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Review

Potential of Qust Al Hindi *(Saussurea lappa)* Root as Anti-hyperuricemia: Literature Review

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ABSTRACT: Hyperuricemia is a condition characterized by increased levels of uric acid due to dysfunction in production or excretion. Uric acid is the product of purine catabolism originating from the degradation of purine nucleotides that occur in all cells. The first-line treatment for hyperuricemia is allopurinol. have side effects so that the use of traditional medicine with natural ingredients can be used as an alternative treatment. Therefore, it is necessary to develop compounds with xanthine oxidase inhibitor activity derived from natural plants with lower side effects. Xanthine oxidase is an enzyme that plays a role in catalyzing the oxidation of hypoxanthine to xanthine and uric acid. Qust al hindi contains several chemical compounds including flavonoids, steroids, terpenes, alkaloids, sesquiterpenes, costunolide, dehydrocostus lactone, cynaropicrin, and chlorogenic acid. This review will discuss the qust al hindi plant which has the potential to be an antihyperuricemia drug using the library study method. Data search was carried out using online search engine instruments such as Google, PubMed and Science Direct.

KEYWORDS: Uric acid; qust al hindi; xanthine oxidase.

1. INTRODUCTION

Qust al Hindi is a medicinal plant known in several traditional systems of medicine, such as Persian and Indian. This plant is native to India, Pakistan, and China and grows extensively in the Himalayan region. Because of its broader properties, its roots are widely used for various diseases. In traditional medicine, it is used to treat pneumonia, coughs, colds, ulcers, and rheumatism. In addition, it is also used for toothache, asthma, dysentery, and skin diseases (Madhuri *et al*., 2012; Sukmawati *et al*., 2022).

In the Kashmir region of northern India, a hot water extract from the root of *Saussurea lappa* has traditionally been used to treat asthma, inflammation, and rheumatism. Many authors have reported that the root of the *Saussurea lappa* plant has active molecules with cortisol-lowering, bronchodilator, antiulcer, anticancer, anti-inflammatory, antiviral, and hepatoprotective effects (Saleem *et al*. 2013). In traditional herbal medicine, the dried *Saussurea* root of Clarke *lappa* (*Asteraceae*) is regarded as an antiseptic, astringent, diuretic, aphrodisiac, antispasmodic, anthelmintic, and sedative. It is used to treat asthma, dyspepsia, rheumatism, cough, throat infections, tuberculosis, leprosy, malaria, convulsions, fever, worm infestation and many other ailments. It can also be used as a treatment for various liver disorders (Yaeesh *et al*., 2010).

Qust al hindi with latin name (*Saussurea lappa)* comes from the Asteraceae family. The Asteraceae family is the main source of sesquiterpene lactones (Amara *et al*., 2017). From fresh roots, Qust Al Hindi has chemical ingredients such as costunolide, dehydrocostus lactone, cynaropicrin, lappadilactone, germacrenes. From 12-methoxydihydro-dehydrocostuslactone essential oil, from cyclocostunolide B hexane extract, dihydrocostunolide From methanolic extracts of lima saussureamines A, B, C, D and E and lignin glycosides via activity-guided fractionation of Betulinic acid, Betulinic acid methyl ester and Mokko lactone (Madhuri, Elango and Ponnusankar, 2012). From *Saussurea lappa* roots, diverse biologically active constituents have been isolated, including sesquiterpenes, flavonoids, lignans, phytosterol alkaloids, terpenes anthraquinones, and flavonoids (Hassan and Masoodi, 2019).

Xanthine oxidase is an important enzyme in catalyzing the hydroxylation of hypoxanthine to xanthine and xanthine to uric acid. In addition, xanthine oxidase also plays a role in producing hydroxyl free radicals and hydrogen peroxide which can increase or initiate oxidative stress. Xanthine oxidase treats gout, neuropathy and kidney stones leading to hyperuricemia. Hyperuricemia is a state of overproduction of uric acid or underexcretion of acid. The production of uric acid is catalyzed by xanthine oxidase, which is produced in the liver. Inhibition of xanthine oxidase may be a therapeutic pathway for gout treatment. Gout is a type of joint pain characterized by swelling in the joints, affecting the decrease in quality of life. Xanthine oxidase comes from the molybdenum iron-sulfur flavin hydroxylase enzyme group, which is found mainly in the liver, kidney, brain, and gastrointestinal tract. In addition, these enzymes are also present throughout the cardiovascular system (Malay and Wicaksono, 2018).

