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ANTIHYPERURICEMIA ACTIVITIES OF SEVERAL ACTIVE COMPOUNDS FROM MEDICINAL PLANTS: A REVIEW

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ABSTRACT
Due to increased uric acid production or renal uric acid excretion, hyperuricemia has been identified as a significant risk factor for gouty arthritis. This condition is characterized by an accumulation of uric acid in the bloodstream. As of now, scientists are commencing their search for novel candidate compounds for hyperuricemia drugs derived from natural substances with antihyperuricemia effects supported by empirical evidence. This is implemented in lieu of the antihyperuricemia medications that presently exhibit numerous adverse effects. Some of the active compounds that have been taken from different plants are curcumin, kaempferol, catechin, piperine, α-mangostin, luteolin, quercetin, andrographolide, apigenin, and betulinic acid. The hyperuricemic activity of numerous active compounds through distinct mechanisms has been scientifically established.

KEYWORDS: Antihyperuricemia, Curcumin, Kaempferol, Catechins, Piperine, α-Mangostin, Luteolin, Quercetin, Andrographolide, Apigenin, Betulinic acid.

INTRODUCTION

Gouty arthritis is currently experiencing a global rise in prevalence; however, despite the fact that there are currently available medications that can effectively treat this condition, these options come with a variety of side effects.[1,2] Low patient adherence to treatment also contributes to the recurrence of elevated uric acid levels.[3,4] Hyperuricemia frequently manifests in conjunction with obesity, metabolic syndrome, hypertension, diabetes, dyslipidemia, and chronic kidney disease. The primary etiologies of hyperuricemia are purine metabolism impairment and uric acid excretion failure.[1] In humans, uric acid serves as the ultimate metabolite of the purine catabolism pathway. Uric acid is formed by the oxidation of hypoxanthine, becoming xanthine and with the help of the xanthine oxidase enzyme (XO), then xanthine is converted into uric acid.[5] Research to obtain new anti-hyperuricemia drugs, both synthetic drugs and those derived from natural ingredients, continues to be carried out, one of which is exploring active compounds from natural ingredients, especially medicinal plants, which have traditionally been used by people to treat hyperuricemia in various countries.[6,7] The aim is to find new anti-hyperuricemia compounds that have mild side effects with low toxicity, so they do not harm patients.[8,9] This review article discusses the active compounds and antihyperuricemia activity of several medicinal plant isolates.

Curcumin

A phytochemical called curcumin (1,7-bis (4′hydroxy-3-methoxyphenyl) 1,6-heptadiene, 3,5-dione) is mostly found in *Curcuma longa* and *Curcuma zanthorrhiza*. It exhibits considerable promise as a therapeutic agent for a wide range of ailments.[10, 11] According to the findings of numerous studies, curcumin possesses a multitude of biological activities, including anti-inflammatory and anti-hyperuricemia properties.[12] After 14 days of treatment with curcumin at doses of 20, 40 mg/kg/day, potassium oxonate-induced uric acid levels in mice are reduced.[13] Furthermore, in tests carried out in vitro, curcumin is reported to inhibit the enzyme xanthine oxidase (XO) and urate transporter 1[14] with an IC_{50} value of 3.33 ± 0.52 μM.[15] In addition, curcumin is also reported to increase uricosuric activity, which results in increased excretion of uric acid through the kidneys.[16]

Kaempferol

Natural flavonol called kaempferol (3,4' 5, 5,7-tetrahydroxyflavone) possesses a multitude of pharmacological activities.[17,18] It works as an anti-hyperuricemia agent. Researchers have found that giving

mice kaempferol at doses of 50 and 100 mg/kg for three days lowered the amount of uric acid in their blood after potassium oxonate is added to the mice' bodies.[19] Also, tests done in a lab show that kaempferol can competitively block the enzyme xanthine oxidase (XO) with an IC_{50} value of 0.338 µM. Molecular docking studies also revealed that kaempferol can connect with some xanthine oxidase amino acid residues by stacking them on top of each other, hydrogen bonding, and hydrophobic interactions. The mechanism of kaempferol's inhibition of xanthine oxidase activity can be the insertion of kaempferol into the active site of xanthine oxidase, which can prevent the entry of xanthine substrate and induce changes in the conformation of xanthine oxidase. These results confirm that kaempferol can be used as a new xanthine oxidase inhibitor for hyperuricemia.[20]

