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**Review Article: Systematic Review, Meta-Analysis, Integrative Review, Scoping Review**

# THE EFFECT OF FLAVONOIDS IN PLANTS AS ANTIHYPERURICEMIA: A LITERATURE REVIEW

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## Abstract

**Background:** Hyperuricemia is a condition on the level of uric acid in the blood increases, it is more than 6.0 mg/dL in women and more than 7.0 mg/dL in men and is currently a public health problem because of its increasing prevalence. Hyperuricemia is believed to have contributed to an increased risk of mortality and morbidity associated with various diseases such as metabolic syndrome, kidney disease, cardiovascular disease, etc. Flavonoids in plants can be used to help treat hyperuricemia due to it is believed to have low side effects.

**Objective:** The aim of this article was to review the effect of flavonoids on plants as anti-hyperuricemia.

**Design:** The design used in preparing this manuscript is a literature review by reviewing articles on the impact of flavonoids as anti-hyperuricemia.

**Data Sources:** Sources of information were obtained from research articles from 2004-2023 which were accessed through PubMed, Scopus, Sciendirect, SpringerLink, and Google Scholar.

**Review Methods:** In the process of selecting articles to ensure the quality of the articles used in preparing this article, the authors used the PRISMA method. In addition, to avoid biased research results, the researchers carried out tests using the Joanna Briggs Institute (JBI) checklist. The authors independently reviewed study abstracts obtained through searches of five databases. In carrying out data extraction, the author held discussions to find out the results of the extraction.

**Results:** In this article, 15 in vivo studies related to the effect of plants containing flavonoids (kaemferol, luteolin, apigenin, rutin quercetin, morin, butein, vitexin, etc.) on reducing uric acid levels by various mechanisms from previous studies. The 15 articles used in preparing this literature review have met the requirements for use and avoided biased research results.

**Conclusion:** Based on several studies reported that flavonoids have an effect on lowering uric acid levels by inhibiting xanthine oxidase (XO) activity, affecting the expression of uric acid transporters in the kidneys which contribute to the increase of excretion of uric acid in urine.

**Keywords:** *Flavonoids, Anti-Hyperuricemia, Uric Acid, Kidneys*



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## INTRODUCTION

Hyperuricemia is a condition where there is an increase of uric acid levels in the blood. Uric acid is the end product of purine metabolism in the body (Gustafsson & Unwin, 2013). Uric acid levels are classified as normal if they range from 2.6 mg/dL to 5.7 mg/dL in women and 3.5 mg/dL to 7 mg/dL in men

(Chen et al., 2016). Currently, hyperuricemia is a public health problem because the prevalence of hyperuricemia has continued to increase over the last 40 years (Edwards, 2009) and has increased to 10% in the world population (Gulab, 2016). The prevalence of hyperuricemia in China is 21% of total population, Italia is 6,7-9,1% (from 2005-2009) and Australia is reaching 16.6% of total population (Hong Liu et al., 2014; Ting et al., 2016; Trifirò et al., 2013).

Hyperuricemia can be caused by decreased excretion of uric acid and increased production of uric acid in the body (Choi, H.K., Mount, DB., Reginato, 2005; Dong et al., 2017; Ichida et al., 2012). Besides, factors that contribute to increase the uric acid levels include modern lifestyles and Western diets (consumption of foods high in purines, alcohol, and foods high in sugar), socioeconomic factors, gender, Body Mass Index (BMI), obesity (which contribute to increased uric acid secretion) and hypertension (C. F. Kuo et al., 2015; Raja et al., 2019; Rho et al., 2011; Tsushima et al., 2013). Epidemiological studies have reported that hyperuricemia is proven to be a factor that can increase the risk of morbidity and mortality associated with several diseases, including hypertension, diabetes mellitus, dyslipedemia, kidney disease, cardiovascular disease and heart failure (Bardin & Richette, 2014; Dong et al., 2017; Gustafsson & Unwin, 2013; Qiu et al., 2013).

Currently, the use of plants containing flavonoids is widely used in the health sector, various studies related to flavonoids are being developed because flavonoids have many benefits and are often used as an alternative or complementary to treat various diseases. In addition to having many benefits, flavonoids are easy to find because of their abundance in plants and have relatively cheap prices (Robinson & Zhang, 2011). onoids have naturally occurring compounds in plants that can be found in vegetables, fruits, and whole grains. Flavonoids contain secondary metabolites that have been shown to have properties of antioxidant, anti-inflammatory, anti-allergic, anti-cancer, anti-diabetic and anti-hyperuricemic (Abu Bakar et al., 2018; Al-Ishaq et al., 2019; Ekalu, 2020; Maheswari et al., 2016).

