International Multidisciplinary Research Journal 2023, 13: 25-31
doi: 10.25081/imrj.2023.v13.8731
https://updatepublishing.com/journal/index.php/imrj

Review Article

ISSN: 2231-6302

Role of Flavonoids in Combating Hyperuricemia

Basavaraj Gorrjanal[1], B. M. Monika[1], R. Mythreyi[1], Karthikeyan Muthusamy[2], Karthikeyan Murugesan[3], Anjuna Radhakrishnan[3], S. Jagannathan[4], Boojhana Elango[5], Kanthesh M. Basalingappa[1]*, Maghimaa Mathanmohun[5]*

[1]Division of Molecular Biology, School of Life Sciences- Mysuru, JSS Academy of Higher Education and Research, Mysuru-570015, Karnataka, India, [2]Department of Bioinformatics, Science Campus, Alagappa University, Karaikudi-630003, Tamil Nadu, India, [3]Department of Microbiology, Faculty of Medicine and Health Sciences, Quest International University, Malaysia, [4]Pasteur Institute of India, Coonoor-643103, The Nilgiris, Tamil Nadu, India, [5]Department of Microbiology, Muthayammal College of Arts and Science, Rasipuram, Namakkal-637408, Tamil Nadu, India

Received: September 27, 2023
Revised: December 25, 2023
Accepted: December 26, 2023
Published: December 30, 2023

***Corresponding Authors:**
Kanthesh M. Basalingappa
E-mail: kantheshmb@jssuni.edu.in
Maghimaa Mathanmohun
E-mail: maghimaam@gmail.com

ABSTRACT

Individuals tend to have an increased blood uric acid level at a younger age due to their dietary choices and lifestyle, which can lead to major health concerns such as hyperuricemia, gout, cardiovascular disease, nephropathy, and inflammation. Flavonoids have been proven to have strong inhibitory action against xanthine oxidase and be able to lower serum uric acid levels, levels of adenosine deaminase, gene expressions of renal glucose transporter type 9 (mGLUT9) and uric acid transporter 1 (mURAT1), along with increased expression of organic anion transporters (mOAT1 and mOAT3) and organic cation transporters (mOCT1 and mOCT2). Furthermore, flavonoids enhanced renal function and antioxidant activity in hyperuricemic rats. In hyperuricemic mice, genistein reduced renal fibrosis by inhibiting the JAK2/STAT3 and Wnt/β-catenin signaling pathways. Overall, this review reveals that the flavonoids have substantial anti-hyperuricemia and associated disease potential and may be utilized as natural supplements for the treatment of Uric acid-related illnesses.

KEYWORDS: Hyperuricemia, Flavonoids, Xanthine oxidase, Hyperuricemic mice, Urate transporters

INTRODUCTION

Globally, there has been an increase in the prevalence of gout, nephropathy, and cardiovascular disease. The onset of these conditions is associated with elevated purines and high blood uric acid (UA) levels. In purine catabolism, adenosine monophosphate (AMP) can be converted to inosine through two pathways: one involves AMP deaminase (AMPD) to produce inosine monophosphate (IMP), followed by 5′-nucleotidase (5′NT) to generate inosine, while the other employs 5′NT to form adenosine, subsequently utilizing ADA to produce inosine. Purine nucleoside phosphorylase (PNP) further transforms inosine into hypoxanthine. Xanthine oxidoreductase (XOR) plays a role in converting hypoxanthine to xanthine and then to urate. There are two enzyme types in this process: xanthine dehydrogenase (XDH), with a preference for NAD+, and xanthine oxidase (XO), which favors O2. Crucial enzymes in urate production and purine metabolism include ADA and XOR, particularly XO (Figure 1) (Nutmakul, 2022) which results in the formation of UA, a heterocyclic organic compound ($C_5H_4N_3O_4$). The main causes of elevated blood UA levels are UA overproduction and underexcretion. When it reaches certain levels of UA, preferably 7 mg/dL for men or 6 mg/dL for women, hyperuricemia (HUA) is indicated (Feng *et al.*, 2022). HUA is a condition in which there is a high level of uric acid in the blood. The overproduction of uric acid by xanthine hydroxylation, which is catalyzed by xanthine oxidase, is one component that leads to this. This can cause gout and kidney stones, as well as renal inefficacy, oxidative stress, inflammation, and cardiovascular disease. This condition is partially genetic, which causes about 60% of the variability in uric acid levels. Some genes, like the SLC2A9 and ABCG2 genes of the same family, are commonly associated with gout, and diabetes increases the risk. The mutations in these genes lead to loss of function, which is responsible for low uric acid levels in blood serum by reducing urate absorption and unopposed urate secretion from the body (Dalbeth *et al.*, 2017).

