferative disease, disease myeloproliferative, polycythemia vera, psoriasis, tumor lysis, hemolysis, and exercise.[7]

The second factor that causes hyperuricemia is a decrease in uric acid excretion which is usually experienced by individuals who have acute or chronic kidney disease, have acidosis, hypovolemia, drugs or toxins (diuretics, niacin, pyrazinamide, ethambutol, cyclosporine, beryllium, salicylates, lead, alcohol). , sarcoidosis, hyperparathyroidism, hypothyroidism, Bartter's syndrome, and Down's syndrome.[7]

3.2.3. Epidemiology

It is estimated that 21% of the general population and 25% of hospitalized patients have asymptomatic hyperuricemia. The most common complication of hyperuricemia is gout, which is seen in 3.9% of the population in the United States. Hyperuricemia does not by itself indicate a condition pathological because it is so prevalent in the general

population.[7] With age, the risk of developing hyperuricemia and gout increases due to decreased kidney function, risk of dehydration, and polypharmacy due to several comorbidities. Thus, the combination of reduced estrogen levels and aging-related comorbid complications suggests that women may be at a higher risk of developing elevated uric acid than men.[11]

3.2.4. Pathophysiology

Hyperuricemia is a metabolic disease characterized by high levels of uric acid in the blood which precipitate uric acid crystals in the kidneys and joints. (Boffetta et al., 2009) In the body, uric acid is the end product of purine metabolism. Uric acid synthesis mainly occurs in the liver and to a lesser extent in the small intestine. Normally, two-thirds of uric acid excretion occurs via the kidneys and one-third via the intestines.[12] Xanthine oxidase is an important enzyme in humans that catalyzes the conversion of purines to uric acid. Where the highest concentration is in the liver, which is the main organ of uric acid production. But in other organs such as intestines, kidneys, lungs, heart, brain, muscles, and vessels blood also contains xanthine oxidase.[1,8] The kidneys play a role in maintaining the balance of uric acid metabolism.[13] In the kidney, uric acid is freely filtered at the glomerulus, reabsorbed, secreted, and then reabsorbed in the proximal tubule. Cloning of specific uric acid transporters will facilitate understanding of the specific mechanisms by which uric acid is handled in the kidney and small intestine.[14] Re-absorption of uric acid by the kidneys involves several transporters such as urate transporter 1 (URAT1) and glucose transporters 9 (GLUT9) whose function is influenced by several factors, such as genes, drugs, elevated serum lead, lactate or ketone concentrations.[1,8] Imbalance between the production and elimination of uric acid, mainly dependent on renal excretion can cause hyperuricemia. The excretion of uric acid in the intestine is handled by uric acid transporters in intestinal epithelial cells, which transport uric acid from the blood to the intestinal lumen. Several transporters participate in this process, the main ones being ABCG2 and SLC2A9. Intestinal excretion also involves the catabolism of uric acid by the intestinal flora.[12] Excretion uric acid appears to be correlated with serum uric acid concentrations due to a slight increase in concentration serum resulting in a marked increase in uric acid excretion.[15]

Hyperuricemia can occur due to Underexcretion, overproduction, or even a combination of the two mechanisms. Mostly, the cause of hyperuricemia is Underexcretion. Treatment of uric acid by the kidneys involves filtration at the glomerulus, reabsorption, secretion, and finally, reabsorption postsecretory. Consequently, altered excretion of uric acid can result from decreased glomerular filtration, decreased tubular secretion, or increased tubular reabsorption. While decreased urate filtration may not cause primary hyperuricemia, it can contribute to hyperuricemia on insufficiency kidney. Decreased tubular urate secretion occurs in patients with acidosis (eg, diabetic ketoacidosis, ethanol or salicylate intoxication, starvation ketosis). Organic acids that accumulate under these conditions compete with urate for tubular secretion. Finally, the increase in reabsorption of uric acid distal to the site of secretion is mechanisms thought to be responsible for the hyperuricemia observed with diuretic therapy and diabetes insipidus. Overproduction accounts for only a small proportion of patients who develop hyperuricemia. Causes of hyperuricemia in overproducercan be either exogenous (purine-rich diet) or endogenous (increased purine nucleotide breakdown). A small part ofoverproducer has enzymatic breakdown cause hyperuricemia.

Mechanism combined (underexcretion and overproduction) can also cause hyperuricemia.[15]

3.2.5. Clinical Symptoms

Most case with hyperuricemia is asymptomatic. Hyperuricemia could classified as hyperuricemia symptomatic when accompanied by gouty arthritis and renal involvement such as urolithiasis or acute uric acid nephropathy.[16,17]

3.2.6. Management

Part big patient no symptomatic and do not require medical therapy for hyperuricemia. Unnecessary medical costs and potential side effects outweigh the benefits start treatment. Urate-lowering drugs in asymptomatic patients are indicated only in those undergoing cytolytic therapy for malignancy to prevent tumor lysis syndrome. The following are drugs that can be used to lower uric acid levels:[7]

a. Allopurinol: inhibitor xanthine oxidase; used as penghambat xantin oksidase; prophylaxis against gouty arthritis, nephrolithiasis, and chemotherapy associated hyperuricemia.
b. Probenecid: inhibits URAT1 resulting in increased uric acid secretion and is used as a second line therapy for gout.
c. Rasburicase: recombinant uricase that converts uric acid to allantoin which is much more water soluble and easy to remove from the kidneys and use as prophylaxis to hyperuricemia related chemotherapy

In addition, hyperuricemic patients should be advised about lifestyle modifications. The following are lifestyle modifications that gout patients can make.[18]

a. Patients who are overweight (overweight) can modify their diet to help have an ideal body weight
b. Avoid eating high-purine and high-protein foods such as red meat, liver, broth, shellfish and yeast extract.
c. Also avoid high-purine drinks such as alcohol.
d. Drink >2 liters of water per day to keep your body well hydrated.
e. Do moderate physical exercise in moderation, because excessive exercise can risk joint trauma and should be avoided.

3.3. How To Make Cherry Leaf Extract

Based on research conducted by Maria Ignatia, cherry leaf extraction is done by taking and selecting fresh and green cherry leaves. Then, cleaning of dirt and dust, can be done by washing thoroughly using running water. After washing, the cherry leaves are then dried, crushed and then blended to make cherry leaf powder. The powder was extracted by maceration method, namely putting it into a bottle and adding 70% ethanol solution, after that it was left for 3 days with shaking 3 times a day. After this was done, it was filtered, washed again, and concentrated using the evaporator. The remaining solvent is then evaporated in a water heater so that a free viscous extract is obtained solvent. The pure cherry leaf condensed extract that will be obtained, is weighed, then the average yield is calculated.[19]

4. Conclusion

Based on the explanation above, it can be concluded that the content of cherry leaves can help reduce uric acid levels so that cherry leaves can be used as antihyperuricemia.

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