The content of flavonoids in plants can be found in all parts, such as roots, stems, leaves, flowers or fruit. The types of flavonoids that are commonly found in plants include apigenin, luteolin, quercetin, genistein, and rutin where these flavonoids are classified into several sub-classes (Panche et al., 2016). Flavonoids have potential as an alternative treatment of hyperuricemia, because flavonoids are believed to reduce uric acid levels (Siciliano et al., 2004). Previous research has stated that flavonoids can inhibit the activity of the xanthine oxidase enzyme, which inhibit xanthine oxidase.

Another research also reported that administration of the flavonoid (quercetin) for 4 weeks at a dose of 500 mg/day to 22 male respondents who had hyperuricemia, showed a decrease in uric acid levels by 26 µM (Y. Shi & Williamson, 2016), administration of the flavonoid luteolin can reduce xanthine oxidase activity so that can reduce uric acid levels (Yan et al., 2013) and administration of apigenin at a dose of 50 mg/200 g/BW and 100 mg/200 g/BW for 7 days can inhibit xanthine oxidase enzyme activity in normal and hyperuricemic rats (Huang et al., 2011).

Based on the statements above, the authors prepared this literature article with the aim of conducting a review regarding the effect of flavonoids in plants as anti-hyperuricemia.

## METHODS

### *Design*

This manuscript was prepared using a Literature Review design.

### *Search Methods*

Sources of information used to search for literature or articles were obtained from PubMed, Scopus, Sciendirect, SpringerLink, and Google Scholar. It searched for published articles from 2004 to 2023. Keywords for searching published articles included

"Flavonoids" OR "Luteolin" OR "Apigenin" OR "Quercetin" OR "Rutin" OR "Kaemferol" OR "Medicinal Plants" OR "Uric Acid" OR "Hyperuricemia" OR/ And "Xanthine Oxidase".

*Search Outcome*

Based on data obtained from five literature search databases, there were 183 articles that matched the keywords set by the authors. After conducting an initial review through abstracts that were in accordance with the objectives of preparing this literature review, 50 articles were obtained that were suitable and could be accessed in full text. After that, the authors carried out another review regarding the inclusion criteria in the form of articles used that were the results of in vivo research. From this selection, 15 articles were obtained which were used in preparing this literature review. The flow of the article selection process used in this literature review is presented in Figure 1 below.