The mechanism for the formation of xanthine oxidase starts from xanthine oxidase catalyzes the oxidation of hypoxanthine to xanthine and then xanthine to uric acid. During the xanthine oxidase reoxidation process, oxygen acts as electron acceptor, producing superoxide radicals and hydrogen peroxide. During this reaction, superoxide anion radicals (O_2) and H_2O_2 are formed. Superoxide anion radicals spontaneously or under the influence of dismutase (SOD) change to hydrogen peroxide and oxygen (Malay and Wicaksono, 2018).

Hyperuricemia is the end product (excretion) in the body of the process of purine degradation as a waste product and has no physiological function. The process of hyperuricemia can be seen through the blood profile; there is an increase in uric acid levels in the blood and exceeds normal levels (in men above 7.0 mg/dL and in women above 6.0 mg/dL). Consumption behavior is one of the factors causing hyperuricemia such as consumption of fat, margarine, coconut milk, butter, and some fruits that are known to contain high levels of fat (durian and avocado) also affect uric acid expenditure.

The synthetic drug commonly used to treat gout is allopurinol. Allopurinol is a uric acid analog that works by inhibiting the formation of uric acid from its precursors (xanthine and hypoxanthine) by inhibiting the activity of the xanthine oxidase enzyme. Allopurinol has a stronger affinity for inhibiting the xanthine oxidase enzyme than xanthine. Therefore, when allopurinol is present together with a xanthine substrate, allopurinol will react more with xanthine oxidase than with the substrate itself so that the effect of inhibiting uric acid formation can last as long as allopurinol levels are present in the body (Pertamawati and Hardhiyuna, 2015).

2. EXPERIMENTAL SECTION

This study used a literature review article to determine the potential of the active compound of the root of the Qust al Hindi (*Saussurea lappa*) plant as an anti hyperuricemia. The process of searching for literature is carried out through online search instruments of national or international publications such as Google Scholar, PubMed, and Science Direct.

3. RESULTS AND DISCUSSION

Qust al hindi with the Latin name *Saussurea lappa* is a plant that is known to be traditionally considered good in various medicines in India. jg is an erect, tall, perennial growing to a height of 1–2 m with erect stems. Sturdy root about 60 cm has a strong and distinctive smell. The cross section clearly shows the periderm where the phloem and xylem are clearly visible. The stems are also sturdy and fibrous. The leaves are stalked and about 1 m long. The flowers are dark bluish purple to black, arranged in the leaf axils. The flower heads are stemless, hard and round in shape, about 3–5 cm in diameter. Fruit about 3 mm long, curved, cupped and compact. Most of the essential root and root oils are used medicinally. The dry, slightly bitter-tasting root is dirty gray to yellow on the outside and about 8-12 cm long, 1-3 cm in diameter. Generally wrinkled, serrated and more or less cylindrical secondary roots. The root section was cut open showing two thinner outer ring regions and a dark brown inner ring. The root has a characteristic strong aromatic odor (Madhuri, Elango and Ponnusankar, 2012).

The results of the article search showed that the qust al hindi (*Saussurea lappa*) plant had the potential as an antihyperuricemia because this planthas a variety of active compounds, including flavonoids, steroids, terpenes, alkaloids, sesquiterpenes, costunolide, dehydrocostus lactones, cynaropicrin, and chlorogenic acid (Eldaim *et al.* 2019). The main components of the roots of this plant are sesquiterpene lactones such as dehydrocostus lactone and costunolide. The secondary metabolite is a terpenoid compound class of sesquiterpene lactones belonging to the Asteraceae family (Muhammad Fakhruri, 2021). According to research Bernardes *et al*., 2019 stated that sesquiterpene lactones have an inhibitory effect on the xanthine oxidase enzyme. Several flavonoid and alkaloid compounds in plants are believed to be able to inhibit the activity of the xanthine oxidase enzyme which plays a role in the manufacture of uric acid, so that plants with flavonoid compounds have potential as alternative medicines (Muhammad Fakhruri, 2021;Septianingsih *et al*., 2012).

