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Submission date: 25-Jun-2024 05:03AM (UTC+0700)

Submission ID: 2408091300

File name: The_effectiveness_of_tempuyung_extract_Sonchus_arvensis_in_the_herbal_treatment_of_gout_arthritis_Literature_review.pdf (168.03K)

Word count: 2695

Character count: 15512

Literature Review

The effectiveness of tempuyung extract (*Sonchus arvensis*) in the herbal treatment of gout arthritis: Literature review

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Abstract: Gout arthritis is a chronic inflammatory disease caused by disorders of nucleic acid metabolism and *monosodium urate* (MSU) deposition with hyperuricemia as one of the main causes. The incidence of gout arthritis in Indonesia is known to have increased, which in 2013 was 11.9%. Pharmacology management for gout arthritis can cause serious side effects so it is necessary to find alternative drugs that have minimal side effects. One of the types of plants known to have antihyperuricemia activity is tempuyung *(Sonchus arvensis)* that were found in some of the major islands in Indonesia. Tempuyung is useful in preventing the inflammation process and accumulation of monosodium urate (MSU) in joints. The mechanism is still uncertain, but it is allegedly due to the presence of flavonoid compounds in tempuyung which act as an inhibitor of the xanthine oxidase enzyme that causes gout arthritis. In addition, the extracts of tempuyung leaves and roots also have anti-inflammatory, antioxidant, antibacterial properties and so on.

Keywords: Gout arthritis, *Sonchus arvensis*, antihyperuricemia, flavonoid, xanthine oxidase.

1. Introduction

Gout arthritis is a chronic inflammatory disease that occurs as a result of disturbances in nucleic acid metabolism and accumulation of monosodium urate (MSU) crystals in the joints. Gout arthritis is described by severe pain and swelling of one or more synovial joints.[1] Hyperuricemia is one of the main causes of gout.[2] Increased uric acid metabolism, and decreased uric acid excretion, or a combination of both are the causes of hyperuricemia.[3]

Based on data by the Global Health Data Exchange (GHDx) by the World Health Organization (WHO), cases of gout in worldwide is estimated 7.44 million people with incidence around 0.097%, and the prevalence in Canada is estimated 41.22 million cases (0.54%).[4] The prevalence of arthritis gout in Indonesia is still unknown with certainty.[5] However, the incidence rate is known to be increasing.

In 2013, the incidence of gout arthritis was 11.9% (Kemenkes RI, 2013). Research on the Sangihe ethnic group on the island of North Minahasa by Ahimsa & Karema K. (2017) found a prevalence of gout was 29.2% while research conducted by Raka Putra et al. (2017) showed that the prevalence of hyperuricemia in Bali was 14.5%.[5]

First-line treatments of gout arthritis include non-steroid anti-inflammatory drugs (indomethacin and naproxen), corticosteroids, and colchicine.[1] Gout arthritis can be cured by using uric acid discharge which works by blocking xanthine oxidase such as allopurinol, febuxostat - or by increasing renal uric acid excretion.[6] However, these drugs can cause serious reactions or side effects, such as nephropathy, kidney toxicity, gastrointestinal toxicity, liver damage myelosuppression, allergic reactions and increased 6-mercaptopurine toxicity. Therefore, it is necessary to find new alternative agents with better efficacy to reduce uric acid that have minimal side effects.[1,7]

Exploration of natural materials in Indonesia can be carried out by using plants as herbal medicines with therapeutic potential as anti-hyperuricemia.[8] Xanthine oxidase inhibitors need to be developed as an alternative treatment because they have lower side effects than allopurinol, for example, tempuyung leaves.[9]

The purpose of writing this literature review is to determine the potential use of tempuyung (*Sonchus arvensis*) in the herbal treatment of gout arthritis and to determine the content of bioactive compounds that have anti-hyperuricemic activity.

2. Methods

The research method uses a descriptive approach by reviewing the literature from research articles. Search for articles was carried out through the google site (www.google.co.id), google scholar (www.scholar.google.co.id) and PubMed (pubmed.ncbi.nlm.nih.gov) with keywords namely tempuyung, *Sonchus arvensis* and gout arthritis.