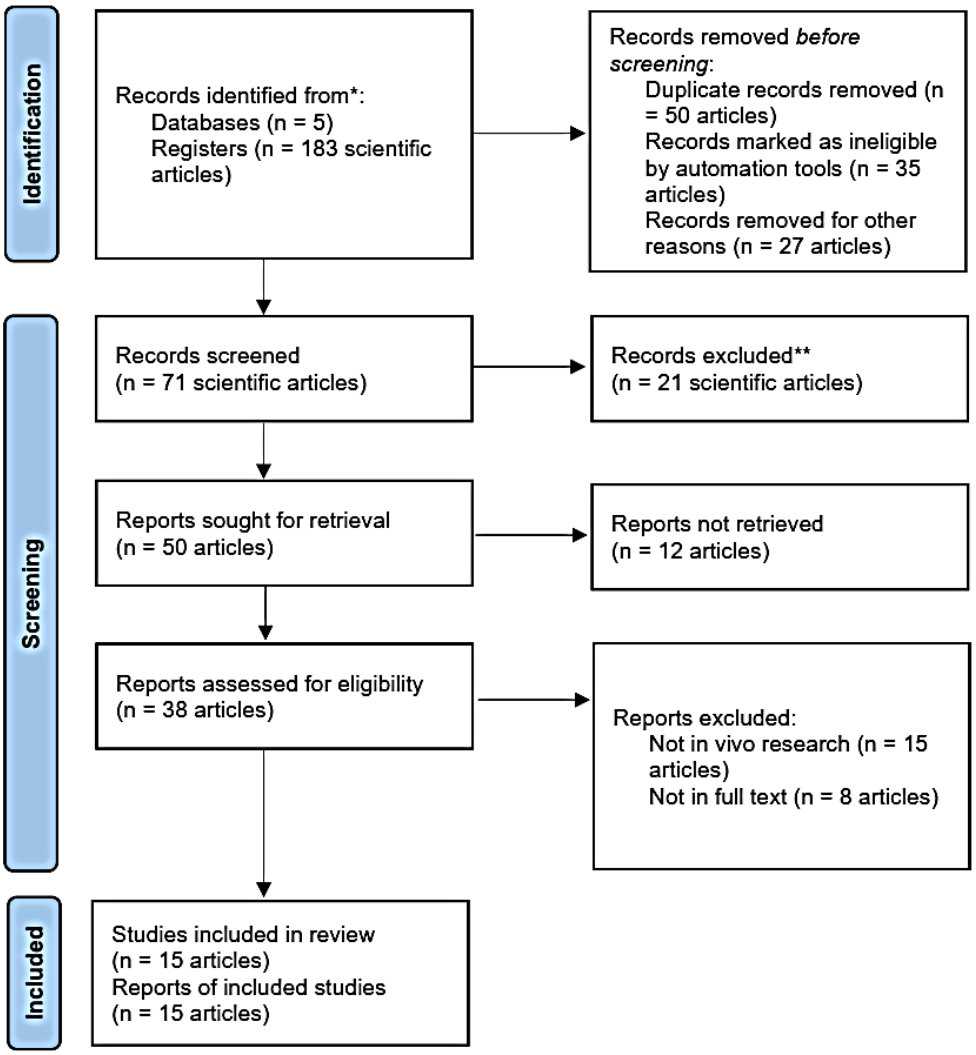


**Figure 1.** Flow Diagram for Identifying Scientific Articles used in Preparing Literature Reviews

*Quality Appraisal*

The author is guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) method in conducting Quality Appraisal assessments. Apart from that, the authors also used The Joanna Briggs Institute (JBI) checklist in assessing the risk of bias of the articles used. After conducting a Quality Appraisal using the PRISMA Methods and JBI Checklist, all

articles used in preparing this literature review met the requirements and did not show bias in the research results.

*Data Abstraction*

The authors independently reviewed research abstracts obtained through searches of five databases. After obtaining the full texts of relevant articles, the authors carried out data extraction independently using standard data extraction templates. In carrying out the data extraction, the authors held discussions to determine the results of the extraction.

*Data Analysis/ Synthesis*

The research used in preparing this literature review was fifteen articles which were the results of in vivo research. The results of data analysis from the fifteen articles are presented in Table 1 below.

## RESULTS

Based on the results of selecting articles used in this literature review, it was found that 15 scientific articles met all the criteria set by the authors of which 15 scientific articles are the results of in vivo research. An overview of the 15 scientific articles can be seen in **Table 1** below.

**Table 1.** *In Vivo* Study The Effect of Flavonoid on the Decrease of Uric Acid Level.

| Source | Bioactive Compound | Dose | Results | Mechanism |
|---|---|---|---|---|
| *Toona Sinensis* (Yuk et al., 2018), Korea. | Rutin, isoquercetin, pentagalloyl glucose, quercetin, afzelin. | 300 mg/kg. | Isolates of bioactive compounds from *Toona sinensis* can reduce uric acid levels in rats induced by hyperuricemia with potassium oxonate. | It inhibits xanthine oxidase (XO) activity. Inhibitory potency 96.4% (pentagalloyl glucose), isoquercetin (47.8%), rutin (42.9%), quercetin (38.9%) and afzelin (31.7%). |
| *Aster Glehni* (Park et al., 2018), Korea. | Quercetin. | 50, 100 and 200 mg/kg for 7 days intervention. | It can decrease uric acid level in hyperuricemic rats by 0,50 mg/Dl (dose of 50), 3m53 mg/Dl (dose of 100), 3,00 mg/Dl (200) dose. | It inhibits the activity of xanthine oxidase. |
| *Perilla Frutescens* (Huo et al., 2015), China. | Apigenin. | 500,1000 and 2000 mg/kg for seven days. | It can reduce uric acid level from 300,7µmol/L to be 193,7 7µmol/L (500 dose), 188,77µmol/L (1000 dose), and 1317µmol/L (2000 dose). | It inhibits the activity of xanthine oxidase. |
| *Urtica Hyperborean* (Han et al., 2020), China. | Flavonoid (no specific kind of flavonoid). | 0,78 and 2,34 mg/kg for seven days. | It can decrease uric acid level. | It decreases XOD (xanthine oxidase dehydrogenase) activity and ADA (adenosine deaminase), reduces URAT1 expression and increases OAT1 (uric acid transporter). |
| *Gnaphalium Affine* (Lin et al., 2018), China. | Luteolin 4-O-glucoside. | 20, 40, 100 mg/kg for seven days. | It can increase of renal excretion of uric acid in the kidney of hyperuricemia rats. | It has the effect of uricosuric (increases the excretion of uric acid through urine) in hyperuricemic rats by reducing the expression of the organic ion transporter (URAT1) in the liver and inhibits the activity of the xanthine oxidase enzyme. |