Flavonoid compounds that we already know can inhibit xanthine oxidase and are capable of capturing superoxide free radicals and this is what can reduce uric acid levels (Fawwaz et al., 2023). However, types of flavonoids such as apigenin, luteolin, quercetin, and kaempferol have good potential to inhibit xanthine oxidase activity, while derivatives of flavonoids such as 7-glucosyl apigenin have lower inhibition than the original flavonoid, namely apigenin (Cendrianti, Muslichah and Ulfa, 2014). Quercetin can inhibit the formation of uric acid catalyzed by xanthine in a concentration-dependent manner. Quercetin exhibited a similar inhibitory ability on xanthine oxidase activity. Quercetin reversibly inhibited the formation of uric acid and O_2 in a mixed-type manner, and quercetin's inhibition of O_2 generation was ascribed to its reduced form of xanthine oxidase. Quercetin can spontaneously enter the xanthine oxidase active cavity to form a xanthine oxidase complex (Zhang *et al.*, 2018). Kaempferol binds to the active site. It can be concluded that the binding mode with xanthine oxidase strengthens the inhibition by occupying the entrance of the xanthine substrate and influencing the structure of xanthine oxidase. Inhibition kinetics test showed that kaempferol reversibly competitively inhibited xanthine oxidase activity. The main mechanism of kaempferol's inhibition of xanthine oxidase activity may be due to the insertion of kaempferol into the active site of xanthine oxidase, which occupies the catalytic center of the enzyme to avoid substrate entry and cause a conformational change of xanthine oxidase. The results showed that kaempferol could be a promising xanthine oxidase inhibitor, and kaempferol is a food that benefits the treatment of gout (Wang *et al.*, 2015). In addition to inhibiting xanthine oxidase, flavonoids also have anti-inflammatory mechanisms (Fawwaz et al., 2023), so there is an additional mechanism in treating gout besides xanthine oxidase inhibitors from flavonoid compounds (Gunarti *et al*., 2021).

The xanthine oxidase pathway is an important pathway in tissue oxidative damage, particularly after ischemia-reperfusion. Both enzymes, xanthine dehydrogenase and xanthine oxidase, catalyze the conversion of xanthine to uric acid. Xanthine dehydrogenase is the form of the enzyme that exists under physiological conditions, but its structural configuration is changed to that of xanthine oxidase during ischemic conditions. Xanthine oxidase is an enzyme that produces oxygen-free radicals. In the reperfusion phase, xanthine oxidase reacts with oxygen to release superoxide free radicals. Flavonoids containing quercetin and silybin groups can inhibit xanthine oxidase activity, reducing oxidative damage. Luteolin compound (3',4',5,7-tetrahydroxyflavone) is the best xanthine oxidase inhibitor (Simanjuntak, 2012). The xanthine oxidase enzyme is

an oxidoreductase class of enzymes. The xanthine oxidase enzyme catalyzes the hypoxanthine oxidase reaction to xanthine and then to uric acid. In oxidation reactions, oxidase enzymes catalyze the removal of electrons from a substrate by using oxygen as a hydrogen or electron acceptor. In this oxidation reaction, xanthine, which is a substrate, will bind to oxygen with the help of the xanthine oxidase enzyme, resulting in the formation of a product in the form of uric acid and a by-product in the form of H_2O_2 (Arcinthya Rachmania *et al.,* 2021).

According to research Akram *et al*., 2013 can healjoint pain from gout. Where gout or more precisely arthritis can be defined as inflammation caused by a buildup of uric acid in the body. High levels of uric acid in the blood prevent some of the uric acid from being filtered by the kidneys and remain in the body. Because the levels in the body are high, crystals will form and accumulate in the joints. This will cause swelling, inflammation, stiffness and pain (Lestari, Kusrini and Anam, 2014).

Uric acid in the body is filtered by the kidney, namely by the glomerulus and secreted by the proximal tubule into the urine. Most of it is reabsorbed into the proximal tubule. Increased levels can cause storage in joints and tissues so that they can cause inflammation (Gunarti *et al*., 2021). Naturally, uric acid is produced in the body through metabolic pathways that use food and drink as a substrate. Consuming foods with high purine content, such as nuts, melinjo or chips, offal, and drinks containing caffeine, such as coffee, tea, and cola, can increase uric acid levels in the blood (Septianingsih, Susanti and Widyaningsih, 2012).

Gout can be prevented by inhibiting xanthine oxidase activity through synthetic or traditional treatments using alternative plant ingredients. Synthetic drugs are used to cure gout by consuming allopurinol, which inhibits the activity of the xanthine oxidase enzyme. However, this synthetic drug has many side effects and allergic reactions. Therefore, we need alternative treatments that are safer and have lower side effects (Lestari, Kusrini and Anam, 2014).

4. CONCLUSION

Qust al hindi *(Saussurea lappa)* has the potential to be an alternative medicine for treating hyperuricemia.

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