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POTENTIAL OF *Arcangelisia flava* AS ANTIHYPERURICEMIA THERAPY: LITERATURE REVIEW

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ABSTRACT

This study is a literature review that aims to evaluate the potential of *Arcangelisia flava* (*A. flava*) as an anti-hyperuricemia therapy. *Hyperuricemia* is a condition that is closely related to several diseases, such as obesity, diabetes, hypertension, and cardiovascular disease. As the final product of purine conversion catalyzed by the enzyme xanthine oxidase (XO), Uric acid is an essential focus in managing hyperuricemia. In vitro test results show that ethanol extract from yellow wood leaves and roots has the potential to inhibit the activity of the XO enzyme, thereby reducing the formation of uric acid. Although yellow wood is traditionally known in herbal medicine, more in-depth scientific information is still needed, especially in the context of anti-hyperuricemia therapy, which is still limited in clinical studies. This review study aims to present a comprehensive overview of research related to the use of *A. flava* in anti-hyperuricemia therapy, with the hope of providing a better understanding of this plant's potential in treating this condition.

Keywords: *Arcangelisia flava, hyperuricemia, and therapy*

INTRODUCTION

Indonesia is a tropical country with high biodiversity and is included in the eight mega biodiversity countries in the world, both in terms of flora and fauna. The distribution of flora and fauna in Indonesia is extensive, with several types being endemic, meaning that these species can only grow or be found in one particular place. Around 30,000 plant species exist in Indonesia, of which 940 can be used to treat various diseases (Aprilianti, 2022; Subiandono & Heriyanto, 2019).

Indonesia's ethnic diversity has produced various cultures, traditions, and local wisdom. One of this local wisdom is to utilize the diversity of the surrounding environment as a medicine for various diseases. So far, people have known and used the properties of various plants for generations as medicines that can cure various diseases. However, even though they know the substances contained in these plants, people rarely use them. The use of medicinal plants in Indonesia is related to knowledge of their properties and involves proving their compound content. Thus, the use of these medicinal plants can be developed in the pharmaceutical industry (Diliarosta et al., 2021).

Arcangelisia flava Merr., also known as yellow wood, is one of the medicinal plants that is the focus of this review. This plant is native to Indonesia, grows up to 20 m long, and lives in the lowlands up to 800 m above sea level (ASL). The leaves are thick and robust like leather, oval in shape, obtuse, not sharp, with a leaf width of between 7 cm and 20 cm, and a shiny upper

surface and long stems. The flowers are placed in two small sizes arranged in a glabrous series with a length of between 20 cm to 50 cm, greenish-white or yellowish-white, with buds (Aprilianti, 2022; Diliarosta et al., 2021; Subiandono & Heriyanto, 2019).

Based on research that has been conducted, *A. flava* Merr. It has been proven to have antimicrobial, antioxidant, antihyperlipidemic, and anticancer activity. This plant is used as an herbal medicine to treat jaundice, digestion, worms, strong medicine or tonic, fever, menstrual laxatives, and canker sores. Secondary metabolite content found in *A. flava* Merr. Includes alkaloids, phenolics, flavonoids, saponins, tannins, and berberine (Aprilianti, 2022).

Hyperuricemia is closely related to gout, obesity, diabetes, hypertension, and cardiovascular disease. Uric acid is formed as the end product of purine conversion, which is oxidized by the liver's enzyme xanthine oxidase (XO). In vitro tests have shown that ethanol extract from yellowwood leaves and roots can inhibit the activity of the enzyme xanthine oxidase, which is responsible for the formation of uric acid (Fatmawati et al., 2022). Considering the wide variety of uses of yellowwood but still relying on hereditary knowledge, supporting scientific information regarding its efficacy, especially in the context of anti-hyperuricemia therapy, which has little research in clinical studies, is essential. This review article investigates the uses of the plant *A. flava* Merr. in anti-hyperuricemia therapy.

Hyperuricemia and Related Health Problems

Definition of hyperuricemia and its relationship to medical conditions: gout, heart disease, and kidney failure

Hyperuricemia is a condition that occurs when there is an increase in uric acid levels in the blood, which is associated with the emergence of gout and kidney stones (Jin et al., 2012; Suratno et al., 2019). The upper limit of normal is 6.8 mg/dL for women and 7 mg/dL for men. This increase can be caused by increased production, decreased excretion, or both processes (Li et al., 2020; Skoczyńska et al., 2020). Hyperuricemia can also occur due to accelerated purine degradation in conditions of high cell turnover, such as hemolysis, rhabdomyolysis, and tumor lysis (Li et al., 2020). Hyperuricemia can cause gout, an arthritic condition caused by uric acid crystals building up in the joints. Kidney stones can also appear due to hyperuricemia because uric acid crystals accumulating in the bloodstream can cause stones resembling uric acid crystals. Impaired kidney function can also increase the risk of hyperuricemia because kidneys that cannot work correctly will help increase uric acid levels in the blood (Jin et al., 2012; Mantiri et al., 2017).