Allopurinol, along with its derivative 4-hydroxy pyrazole (3,4-d) pyrimidine (4-HPP), has emerged as a novel and effective

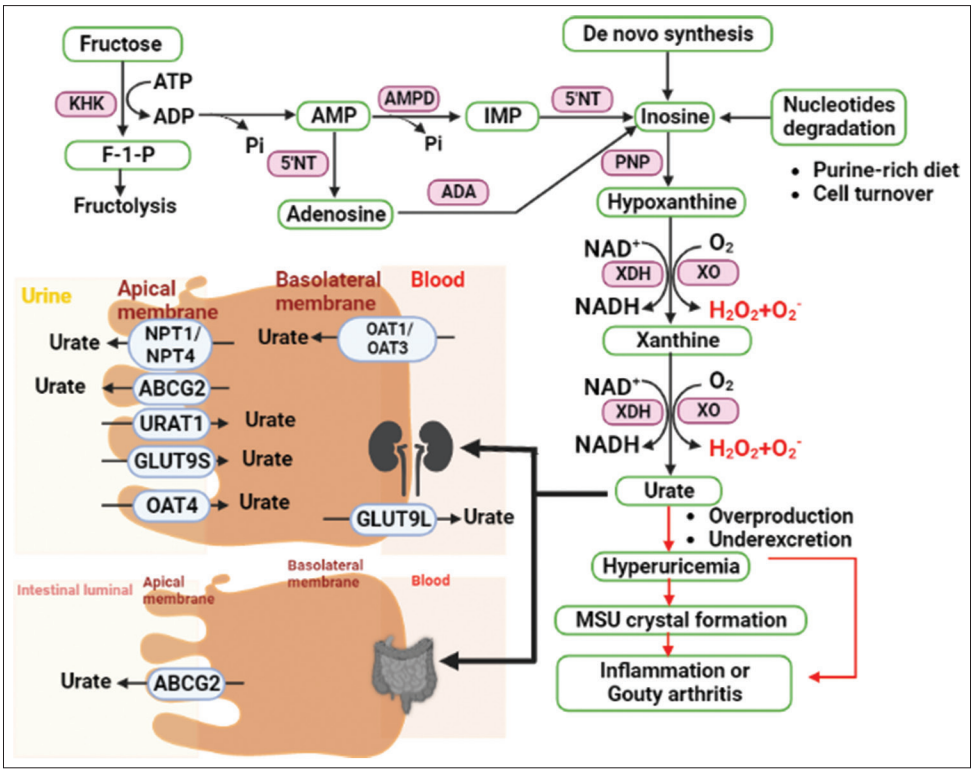

Figure 1: Urate production and excretion in the human body

agent in the treatment of gout, offering promising therapeutic benefits in managing this condition (Rundles *et al.*, 1966). Allopurinol commonly induces hypersensitivity reactions, skin rashes, and gastrointestinal distress as its primary side effects. It's noteworthy that these effects are predominantly observed in individuals with compromised glomerular filtration. Additionally, allopurinol toxicity syndromes may manifest as rashes, fever, deteriorating renal function, vasculitis, eosinophilia, and, in severe cases, can lead to fatal outcomes (Horiuchi *et al.*, 2000). These diseases show signs and symptoms that are more common in elderly patients with renal inefficiency. The safety of children and pregnant women has not been established (Borges *et al.*, 2002). Flavonoids are an important class of natural products, specifically polyphenolic secondary metabolites found in fruits, vegetables, and certain beverages. Flavonoids have been associated with various health-promoting benefits and are integral to numerous applications in nutraceuticals, pharmaceuticals, medicine, and cosmetics. Their significance lies in their ability to regulate crucial cellular enzyme functions, coupled with their antioxidative, anti-inflammatory, anti-mutagenic, and anti-carcinogenic properties. Additionally, flavonoids are recognized for their inhibitory effects on several metabolites, including xanthine oxidase (XO), cyclo-oxygenase (COX), lipoxygenase, and phosphoinositide 3-kinase (Panche *et al.*, 2016). Flavonoids are a kind of low molecular weight phenolic compound found throughout the plant kingdom. Many angiosperm families exhibit numerous flavonoids, which are readily recognizable as flower pigments. However, their distribution extends beyond flowers, encompassing all parts of the plant. Flavonoids feature a C15 skeleton comprising two phenolic rings connected by three carbon units, and their classification is based on the presence of various substituents on the rings and the degree of ring saturation. To enhance their water solubility, flavonoids often attach to a sugar moiety (Omar *et al.*, 2007). Dietary flavonoids are abundant in plant-based foods and beverages like fruits, vegetables, tea, chocolate, and wine. Various subclasses categorize flavonoids, such as chalcones, flavones, flavonols, and isoflavones, each with distinct primary sources.

Classification

Flavonoids are classified into subgroups based on the linkage of the B ring to the carbon of the C ring, as well as the degree of unsaturation and oxidation of the C ring. Isoflavones, for instance, are flavonoids where the B ring is attached to position 3 of the C ring. Neoflavanoids have the B ring linked to position 4, while those with the B ring connected to position 2 can be further categorized into various subgroups based on the structural properties of the C ring. The subgroups include flavones, flavonols, flavanones, flavanonols, flavanols or catechins, anthocyanins, and chalcones (Panche *et al.*, 2016).

FATE OF FLAVONOIDS IN HYPERURICEMIA

Flavonols

Quercetin, morin, myricetin, and kaempferol share a common structural feature—a C-2-C-3 double bond with hydroxyl groups at positions 3–7. Glycosylation at position 7 has been observed to potentially diminish the hypouricemic and

XOD-inhibiting properties of icariin (a compound categorized as a flavonoid). Notably, the absence of the 3-hydroxyl group has been linked to a reduction in the hypouricemic effects of flavones, as demonstrated in compounds such as luteolin. Similarly, the elimination of the 4-hydroxyl group might render flavone (baicalein) ineffective in exerting hypouricemic effects. Structural analyses have revealed the pivotal role of 4-hydroxyl groups in protein interactions, and the hypouricemic actions of quercetin, morin, myricetin, and kaempferol, each possessing 4-hydroxyl groups, are believed to operate by directly reducing XOD activity (Mo *et al.*, 2007).