| | | | | |
|---|---|---|---|---|
| *Petroselinum Crispum* (Haidari et al., 2011), Iran. | Quercetin and kaemferol. | 5 mg/kg for 14 days. | It can reduce uric acid levels, increase antioxidant capacity and increase MDA in hyperuricemic rats. | It has hyperuricmia effect by inhibiting of xanthine oxidase and xathine dehydrogenase (XDH) activity. |
| *Marantodes Pumilum* (Rahmi et al., 2020), Malaysia. | Myricetin, quercetin and kaemferol. | 250mg/kg for 14 days. | It can reduce uric acid levels, (anti-hyperuricemia) and inhibit the inflammation of gout (anti-inflammatory) in the rat that has been induced. | It has hyperuricemic effect by inhibiting xanthine oxidase activity in the liver and uricosuric effect, while anti-inflammatory effect by inhibiting cytokines and PGE2 (prostaglandin E2). |
| *Ramulus Mori* (Y. W. Shi et al., 2012), China. | Morin, quercetin, butein, kaemferol. | 10, 20 dan 40 mg/kg for 7 days. | It can reduce uric acid, BUN and creatinine levels in hyperuricemic rats. | It has a uricosuric effect by downregulating renal URAT1 and GLUT9 expression and renal mOAT1 expression contributing to increased uric acid excretion. |
| *Sonneratia Apetala* (I. T. Jang et al., 2014), Korea. | Vitexin dan isorhamnetin. | 50, 100 dan 200 mg/kg for 7 weeks. | It can reduce levels of uric acid, BUN, d, creatinine and can regulate kidney uric acid transporter in rats that have been induced by potassium oxonate. | It inhibits XO activity in the liver, reduces the expression of URAT1 and URAT9 and increases OAT1 in the process of inhibiting uric acid production and increasing uric acid excretion in the kidneys. |
| *Lippia Nodiflora* (Cheng et al., 2015), Malaysia. | 6-hydroxyluteolin, 6-hydroxyluteolin-7-O-glycoside, nodifloretin. | 200 mg/kg for 10 days. | It can reduce uric acid levels in hyperuricemic rats. | It inhibits xanthine oxidase and xathine dehydrogenase activity and increases uric acid excretion in the kidneys. |
| *Apium Graveoluolens* (Dolati et al., 2018), Iran. | Apiin dan apigenin. | 250,500 and 1000 mg/kg. | It can reduce uric acid levels in hyperuricemic rats. | It inhibits of xanthine oxidase and xathine dehydrogenase activity in the liver. |
| *Hibiscus Sabdariffa* L. (C. Y. Kuo et al., 2012), Taiwan. | Catechin. | 1%,2% and 5% for 5 weeks. | It can reduce uric acid levels in hyperuricemia induced potassium oxonate. | It decreases uric acid levels by inhibiting xanthine oxidase activity and increasing uricase activity to increase uric acid excretion. |
| *Plumeria Rubra* (Mohamed Isa et al., 2018), Malaysia. | kaempferol-3-O-glucoside, kaempferol-3-rutinoside, kaempferol, quercetin 3-O-α-L-arabinopyranoside, quercetin. | 50,100 and 200 mg/kg for 7 days. | It can reduce uric acid levels in hyperuricemic rats. | It inhibits the activity of xanthine oxidase. |
| *Tinospora Crispa* (Harwoko & Warsinah, 2020), Indonesia. | Rutin. | - | It can reduce uric acid levels in hyperuricemic rats induced by potassium oxonate. | It inhibits the activity of xanthine oxidase. |
| *Biota Orientalis* (Zhu et al., 2004), Iran. | Quercetin dan rutin. | 50 mg/kg (quercetin), 100 mg/kg (routine). | It can reduce uric acid levels in hyperuricemic rats induced by potassium oxonate. | It inhibits the activity of xanthine oxidase. |

## DISCUSSION

*Hyperuricemia*

Hyperuricemia is a condition in which uric acid levels exceed normal values. Normal uric acid levels in humans are 2.6-5.7 mg/dL for premenopausal women and 3.5-7.0 mg/dL for men and postmenopausal women (Desideri et al., 2014; Khanna, 2012; Zhu, Y., Pandya, B., Choi, 2011). Increased of uric acid level in the blood can be caused by excessive uric acid production, decreased uric acid excretory function in the kidneys or a combination of both (Merriman, 2015; Su et al., 2014). Decreased uric acid excretory function in the kidneys can be caused by acute or chronic kidney disease, acidosis (ketoacidosis, lactic acidosis), drugs/toxins (diuretics, niacin) and hyperthyroidism (Dong et al., 2017).