Treatment for hyperuricemia depends on the level of the condition and the symptoms that appear. To reduce uric acid levels, actions can be taken, such as reducing the consumption of high-purine foods, reducing alcohol consumption, and consuming drugs such as colchicine or allopurinol. In severe cases, such as conditions that cause kidney problems, therapy such as hemodialysis can be used (Jin et al. 2012; Gaubert et al. 2020; Skoczyńska et al. 2020).

The health impacts of hyperuricemia and the need for effective therapy

Hyperuricemia, defined as elevated serum uric acid levels, is a common disorder affecting approximately 38 million Americans and is associated with a variety of health impacts. The most common

manifestations of hyperuricemia are gout, which can be painful and treatable, and uric acid and calcium nephrolithiasis. Hyperuricemia is also associated with an increased risk of hypertension, cardiovascular disease, and chronic kidney disease (Benn et al., 2018). The health impacts of hyperuricemia include: 1) Gout: Hyperuricemia can cause the formation of uric acid crystals, which can cause painful gout attacks in the joints, especially the big toe joint. 2) Nephrolithiasis: Increased uric acid levels can contribute to the formation of kidney stones. 3) Hypertension: Hyperuricemia is associated with an increased risk of hypertension. 4) Cardiovascular disease: Epidemiological studies show that hyperuricemia is associated with the development of cardiovascular disease. 5) Chronic kidney disease: Hyperuricemia is associated with an increased risk of chronic kidney disease. 6) Type 2 diabetes: Several studies show hyperuricemia is an independent risk factor for developing type 2 diabetes (Benn et al., 2018; George et al., 2023).

Effective therapy for hyperuricemia aims to lower uric acid levels and reduce the risk of associated complications. Treatment options include lifestyle modifications, such as following a low-purine diet, maintaining a healthy weight, and staying hydrated. Pharmacological interventions include xanthine oxidase inhibitors such as allopurinol and uricosurics such as probenecid. In some cases, medications such as SGLT2 inhibitors may be used to reduce uric acid levels (Benn et al., 2018; George et al., 2023; Sugano et al., 2019).

Active Components in Arcangelisia flava

Identification and characterization of active compounds contained in Arcangelisia flava

Arcangelisia flava, also known as yellow root or yellow wood, is a medicinal plant traditionally used to treat various diseases, including jaundice, liver disease, diarrhea, fever, and inflammation. It is widespread in Indonesia and is reported to produce several bioactive compounds, including alkaloids, flavonoids, and terpenoids (Fatmawati et al., 2022). The 70% ethanol extract of *A. flava* stems was studied for its phytochemical compounds using LC-MS/MS and molecular docking approaches. Several compounds that have been identified include isopycnarrhine, pycnarrhine, and 3-hydroxy-3',4',5'-trimethoxyflavone. This compound has exhibited anti-inflammatory, antibacterial, and antifungal activity against various pathogens (Pratama et al., 2023). Endophytic bacteria isolated from *A. flava* leaves are also known to produce antimicrobial compounds. For example, the endophytic fungus Coelomycetes AFKR-18 produces each basin which has potent antimicrobial activity against *Escherichia coli, Bacillus subtilis, Micrococcus luteus, Candida albicans*, and *Aspergillus flavus* (Marinas et al., 2010; Sipriyadi et al., 2022).

The potential mechanism of action of these compounds in reducing uric acid levels in the body

The potential mechanism of action of this compound in reducing uric acid levels in the body can be explained through several pathways:

- **Inhibition of xanthine oxidase (XO):** XO is the enzyme responsible for converting xanthine and hypoxanthine to uric acid. By inhibiting XO, this compound can prevent the formation of uric acid from these precursors, thereby reducing uric acid levels in the body (Fatmawati et al., 2022).

- **Uric acid transporter inhibition:** Some compounds, such as probenecid and benzbromarone, inhibit uric acid reabsorption from the kidney's proximal tubule. This is achieved by blocking the activity of specific transporters, such as SLC22A12 (URAT1) and SLC2A9 (GLUT9), which are involved in uric acid transport (McDonagh et al., 2014).
- **Increased uric acid excretion:** Other compounds, such as febuxistat and allopurinol, reduce uric acid formation in the body. By inhibiting the xanthine oxidase enzyme, this drug can reduce uric acid production, which ultimately causes a decrease in uric acid levels in the body (McDonagh et al. 2014; Gaubert et al. 2020).
- **Antioxidant effect:** Uric acid has antioxidant properties because it can donate electrons and reduce oxidative stress. Some studies suggest that uric acid may have neuroprotective effects due to its antioxidant properties, potentially contributing to its ability to reduce uric acid levels (Fatmawati et al., 2022; Nur & Sumiwi, 2020; Sugano et al., 2019).