3. Results and Discussion

Sonchus arvensis (Tempuyung)

Tempuyung, a plant from the genus Sonchus and in the Asteraceae family, is a traditional plant that grows in Indonesia and found in Sumatra, Java, Bali, Sulawesi and Papua. Therefore, tempuyung is also known as a native Indonesian medicinal plant (OAI).[10] Tempuyung is found to grow at an altitude of 50 to 2400 meters above sea level and is often found in rice fields, roadsides and cliffs.[11] There are several Sonchus species found, namely *Sonchus arvensis, Sonchus oleraceus, Sonchus asper,* and *Sonchus erzincanicus.* However, *Sonchus arvensis* is the easiest to obtain and use as research materials. The difference is not very visible, both in morphology and anatomy.[12]

Tempuyung has a spear-like with a long shape, jagged leaf edges, smooth and thin surface. The stems of tempuyung are round and erect, the roots are taproot type and the fruit is small brown with a hard and wrinkled texture (Wahyuni *et al*.,2019). In Chinese pharmacology, it is stated that tempuyung has a dominant bitter taste.[13]

Tempuyung has many beneficiences, including treating gout, asthma, diuretics, cough, stone urination, fever and others so it is often referred to as an anti-hyperuricemia and anti- inflammatory plant[1], antioxidants[14], antibacterial[15] and so on. In fact, research by Wadekar et al in 2012 found that tempuyung can be consumed for the treatment of helminthiasis, diarrhea and dysentery.[13]

Tempuyung (*Sonchus arvensis*) is a traditional medicinal plant that has benefits to reduce uric acid levels in the body due to its nature as an inhibitor of the xanthine oxidase enzyme.[9] Several studies have found that tempuyung contains secondary metabolites such as tannins, phenols and flavonoid.[16] Flavonoid compounds that contains in tempuyung are apigenin 7-O- glucoside as the highest levels compound with 0.5% in total, 5,7,4-trihydroxy flavone (apigenin), luteolin 7-O-glucoside and 5,7,3,4'-tetrahydroxy flavone (luteolin). [10,17]

Gout Arthritis

Gout arthritis is a disease that is often found around the world. Gout arthritis is a heterogeneous group as a result of uric acid supersaturation in extracellular fluid or due to deposition of MSU crystals in the tissue.[18] Gout arthritis mostly occurs in adult men to old age and in women usually occurs in the post-menopausal period.[19]

Pathogenesis

Purine metabolism arises from the conversion of adenosine and guanosine to uric acid in the human body. Initially, adenosine is converted to inosine by the role of adenosine deaminase. In higher primates, uric acid is converted to alatoin (a water-soluble product in mammals) by uratase (*uricase*). Humans do not have uratase, so the end product of purine metabolism is uric acid.[20]

The cause of gout is a metabolic disorder of purine catabolism in which the production and excretion of various purine catabolites becomes excessive. This overproduction and excretion is caused by various genetic defects in PRPP synthetase. When uric acid levels exceed the solubility limit, sodium urate / *monosodium urate* in soft tissues and joints crystallizes. This is what causes an inflammatory reaction in the form of gout arthritis.[20]

Phagocytosis by macrophages occurring in the joint cavity causes an inflammatory response in gout arthritis. Furthermore, there is the formation of the inflammasome as a protein complex that mediates the enzymatic process of pro-IL-1β which is initially inactive to biologically active IL-1β which is

then secreted from cells. MSU crystals with a co-stimulating role and lipopolysaccharides trigger the activation of IL-1β.[21]

The onset of gout attacks will be associated with changes in the increase and decrease of uric acid serum levels. Attacks rarely occur when uric acid serum levels are stable. The decrease in uric acid serum can precipitate the release of monosodium urate crystals from their deposits. In some patients with gout arthritis or with asymptomatic hyperuricemia urate crystals are found in the knee area that has never had an acute attack and in the metatarsophalangeal joint.

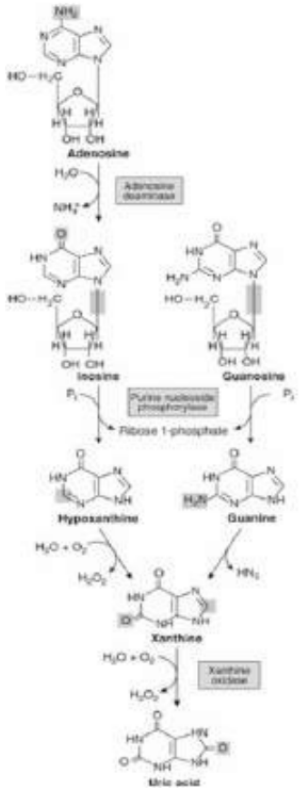

Figure 1. Uric acid metabolism[20]