Rutin

Rutin or (3,3′,4′,5,7-pentahydroxyflavone-3-rhamnoglucoside), is a flavonol present in several plants, including passionflower, buckwheat, tea, and apple. It is an important source of nutrients in food. Rutin, a citrus flavonoid glycoside, is present in buckwheat and is alternatively referred to as rutoside, quercetin-3-rutinoside, and sophorin. The name "rutin" is derived from the plant Ruta graveolens, which also contains this flavonoid (Mo *et al.*, 2007).

Research indicates that rutin exhibits the potential to decrease reactive oxygen species (ROS) production, restore the balance in oxidative stress, inhibit the activation of the NLRP3 inflammasome, and function as an anti-inflammatory agent. In a groundbreaking study conducted by Wu *et al.* (2023) fibroblast-like synoviocytes (FLS) were isolated and identified for the first time. Rutin was observed to effectively inhibit the generation of ROS and the activation of the NLRP3 inflammasome in FLS following uric acid stimulation. The study suggests that rutin could be beneficial in addressing gout by reducing xanthine oxidase (XOD) activity, suppressing ROS production, and modulating the NLRP3 inflammasome (Ganeshpurkar & Saluja, 2017; Wu *et al.*, 2023).

Tea

Tea is notably rich in three main types of flavonoids: flavan-3-ols, commonly known as catechins, oligomeric flavonoids, which include thearubigins and theaflavins produced during the fermentation process, and flavonols, such as quercetin. Green tea is distinguished by six specific monomer catechins that contribute to its chemical composition, including epigallocatechin-3-gallate and epicatechin-3-gallate. These catechins undergo processes during the fermentation of green to black tea, forming dimers called theaflavins (derived tannins), larger molecules referred to as pro-anthocyanidins (condensed tannins), and very large oligomers and polymers known as thearubigens (condensed/derived tannins) (Dwyer & Peterson, 2013).

According to Wu *et al.* (2022) TWEs (tea water extracts) groups exhibited considerably decreased serum levels of uric acid, urea nitrogen, and creatinine induced by HUA. Additionally, the researchers investigated the activity of xanthine oxidase (XOD) in the liver of mice, finding a significant increase in XOD activity in the model group (Wu *et al.*, 2022). The impact of total flavonoid extracts (TWEs) on the regulation of renal uric acid transporters was assessed, examining the expression of uric acid secretion transporters ABCG2, OAT1, OAT3, and uric acid reabsorption transporter URAT1. Treatment with TWEs led to a notable increase in the levels of ABCG2, OAT1, and OAT3 in the kidney, while reducing the levels of URAT1 (Figure 3). The study also analyzed the heightened oxidative stress induced by the model group, revealing that TWE therapy substantially alleviated oxidative stress in mice. Western blot analysis was employed to evaluate the protein expression levels of Nrf2 and HO-1 in mouse renal tissue, providing further insights into the impact of TWEs on reducing oxidative stress. The data demonstrated significantly lower Nrf2 and HO-1 expression levels in the model group compared to the control group, but administration of TWEs resulted in markedly higher levels of these proteins than in the control group (Qian *et al.*, 2019).

Anthocyanins

In the hyperuricemic mouse model, both serum and liver xanthine oxidase (XOD) activities in the control group were 27.3% and 90.9% higher than those in normal mice, respectively. Allopurinol therapy significantly decreased both serum and hepatic XOD activities compared to the model control group. Anthocyanin treatment demonstrated a notable reduction in liver XOD activities by approximately 30.5% ($P < 0.01$) and 45.3% ($P < 0.05$) when compared to the model control group, respectively. However, it's noteworthy that low-dose anthocyanin treatment did not lead to a reduction in blood XOD activity in hyperuricemic mice (Qian *et al.*, 2019).

The impact of anthocyanins (ACNs) on the expressions of renal organic ion transporters was investigated. In comparison to the model control group, high-dose ACN therapy significantly elevated mRNA expression levels of OAT1, OAT3, and ABCG2 ($P < 0.05$, $P < 0.05$, $P < 0.01$). Additionally, ACNs at both dosages led to a reduction in mRNA expression levels of URAT1 ($P < 0.01$, $P < 0.001$) and GLUT9 ($P < 0.05$, $P < 0.001$). These findings suggest that ACNs may decrease urate reabsorption and enhance its excretion. It's noteworthy that allopurinol did not have an influence on renal urate transport (Qian *et al.*, 2019).

Quercetin

Quercetin (3, 3′, 4′, 5, 7-pentahydroxyflavanone) is a flavonoid that belongs to the flavonol subgroup. Quercetin is abundant in various plants and fruits such as onions, apples, berries, dill, fennel leaves, oregano, chili pepper, kale, lettuce, and broccoli. As a bioactive molecule, quercetin has been extensively studied and is purported to exert an anti-hyperuricemic effect through multiple mechanisms. These include reducing urate formation by inhibiting relevant enzymes and enhancing urate elimination by modulating renal urate transporters (Kutryb-Zajac *et al.*, 2020).