Supporting Evidence from In Vitro and In Vivo Studies

In vitro research shows that *A. flava*, a herbal medicine containing flavonoids, can inhibit xanthine oxidase, which produces uric acid in the body. The ethanol extract of *A. flava* leaves and stems is known to have xanthine oxidase inhibitory activity, with IC50 values of 174.62, 30.44, and 24.03 ppm for leaves, stems, and allopurinol (positive control) respectively (Fatmawati et al., 2022). These findings suggest that *A. flava* may effectively lower uric acid levels and potentially treat hyperuricemia, a condition associated with gout and other health problems. In vivo, research on 70 female Wistar rats divided into seven groups where three groups were given yellow root boiled water and, three groups were given yellow root brackish water boiled with doses equivalent to 1.25 g/kg BW, 2.5 g/kg BW, and 5 g/kg BW of dry yellow roots. In contrast, the control group was only given Aquadest. After 28 days of treatment, it showed that boiled yellow root (*A. flava* (L.) Merr.) water significantly changed *blood urea nitrogen* (BUN) levels between groups. The group given the brackish water decoction did not show any significant changes, except at the highest dose (Pramono et al., 2020).

Clinical Studies and Side Effects

Clinical studies involving the use of *A. flava* in patients with hyperuricemia or related conditions have focused on xanthine oxidase inhibitory activity. The study determined the effectiveness of the ethanol extract of *A. flava* leaves and stems in inhibiting xanthine oxidase, with the IC 50 value of the ethanol extract of *A. flava* stems being lower than that of the leaves. This indicates that the stems of *A. flava* may be better able to reduce uric acid levels than the leaves. However, more research is needed to fully understand the potential benefits of *A. flava* in managing hyperuricemia and related conditions (Fatmawati et al., 2022). Another study published in the Indonesian Journal of Cancer Chemoprevention 2020 investigated the cytotoxicity of ethanol extract of yellow root (*Arcangelisia flava*) on HepG2 hepatocellular cancer cells. The study found that the extract had cytotoxic activity against HepG2 cells, but no information was provided regarding the side effects or safety of the extract (Fatmawati et al., 2022). A study published in the Journal of Pharmacognosy and Phytochemistry in 2013

evaluated the antidepressant effects of a water-soluble A. flava extract on mice. The results showed that the extract had antidepressant effects, but no information was provided regarding the side effects or safety (A et al., 2015). In summary, although some evidence suggests that *A. flava* has medicinal properties, its safety and side effects have yet to be widely studied. Available information suggests that brackish water decoctions may be safer than water decoctions. However, more research is needed to fully understand the safety and side effects of using these plants for medicinal purposes.

Clinical implications of this study and future research directions

The clinical implications of *A. flava* research are significant due to its potential as a source of natural compounds with therapeutic properties. This plant is traditionally used to treat various ailments, including jaundice, liver disease, diarrhea, fever, and inflammation. The latest research aims to identify phytochemical compounds in 70% ethanol extract of *A. flava* stems using LC-MS/MS and in-silico tools. The results of this research may lead to the development of new drugs or therapeutic agents to treat this condition. Regarding future research directions, several areas could be explored. One potential direction is to investigate the anti-osteoarthritis properties of *A. flava*. Previous research used LC-MS/MS analysis to identify compounds present in plants, which were then used as ligands in molecular docking to investigate their binding to target enzymes. This approach can be further developed to identify new compounds with potential therapeutic effects in osteoarthritis (Pratama et al., 2023).

Another area of research is exploring the potential of *A. flava* as an insecticide or acaricide. This plant has been proven to have antibacterial activity against *Bacillus subtilis* and *Escherichia coli*, so it has potential as a natural pesticide (Diliarosta et al., 2021). Future research could focus on isolating and identifying the specific compounds responsible for this activity and developing them as environmentally friendly alternatives to synthetic pesticides. In addition, the potential of *A. flava* as a source of antimicrobial compounds can be further explored. Previous research shows that plant alkaloid extracts can potentially treat fungal skin infections caused by *Candida albicans* and *Trichophyton mentagrophytes* (Suratno et al., 2019). Further research could focus on isolating and identifying the specific compounds responsible for this activity and developing them as new antimicrobial agents. Overall, research on *A. flava* has significant clinical implications and provides a foundation for future research directions in developing new therapeutic agents and natural pesticides.

CONCLUSION

Arcangelisia flava is a plant studied for its potential as an anti-hyperuricemia therapy characterized by increased uric acid levels in the blood. Based on existing findings, the use of *A. flava* shows promising effects in reducing uric acid levels in the blood. Studies have found that the active compounds in *A. flava*, such as flavonoids, alkaloids, and saponins, have anti-inflammatory properties and inhibit enzymes involved in uric acid production. Recommendations for using *A. flava* as anti-hyperuricemia therapy include its use in extract or supplement form, with doses adjusted individually. However, further research is needed for broader use to verify its effectiveness, determine appropriate dosage, and evaluate possible side effects. In clinical practice, consultation with a healthcare professional before taking *A. flava* or any other supplement is essential,

especially for individuals with underlying medical conditions or taking other medications. Additionally, a holistic approach that includes healthy lifestyle changes, such as a low-purine diet and regular exercise, may also be recommended to manage hyperuricemia.

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