Uric acid is the final product of purine metabolism that forms biological particles such as DNA, RNA, ATP and GTP (Chen et al., 2016). Endogenous purine products are estimated to be around 500-600 mg/day, while exogenous purine intake from food is around 100-200 mg/day (Desideri et al., 2014). The biosynthesis of uric acid in the body is catalyzed by the enzyme xanthine oxidase (XO), which is also known as xanthine oxidoreductase (XOR). XO enzyme is an enzyme that converts hypoxanthine to xanthine and then converts xanthine to uric acid. If the enzyme activity is not inhibited, it can increase uric acid levels in blood serum (Grabowski et al., 2010). In the body, the kidneys play a key role in maintaining the balance of uric acid metabolism. The kidneys excrete 70% of the uric acid produced daily and 30% are excreted through the digestive tract. If the body is in excess of purines and the excretion of uric acid in the kidneys decreases, it will lead to the hyperuricemia **(Figure 2).**

Meanwhile, the increase of production of uric acid can be caused by: 1). High-purine diet. The intake of foods and beverages containing purines will cause more purines to be metabolized and produce uric acid (Chen et al., 2016; Villegas et al., 2012); 2). Other studies have also reported that an increase in meat and seafood consumption, followed by an increase in uric acid level (Yu et al., 2008); 3). Alcohol consumption. The consumption of alcohol is related to the increase of lactic acid and ketones and cause dehydration and decrease uric acid excretion in the kidneys (M. Wang et al., 2013). 4). Fructose consumption. Previous studies reported that fructose consumption can increase uric acid levels through the degradation process of ATP (H. K. Choi & Curhan, 2008). In addition, fructose consumption can also increase the risk of insulin resistance and hyperinsulinemia which can cause a decrease in uric acid excretion (H. K. Choi et al., 2010).

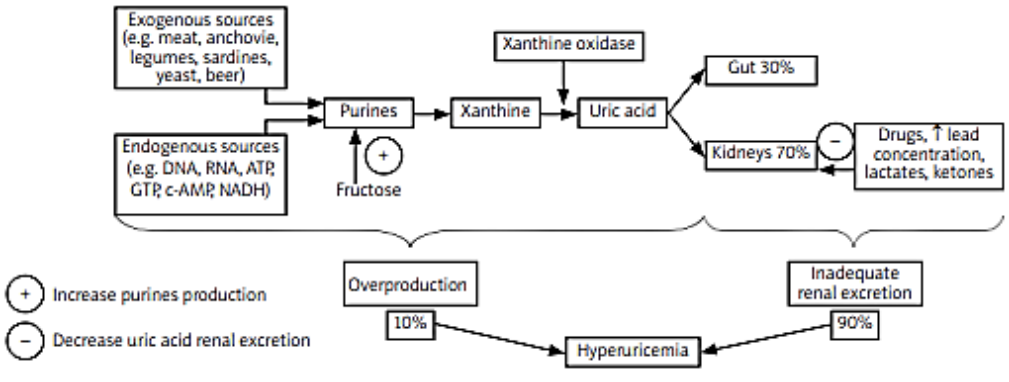


**Figure 2.** Mechanism of Hyperuricemia (Skoczyńska et al., 2020)

Other factors that can increase the risk of hyperuricemia include: Gender and BMI. Gender also affects the occurrence of hyperuricemia. The results of previous studies reported that men have a higher risk of hyperuricemia than women, this is because

women have the hormone estrogen. The hormone estrogen has a role in increasing the excretion of uric acid and preventing the appearance of arthritis in women (Hak et al., 2010; C. F. Kuo et al., 2015). BMI also has a risk of increasing the incidence of hyperuricemia. A cross-sectional study in Hong Kong, stated that BMI and waist-to-hip ratio were also closely related to hyperuricemia. There are 2 factors associated with BMI and obesity, including excessive uric acid production and low uric acid excretion(Tanaka et al., 2015; Honggang Wang et al., 2014). The previous studies in obese experimental animals showed an increase in XO enzyme activity in white adipose tissue. Adipose tissue is produced and secretes uric acid, which ultimately contributes to the increase of serum urate levels in obese rats (Tsushima et al., 2013).