Adenosine deaminase (ADA) is a crucial enzyme in purine metabolism that converts adenosine to inosine irreversibly (Kutryb-Zajac *et al.*, 2020; Melzig, 1996). Indeed, quercetin has demonstrated the ability to suppress adenosine deaminase (ADA) activity in aortic endothelial cells, as evidenced by an

IC50 value of 26 mol/L (Qian *et al.*, 2019; Kutryb-Zajac *et al.*, 2020). In a subsequent study, quercetin exhibited a broader inhibitory effect, reducing not only adenosine deaminase (ADA) activity but also xanthine oxidase (XO) and purine nucleoside phosphorylase (PNP) activities. The respective IC50 values for quercetin were found to be 55.6 µM, 3.0 µM, and 36.9 µM (Kutryb-Zajac *et al.*, 2020; Ozyel *et al.*, 2021).

Several studies have shown that quercetin can lower blood urate levels not just by blocking urate-producing enzymes but also by enhancing renal urate excretion. In a study involving fructose-fed rats with Metabolic Syndrome (MetS), hyperuricemia, and renal dysfunction, the administration of 100 mg/kg quercetin resulted in a significant reduction in serum urate levels. This treatment also mitigated the dysregulation of SLC2A9v2, a renal-specific transporter (homologous to human URAT1), as well as organic anion transporters (OAT1 and UAT) and organic cation transporters (OCT1 and OCT2). Consequently, there was an improvement in urinary urate elimination. In another study, quercetin doses of 25, 50, and 100 mg/kg were found

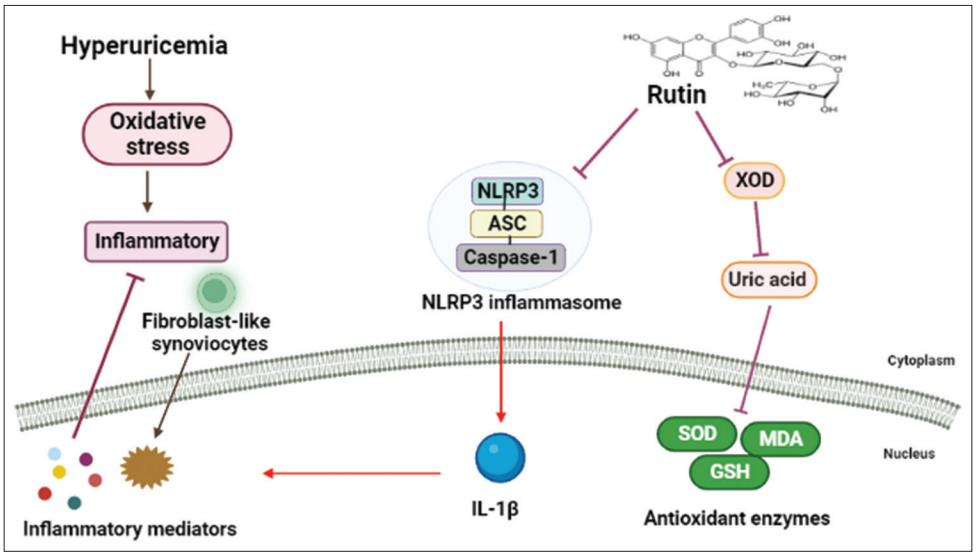

Figure 2: Schematic representation of inhibitory impact of rutin on hyperuricemia through NLRP3 activation (NLRP3: Nucleotide-Binding Domain, Leucine-Rich-Containing Family, Pyrin-Domain-containing-3 (Wang *et al.,* 2018), ASC: Apoptosis-associated speck-like protein containing a CARD (Fang *et al.,* 2019))