Management

The management of gout arthritis must be done early to prevent the complications. The goal of treating acute gout arthritis is to eliminate complaints of joint pain and inflammation with drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids, or the ACTH

hormone.[22] In the intercritical and chronic stages, the goal of treatment is to lower uric acid levels to normal levels to prevent recurrence by administering a low- purine diet and taking the drug allopurinol together with other uricosuric drugs. However, long-term use of these medicines can cause serious side effects, including nephropathy, kidney toxicity, gastrointestinal toxicity, liver damage, myelosuppression, allergic reactions and increased 6-mercaptopurine toxicity. Therefore, it is necessary to find alternative new agents with better efficacy to reduce uric acid that have minimal side effects, for example, such as herbal treatment with tempuyung.[1,7]

Activity of *Sonchus arvensis* Extract as Xanthine Oxidase Inhibitor

Research on the use of tempuyung showed that compounds that have xanthine oxidase enzyme inhibitor activity are flavonoids. The flavonoid content in tempuyung leaves was 0.1044%, while in the tempuyung root it was 0.5% and the largest flavonoid was apigenin 7-0- glucoside.[3,10] There is a change in decreased uric acid levels from each different dose of tempuyung extract which shows the activity of tempuyung leaves as an anti-hyperuricemia with the most effective dose of 0.35 mg/gBB.

Apart from the tempuyung leaf extract, anti-hyperuricemic activity was also found in the tempuyung root infusion. In the research of Retnowati et al. (2014) found that tempuyung root infusion had an effect on reducing uric acid levels where the concentration of 40% of tempuyung root infusion was almost equivalent to allopurinol. The 40% concentration group was the group with the most people where the average uric acid level measurement was the greatest when compared to the other dose groups (10% and 20%).

Flavonoids

Flavonoids are one of a group of phenolic compounds that are commonly found in plant tissue.[23] Flavonoids can also be found in fruits, vegetables, whole grains and bark.[24]

Flavonoids consist of a solitary benzene ring along with a benzo-gamma- piron structure that are shaped by three acetic acid derivation units and phenylpropane units (through shikimic acid route). More than 500 compounds from a total of 2000 compounds undergo formation in the free state (aglycones) and the rest as O- or C- glycosides.[25] Classifications of flavonoids include flavones, flavonols, flavanols, flavanones, isoflavonoids, neoflavonoids, chalcone, and catechins. The difference in the substitution of the flavonoid structure causes this classification. This difference also results in diverse pharmacological activities.[26] Some of its pharmacological activities are as antioxidants, anti-inflammatory, anti- mutagenic, and even anti-cancer.[23,24]

One of the pharmacological activities in this case is as an antioxidant which works as an inhibitor of the xanthine oxidase enzyme so that there is inhibition or reduction of uric acid formation in the body.[3] Flavonoids have potential as antioxidants by acting as electron donors to prevent reactive

oxygen species (ROS). ROS is a trigger for inflammation due to accumulation of *monosodium urate* (MSU) in joints, which causes complaints and disorders of gout arthritis.[1]

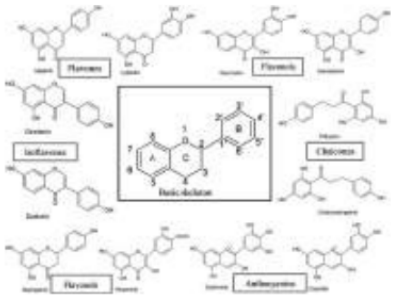

Figure 2. Basic skeleton structure of flavonoids and their classes[24]

The xanthine oxidase pathway is an important pathway that contributes to oxidative injury to tissues, particularly after the ischemia-reperfusion stage. Xanthine dehydrogenase is a type of the compound that exists under physiological conditions, however its design is changed to xanthine oxidase during ischemic conditions. Xanthine oxidase is a provenance of oxygen free radicals. Xanthine oxidase reacts with molecular oxygen and releases superoxide free radicals in the reperfusion phase.[24]

According to research conducted by Lin, et al. (2015) known that apigenin has strong activity as a xanthine oxidase inhibitor, followed by luteolin, and kaempferol.[27]

4. Conclusions

Based on the literature review, it can be concluded that tempuyung, which is a native Indonesian medicinal plant (OAI), is effective as an herbal treatment for gout arthritis. Tempuyung leaf and root extracts can be useful for reducing uric acid levels because they prevent inflammation and accumulation of *monosodium urate* (MSU) in joints. The mechanism is still uncertain, but it is allegedly due to the presence of flavonoid compounds in tempuyung which act as an inhibitor of the xanthine oxidase enzyme that causes gout arthritis. Therefore, consuming tempuyung can be an alternative therapy in addition to medical and healthy lifestyle behaviors.

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