Currently, hyperuricemia has been shown to be a co-morbidity of several diseases. Several studies have proven that hyperuricemia is a risk factor for hypertension, heart failure, ischemic heart, and stroke (Storhaug et al., 2013; Zalawadiya et al., 2015). A study showed that respondents with uric acid levels > 7 mg/dL (Male), will increase the risk of hypertension by up to 80% (Benn et al., 2018). Hyperuricemia can cause hypertension by blocking the production of Nitric Oxidative (NO). NO can induce vasodilation to increase bloodstream, blood vessels, reduce the proliferation of vascular smooth muscle cells and modulate thrombosis thus playing an important role in protecting blood vessels (Förstermann et al., 2017).

The development of hypertension will also increase the risk of CAD (Coronary Artery Disease) in hyperuricemic patients (Baker et al., 2007; Wu et al., 2017). Hyperuricemia can contribute to lipid peroxidation and increase cholesterol oxidase which plays a role in the development of atherosclerosis and will be associated with the incidence of CAD (Coronary Artery (Gómez et al., 2014).

Another diseases which associated with hyperuricemia are kidney disease Ather diseases which associated with hyperuricemia are kidney disease, gout and metabolic syndrome disease (Abbasian et al., 2016; H. Choi et al., 2016; Shih et al., 2015; Hongsha Wang et al., 2018; H. Yuan et al., 2015). The mechanism of hyperuricemia in increasing kidney disease (CKD) is through increased oxidative stress caused by NADP (Nicotinamide Adenine Dinucleotide Phosphate) and xanthine oxidase (Bove et al., 2017; Li et al., 2016) and reduces the production and bioavailability of notric oxide (NO) and induces endothelial dysfunction (Y. J. Choi et al., 2014). Uric acid can also increase the production of inflammation including IL-1, IL-6 and cause glomerular hypertrophy and renal tubular fibrosis (Huifang Liu et al., 2017; Romi et al., 2017).

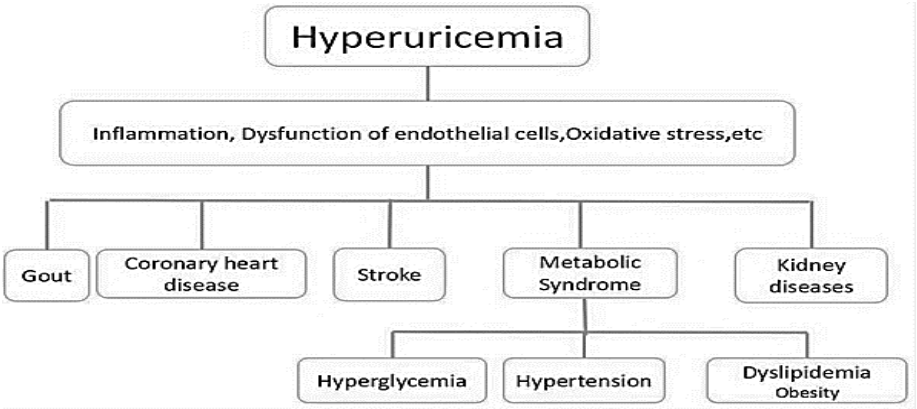


**Figure 3.** Diseases caused by Hyperuricemia (Hongsha Wang et al., 2018)

Metabolic syndrome is characterized by five health disorders, including abdominal obesity, hypertension, hypertriglyceridemia, dyslipidemia and diabetes mellitus (Alberti et al., 2009; Grundy, 2007). Previous studies reported that men who have uric acid > 7 mg/dL will have a 1.6-fold risk of developing metabolic syndrome compared to men with low uric acid levels and women who have uric acid levels >4.6 mg/dL are at risk have metabolic syndrome 2 times compared to women with low uric acid levels (Sui et al., 2008).

The decrease of excretion of uric acid in the kidneys is the first mechanism in developing metabolic syndrome. The second mechanism is impaired endothelial function which can lead to decreased release of nitric oxide (NO) from endothelial cells (Khosla et al., 2005). ). Uric acid can reduce insulin resistance (IR) by suppressing NO bioavailability, whereas hyperinsulinemia contributes to hyperuricemia by decreasing uric acid secretion in the kidneys and increasing uric acid-producing substrates (Kodama et al., 2009). The third mechanism, involving inflammation and oxidative changes in adiposity induced by uric acid, results in the metabolic syndrome (Sautin et al., 2007). The IR caused by an increase in the uric acid level causes the accumulation of liver lipids which is the main cause in the development of NAFLD. NAFLD is not merely associated with the metabolic syndrome but also functions as a manifestation of liver disease, oxidative stress that is directly caused by high uric acid and inflammatory processes **(Figure 4)**.