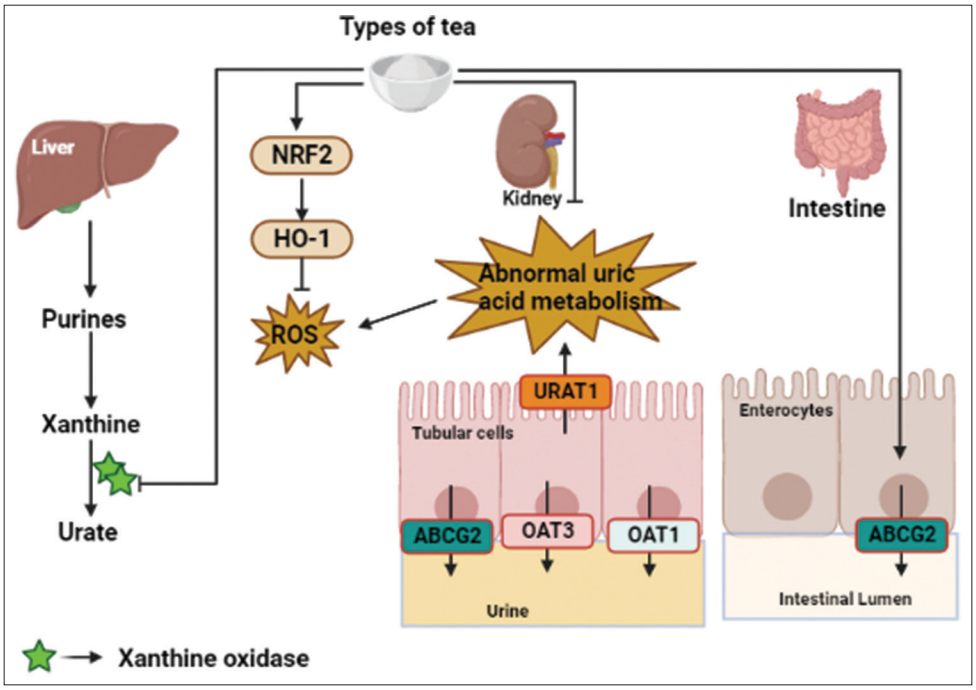

Figure 3: Representation of effect of Tea on HUA (URATE: urate anion transporter 1; GLUT9: glucose transporter 9; OAT1 & 3: organic anion transporters 1 & 3; ABCG2: ATP binding cassette sub-family G member 2; Nrf2: nuclear factor erythroid2-related factor 2; HO-1: heme oxygenase 1; ROS: reactive oxygen species)

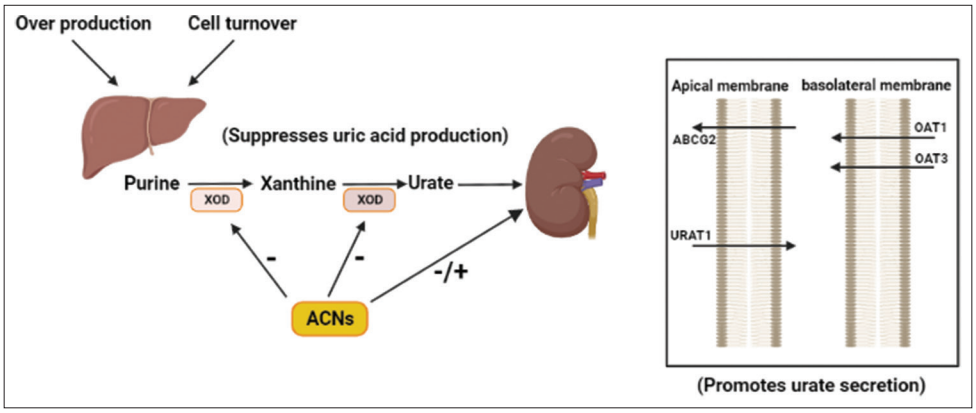

Figure 4: Representation of the purine route of the impact of ACNs on XOD activity and renal urate secretion

to significantly lower serum urate and uromodulin levels. Moreover, renal uromodulin concentration was reduced, while urate and uromodulin excretion increased. This effect was attributed to the regulation of renal organic ion transporters, including OAT1, OCT1, OCT2, OCTN1, OCTN2, URAT1, and GLUT9 (Melzig, 1996) (as demonstrated in Figure 2). Through these results, we can understand quercetin is not only an XOD inhibitor but can also enhance renal urate excretion through urate excretion transporters and suppress the activity of urate reabsorption transporters (Figure 4).

Anti-inflammatory effect: Some hyperuricemic patients have signs of monosodium urate (MSU) crystal deposition, and some people with MSU crystal deposition have suffered gout flares. A gout flare is a clinically visible bout of acute inflammation that generates a painful, swollen, heated, and red joint (Dalbeth *et al.*, 2019). In the context of inflammation, the interaction between monosodium urate (MSU) crystals and local macrophages is recognized to activate the NLRP3 inflammasome, leading to the production of IL-1β. In an in vitro study, quercetin demonstrated the ability to reduce ligand-induced activation of Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4). Additionally, quercetin lowered the activation of NF-κB induced by MyD88 overexpression. These findings suggest that quercetin functions as a Toll-like receptor signaling inhibitor, influencing the TLR-MyD88-NF-κB signaling network (Shibata *et al.*, 2014).

Genistein

Genistein is an isoflavone. It is a naturally occurring chemical found in soybeans and soybean products. It has previously been demonstrated that genistein can be utilized to prevent a variety of metabolic disorders, such as cardiovascular disease (CVD), diabetes, cancer, and obesity (Rehman *et al.*, 2019; Pavese *et al.*, 2010; Wei-Yun & Cailin, 2021). As per a study, treatment with potassium oxalate (PO) led to a significant increase in blood uric acid (UA) levels and a decrease in urine UA levels in the model group compared to the normal control group. This indicated the successful generation of a hyperuricemic animal model. In mice with hyperuricemia, both allopurinol and genistein therapy significantly ($p<.05$) reduced serum UA levels while increasing urine uric acid (UUA) levels compared to the

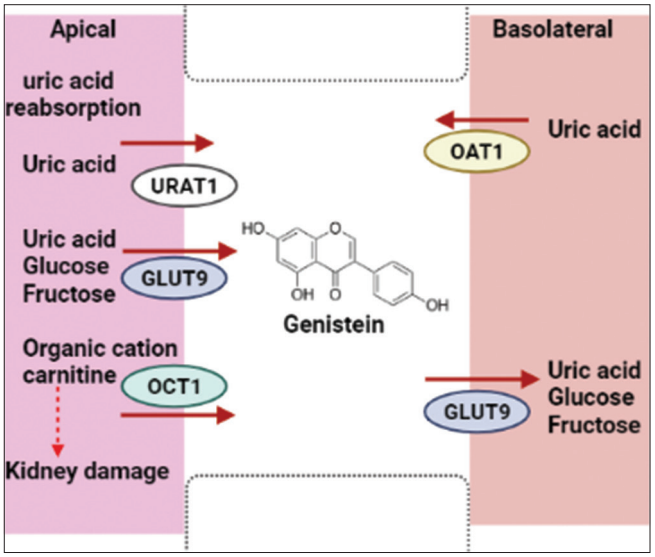

Figure 5: A potential mechanism of uric acid lowering via genistein

model control group. Additionally, compared to the PO group, both allopurinol and genistein at doses of 10 and 20 mg/kg concurrently suppressed xanthine oxidase (XOD) ($p<.05$) and adenosine deaminase (ADA) ($p<.05$) enzymes. Furthermore, they substantially ($p<.05$) restored blood urea nitrogen (BUN) and creatinine (Cr) levels, suggesting that genistein alleviated UA-mediated renal injury (Figure 5) (Pavese *et al.*, 2010).

In contrast to the model group, genistein exhibited a significant ($p<.05$) decrease in the renal gene expression of mURAT1. Similarly, potassium oxalate (PO) increased the gene expression of mGLUT9 in the model group compared to the control group, and this effect was reversed by both allopurinol and genistein therapies. In comparison to the control group, PO treatment led to a significant reduction in the gene expression of mOAT1, mOAT3, mOCT1, and mOCT2. However, both allopurinol and genistein treatments significantly ($p<.05$) elevated the expression levels of these organic anion and cation transporters when compared to the control group. These findings suggest that genistein serves a dual function by inhibiting critical enzymes and enhancing uric acid (UA) secretion through interactions with urate transporters (Rehman *et al.*, 2019).

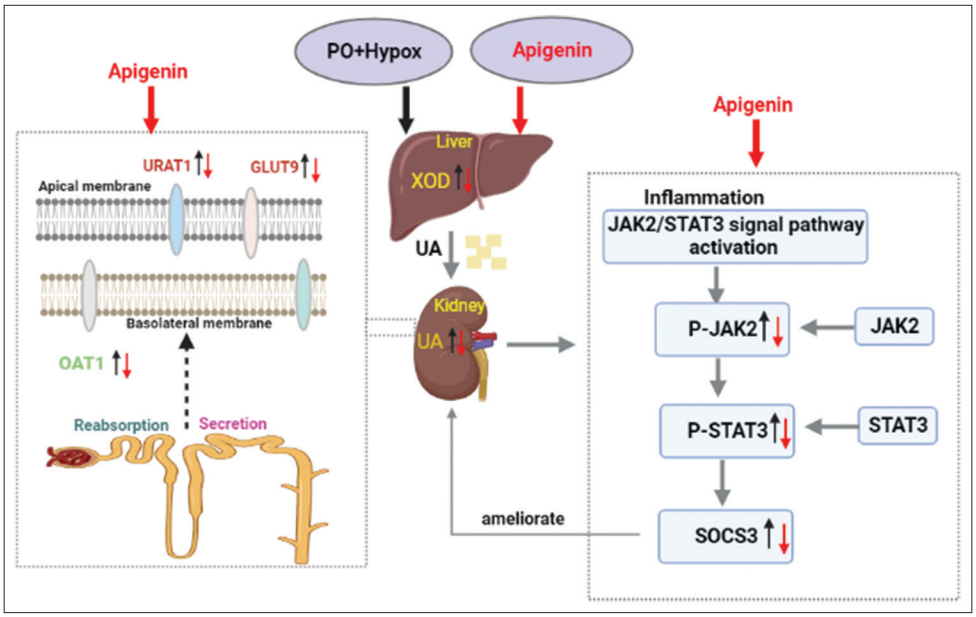

Figure 6: Effect of Apigenin against HUA and renal damage by regulating UA metabolism and the JAK2/STAT3 signaling pathway (The black arrow represents biomarker changes in HUA mice produced by PO and Hypox, whereas the red arrow represents biomarker modifications in HUA mice following apigenin treatment)

Apigenin

Apigenin, a natural flavonoid known as 4,5,7-trihydroxy flavone, is predominantly derived from *Apium graveolens* L. (celery) but can also be found in various plants, fruits, and vegetables. Emerging data suggests that apigenin has the potential to reduce uric acid (UA) levels in purine-rich diets or potassium oxonate (PO)-induced hyperuricemia (HUA) rats. Moreover, apigenin demonstrates protective effects against HUA-induced kidney fibrosis by inhibiting the Wnt/β-catenin signaling pathway. Additionally, studies have shown that apigenin can protect rats from renal ischemia/reperfusion damage (IRI) through modulation of the JAK2/STAT3 signaling pathway (Liu *et al.*, 2022).