*Flavonoids for Hyperuricemia*

Flavonoids are natural compounds found in plants and flavonoids contain secondary metabolites that are antioxidants (Maheswari et al., 2016). Flavonoids are found in many fruits, vegetables, nuts, seeds, cocoa, roots, stems, flowers, tea, and red wine (Pérez-Cano & Castell, 2016). Flavonoids can be classified into various classes, including anthocyanins, chalcones, flavanones, flavones, flavonols, and isoflavonoids (Treml & Šmejkal, 2016).

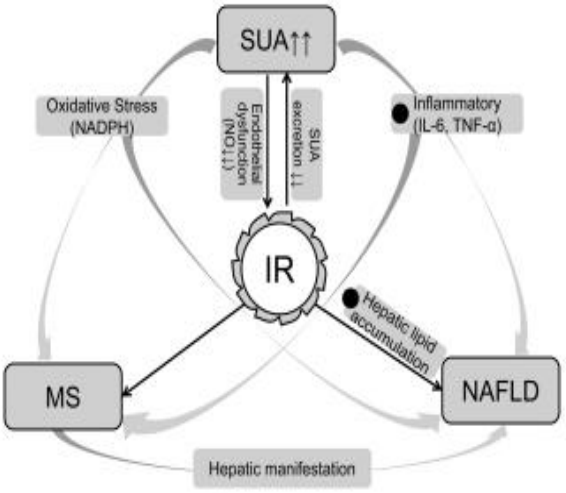


**Figure 4.** Mechanism Hyperuricemia for Metabolic Syndrome (H. Yuan et al., 2015).

Flavonoid is related to various health benefits, so flavonoid is often used in various nutraceutical, pharmaceutical, medicinal, and cosmetic (Panche et al., 2016; Romano et al., 2013). Flavonoid has antioxidant, anti-inflammatory, antimutagenic, and anti-carcinogenic properties and has the capacity to modulate the function of cellular enzymes. Besides, flavonoid also has function as inhibitors for several enzymes, such as XO, COX *(cyclo-oxygenase), lipoxygenase and phosphoinositide 3- kinase* (Ekalu, 2020). Currently, 65-80% of people in developing countries use flavonoids contained in plants as a complement or alternative to treat disease (Robinson & Zhang, 2011). Flavonoids are widely used because they have lower side effects compared to chemical drugs.

Several studies have indicated that the flavonoids contribute to anti-hyperuricemia activity by reducing uric acid levels and inhibiting the activity of the xanthine oxidase enzyme (De Souza et al., 2012; M. G. Jang et al., 2019; Spanou et al., 2012). This is evidenced by previous studies that reported that flavonoid in *Pleoratus* extract, *Momdica charantia ostreatus* extract and extract Red guava (*Psidium guavajana* Linn.) in rats

induced to hyperuricemia has been shown to reduce uric acid levels through inhibition of xanthine oxidase activity (Alsultanee et al., 2014; I. Jang et al., 2014). Other studies reported that administration of *T. crispa* stem extract at a dose of 100 mg/kg was able to reduce uric acid levels in hyperuricemia rats induced by potassium oxonate. This is influenced by the high content of flavonoids (31.08%) in the stem extract of *Tinospora crispa* which has the potential as a uricostatic in the treatment of gout (Harwoko & Warsinah, 2020). Secondary mechanism of flavonoid to anti-hyperuricemia that have high inhibitory in reducing the activity of the xanthine oxidase enzyme. Plants that have low flavonoid content may not be able to optimally reduce xanthine oxidase inhibition 50. The presence of methylation of hydroxyl and hydroxylation groups at positions C5 and C7, as well as glycosylation and hydrogenation of C2=C3 in ring B contained in flavonoids are believed to inhibit enzyme affinity. xanthine oxidase (M. Yuan et al., 2019) In addition, the presence of a C2=C3 double bond in conjugation with a 4-keto group in the C-ring, an ortho-dihydroxy (catechol) group in the B-ring and a hydroxyl group at position 5 have an important role in the single electron transfer mechanism, so that flavonoids can play a role. in inhibiting XO activity. The results of previous studies also reported that the basic chemical structure of the flavonol group with C2 and C3 double bonds was found to be very influential in the inhibition of high xanthine oxidase activity (Van Hoorn et al., 2002). Other studies reported that the hydroxyl groups C2, C5 and C7 in flavonoids (quercetin) had the effect of suppressing uric acid production by inhibiting xanthine oxidase activity in AML12 (alpha mouse liver 12) (Adachi et al., 2019).