A study uncovered significantly elevated serum concentrations of uric acid (UA), creatinine (CRE), and blood urea nitrogen (BUN) in the hyperuricemia (HUA) model control (HC) group compared to the normal control (NC) group of mice ($p < 0.01$). The administration of apigenin therapy at doses of 25, 50, and 100 mg/kg notably reduced UA and BUN levels in HUA mice significantly more than vehicle treatment ($p < 0.01$). Notably, only the high dosage of apigenin (100 mg/kg) was effective in reducing blood CRE levels in HUA animals (Liu *et al.*, 2022). The study further investigated the impact of apigenin on protein expressions involved in UA production and excretion in HUA mice. Western blot results indicated a significant increase in the expression levels of GLUT9 and URAT1, while OAT1 expression levels were notably decreased in the kidneys of the HC group compared to those in the NC group ($p < 0.05$). These findings suggested that apigenin might facilitate increased UA elimination in the kidneys. Moreover, the study identified improved renal pathological microstructures in this acute HUA mouse model. Apigenin was also observed to maintain serum levels of IL-6, IL-1, TNF-α, IL-18, and IL-10 in HUA mice (Liu *et al.*, 2022).

Furthermore, the study presented evidence of apigenin's activities on hyperuricemia (HUA) mice, demonstrating a decrease in liver xanthine oxidase (XOD), renal GLUT9, and URAT1 expression. Conversely, there was an increase in OAT1 expression, and apigenin was found to inhibit the JAK2/STAT3 signaling pathway. These findings contribute to understanding the multifaceted impact of apigenin in mitigating hyperuricemia, involving modulation of key enzymes, and signaling pathways related to uric acid metabolism (Figure 6).

CONCLUSION

HUA life-trading disorder is always accelerating over the earth. Dietary plant foods serve an important function in reducing the HUA load. Vegetables and fruits, being low in purine content and rich in compounds with various health benefits, play a vital role in reducing uric acid (UA) levels. Among the dietary elements known for their UA-lowering effects, flavonoids have received considerable attention. Flavonoids primarily reduce UA by inhibiting xanthine oxidoreductase (XOR) and modulating UA transporters such as GLUT9, URAT1, and OAT1/3. Research spanning animal studies, epidemiological investigations, in vitro experiments, and in vivo trials has consistently affirmed the anti-hyperuricemic properties of numerous dietary plant foods. This is attributed to the presence of a diverse array of physiologically active substances, particularly polyphenols. These bioactive compounds not only inhibit UA production but also enhance renal UA excretion while preventing the reabsorption of UA in the kidneys. According to the findings of the preceding investigations, numerous physiologically active substances have anti-hyperuricemic action comparable to synthetic medications (e.g., allopurinol). More study is needed to identify novel flavonoids from nature's abundance, which will eventually replace the need for risky synthetic drugs.

ACKNOWLEDGMENT

The authors extend their acknowledgment to the JSS AHER management, Mysuru, Karnataka, for providing the required resources and support and DST–FIST Centralized laboratory, Muthayammal College of Arts and Science, Rasipuram, Namakkal DT., Tamil Nadu, India, for preparing this work.

REFERENCES

Borges, F., Fernandes, E., & Roleira, F. (2002). Progress towards the discovery of xanthine oxidase inhibitors. *Current Medicinal Chemistry, 9*(2), 195-217. https://doi.org/10.2174/0929867023371229

Dalbeth, N., Choi, H. K., Joosten, L. A. B., Khanna, P. P., Matsuo, H., Perez-Ruiz, F., & Stamp, L. K. (2019). Gout. *Nature Reviews Disease Primers, 5*, 69. https://doi.org/10.1038/s41572-019-0115-y

Dalbeth, N., Stamp, L. K., & Merriman, T. R. (2017). The genetics of gout: Towards personalised medicine? *BMC Medicine, 15*, 108. https://doi.org/10.1186/s12916-017-0878-5

Dwyer, J. T., & Peterson, J. (2013). J. Tea and flavonoids: Where we are, where to go next. *The American Journal of Clinical Nutrition*, *98*(S6), 1611S-1618S. https://doi.org/10.3945/ajcn.113.059584

Fang, R., Uchiyama, R., Sakai, S., Hara, H., Tsutsui, H., Suda, T., Mitsuyama, M., Kawamura, I., & Tsuchiya, K. (2019). ASC and NLRP3 maintain innate immune homeostasis in the airway through an inflammasome-independent mechanism. *Mucosal Immunology, 12*, 1092-1103. https://doi.org/10.1038/s41385-019-0181-1

Feng, S., Wu, S., Xie, F., Yang, C. S., & Shao, P. (2022). Natural compounds lower uric acid levels and hyperuricemia: Molecular mechanisms and prospective. *Trends in Food Science & Technology, 123*, 87-102. https://doi.org/10.1016/j.tifs.2022.03.002

Ganeshpurkar, A., & Saluja, A. K. (2017). The pharmacological potential of rutin. *Saudi Pharmaceutical Journal, 25*(2), 149-164. https://doi.org/10.1016/j.jsps.2016.04.025

Horiuchi, H., Ota, M., Nishimura, S.-I., Kaneko, H., Kasahara, Y., Ohta, T., & Komoriya, K. (2000). Allopurinol induces renal toxicity by impairing pyrimidine metabolism in mice. *Life Sciences, 66*(21), 2051-2070. https://doi.org/10.1016/s0024-3205(00)00532-4

Kutryb-Zajac, B., Mierzejewska, P., Slominska, E. M., & Smolenski, R. T. (2020). Therapeutic perspectives of adenosine deaminase inhibition in cardiovascular diseases. *Molecules, 25*(20), 4652. https://doi.org/10.3390/molecules25204652

Liu, T., Gao, H., Zhang, Y., Wang, S., Lu, M., Dai, X., Liu, Y., Shi, H., Xu, T., Yin, J., Gao, S., Wang, L., & Zhang, D. (2022, November 21). Apigenin ameliorates hyperuricemia and renal injury through regulation of uric acid metabolism and Jak2/Stat3 signaling pathway. *Pharmaceuticals, 15*(11), 1442. https://doi.org/10.3390/ph15111442

Melzig, M. F. (1996). Inhibition of adenosine deaminase activity of aortic endothelial cells by selected flavonoids. *Planta Medica, 62*(1), 20-21. https://doi.org/10.1055/s-2006-957788

Mo, S.-F., Zhou, F., Lv, Y.-Z., Hu, Q.-H., Zhang, D.-M., & Kong, L.-D. (2007). Hypouricemic action of selected flavonoids in mice: Structure–activity relationships. *Biological and Pharmaceutical Bulletin, 30*(8), 1551-1556. https://doi.org/10.1248/bpb.30.1551

Nutmakul, T. (2022). A review on benefits of quercetin in hyperuricemia and gouty arthritis. *Saudi Pharmaceutical Journal, 30*(7), 918-926. https://doi.org/10.1016/j.jsps.2022.04.013

Omar, B., Mohamed, N., Rahim, R. A., & Wahab, H. A. (2007). Natural Flavonoids for the treatment of hyperuricemia, Molecular Docking studies. In R. Magjarevic & J. H. Nagel (Eds.), World Congress on Medical Physics and Biomedical Engineering (Vol. 14, pp. 178-182) Berlin, Heidelberg: Springer. https://doi.org/10.1007/978-3-540-36841-0_53

Ozyel, B., Le Gall, G., Needs, P. W., & Kroon, P. A. (2021). Anti-inflammatory effects of quercetin on high-glucose and pro-inflammatory cytokine challenged vascular endothelial cell metabolism. *Molecular Nutrition and Food Research, 65*(6), e2000777. https://doi.org/10.1002/mnfr.202000777

Panche, A. N., Diwan, A. D., & Chandra, S. R. (2016). Flavonoids: An overview. *Journal of Nutritional Science, 5*, e47. https://doi.org/10.1017/jns.2016.41

Pavese, J. M., Farmer, R. L., & Bergan, R. C. (2010). Inhibition of cancer cell invasion and metastasis by genistein. *Cancer Metastasis Reviews, 29*, 465-482. https://doi.org/10.1007/s10555-010-9238-z

Qian, X., Wang, X., Luo, J., Liu, Y., Pang, J., Zhang, H., Xu, Z., Xie, J., Jiang, X., & Ling, W. (2019). Hypouricemic and nephroprotective roles of anthocyanins in hyperuricemic mice. *Food and Function, 10*(2), 867-878. https://doi.org/10.1039/c8fo02124d

Rehman, K., Ali, M. B., & Akash, M. S. H. (2019). Genistein enhances the secretion of glucagon-like peptide-1 (GLP-1) via downregulation of inflammatory responses. *Biomedicine & Pharmacotherapy, 112*, 108670. https://doi.org/10.1016/j.biopha.2019.108670

Rundles, R. W., Metz, E. N., & Silberman, H. R. (1966). Allopurinol in the treatment of gout. *Annals of Internal Medicine, 64*(2), 229-258. https://doi.org/10.7326/0003-4819-64-2-229

Shibata, T., Nakashima, F., Honda, K., Lu, Y.-J., Kondo, T., Ushida, Y., Aizawa, K., Suganuma, H., Oe, S., Tanaka, H., Takahashi, T., & Uchida, K. (2014). Toll-like receptors as a target of food-derived anti-inflammatory compounds. *Journal of Biological Chemistry, 289*(47), 32757-32772. https://doi.org/10.1074/jbc.M114.585901

Wang, Z., Hu, W., Lu, C., Ma, Z., Jiang, S., Gu, C., Acuña-Castroviejo, D., & Yang, Y. (2018). Targeting NLRP3 (nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3) inflammasome in cardiovascular disorders. *Arteriosclerosis, Thrombosis, and Vascular Biology, 38*, 2765-2779. https://doi.org/10.1161/ATVBAHA.118.311916

Wei-Yun, B., & Cailin, Z. (2021). Genistein ameliorates hyperuricemia-associated nephropathy in hyperuricemic mice. *Food and Agricultural Immunology, 32*(1), 778-797. https://doi.org/10.1080/09540105.2021.1996540

Wu, D., Chen, R., Zhang, W., Lai, X., Sun, L., Li, Q., Zhang, Z., Cao, J., Wen, S., Lai, Z., Li, Z., Cao, F., & Sun, S. (2022). Tea and its components reduce the production of uric acid by inhibiting xanthine oxidase. *Food & Nutrition Research, 66*. https://doi.org/10.29219/fnr.v66.8239

Wu, H., Wang, Y., Huang, J., Li, Y., Lin, Z., & Zhang, B. (2023). Rutin ameliorates gout via reducing XOD activity, inhibiting ROS production and NLRP3 inflammasome activation in quail. *Biomedicine and Pharmacotherapy, 158*, 114175. https://doi.org/10.1016/j.biopha.2022.114175