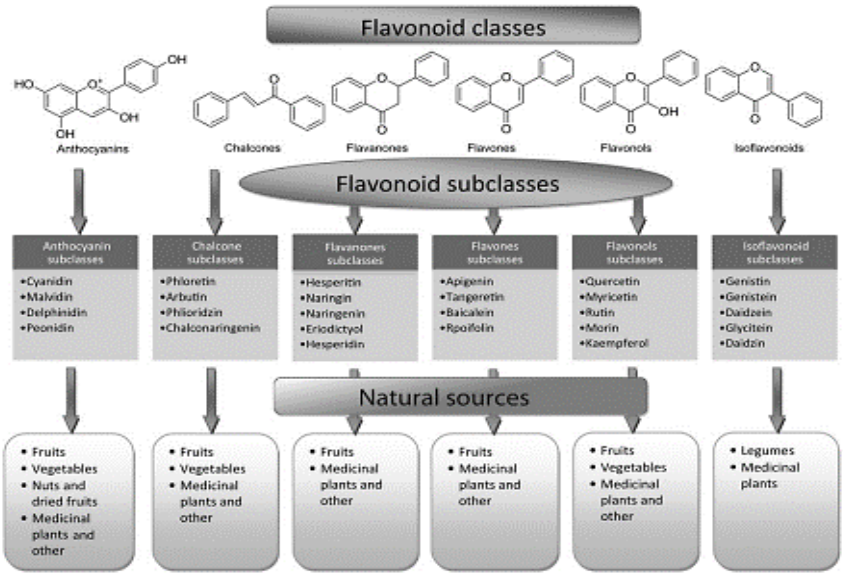


**Figure 5.** Class of Flavonoids (Panche et al., 2016)

Another mechanism of flavonoids can decrease of uric acid by increasing the excretion of uric acid in the kidneys (S. Wang et al., 2019). This is evidenced by several previous studies reporting that flavonoid (chrysin/(5,7-dyhydroxyl) has anti-hyperuricemic effect, regulates the expression of URAT1, GLUT9, OAT1 and ABCG2 in increasing uric acid excretion and has anti-inflammatory effect in hyperuricemic rats by increasing IL concentration. -1β and reduce oxidative stress The administration of mangiferin from the leaf isolate of Mangufera indica L. can increase uric acid excretion and inhibit uric acid reabsorption by inhibiting the regulation of transporter expression in the kidney (reducing the expression of URAT1, GLUT9 and OAT10) (I. Jang et al., 2014), *Tinospora cardifolia* stem

extract can reduce uric acid levels through its uricosuric effect by inhibiting the expression of the uric acid transporter(Shah & Shah, 2015) and other studies reported that biactive compounds (flavonoids) play a role in regulating the expression of the uric acid transporter (Jiang et al., 2020) **(Figure 6)**.

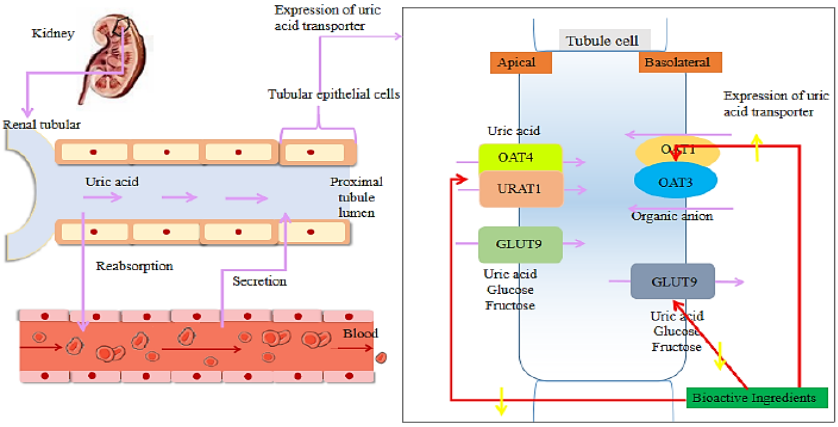


**Figure 6.** Effect of bioactive compounds on uric acid transporters in the kidney (Jiang et al., 2020)

## CONCLUSION

Based on several studies reported that flavonoids have an effect on lowering uric acid levels by inhibiting xanthine oxidase (XO) activity, affecting the expression of uric acid transporters in the kidneys which contribute to the increase of excretion of uric acid in urine. Based on the results of the review that has been carried out, further research is needed to produce a nutraceutical product to help treat hyperisemia.

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## DECLARATION OF CONFLICTING INTEREST

The authors declare that they have no conflict of interest in the preparation of this manuscript.

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## AUTHOR CONTRIBUTION

**Diah Pitaloka Putri:** Contribution in design, perform collecting article and analyze the literature.

**Kusuma Wijaya Ridi Putra:** Contribution for discussed the results and contributed to the final manuscript.

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