Catechin

Green tea plants (*Camellia sinensis*) frequently contain the secondary metabolite catechin (2R,3S)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol, which is classified as a flavonol. A hydroxyl group is attached to carbon 3 of catechins, which also consist of two benzene rings (Ring A, Ring B) and dihydropyran (Ring C).[21] Catechin compounds have been widely recommended for the treatment of hyperuricemia patients because of their antioxidant and anti-inflammatory properties.[22] In addition, testing catechin in green tea at a dose of 0.52 ± 0.09 mg/kg/hour is proven to increase uric acid excretion in urine.[23] Catechin is also reported to inhibit xanthine oxidase activity in the body and reduce uric acid production in the liver.[22]

Piperine

Piper nigrum and *Piper longum* plants contain the active compound piperine (1-[5-(1,3-benzodioxol-5-yl)-1-oxo-2,4-pentadienyl] piperidine).[24] Traditional medicine in numerous countries has made extensive use of the piperine compound to treat a variety of ailments, including rheumatism, digestive disorders, muscle pain, flatulence, bactericide, antiseptic, antipyretic, diuretic, sore throat, and cough.[24] At a dose of 100 mg/kg, piperine is showed to lower levels of lysosomal enzymes, lipid peroxidation, TNF alpha, and the size of a mouse's leg in a model of vascular rheumatoid syndrome.[25] Apart from that, piperine can also inhibit the xanthine oxidase enzyme in vitro with an IC_{50} of 54.87 µg/mL.[26]

α-Mangostin

Mangosteen peel has a chemical called α-mangostin (1,3,6-trihydroxy-7-methoxy-2,8-bis (3methyl-2-butenyl)-9H-xanten-9-one) that is known to lower high blood pressure and reduce inflammation.[27] In research conducted in vivo on male Sprague-Dawley mice at a dose of 100 mg/kg/day, α-mangostin is reported to reduce uric acid levels.[28] In addition, α-mangostin is also reported to increase uric acid clearance in hyperuricemia model mice.[28] α-Mangostin is also reported to reduce uric acid levels at doses of 100 and 200 mg/kg by inhibiting the renal transporter URAT1 in insulin-resistant mouse models.[29]

Luteolin

An abundance of plant species, including fruits, vegetables, and medicinal plants, contain the flavonoid luteolin (3′,4′,5,7-tetrahydroxyflavone). Anti-inflammatory and anti-hyperuricemia properties are attributed to luteolin.[30] In studies using a hyperuricemia mouse model, giving luteolin by mouth is found to lower the production of uric acid at a dose of 7.62 mg/g luteolin.[31] Meanwhile, in in vitro testing, luteolin can inhibit the xanthine oxidase enzyme at a concentration of 100 µM.[32]

Quercetin

An example of a flavonoid compound with the ability to reduce uric acid levels is quercetin (3,3’,4’,5,7-pentahydroxyflavone).[33] Quercetin is found in many fruits, medicinal plants, vegetables and nuts.[34] In studies using a hyperuricemia mouse model, giving quercetin by mouth is found to lower the production of uric acid at doses of 100 and 300 mg/kg/day. Meanwhile, in in vitro testing, quercetin can inhibit the xanthine oxidase enzyme at a concentration of 100 µM.[32]

Andrographolide

The principal compound found in the *Andrographis paniculata* plant is andrographolide (3-[2-[Decahydro-6-hydroxy-5-(hydroxymethyl)-5,8a-dimethyl-2-methylene-1-napthalenyl]ethylidene]dihydro-4-hydroxy-2(3H)-furanone), which possesses a wide range of pharmacological activities.[35] A 30 mg/kg/day dose of andrographolide is given to a mouse model of hyperuricemia and found to lower serum uric acid levels.[36] In addition, in in vitro testing, andrographolide with a concentration of 1,000-1,750 µg/mL for 5 days can reduce the concentration of uric acid by inhibiting the xanthine oxidase enzyme.[37]

Apigenin

Natural flavonoid apigenin (4,5,7-trihydroxyflavone) is obtained from *Apium graveolens* L. Utilizing a mouse model of potassium oxanate-induced hyperuricemia, in vivo studies showed that oral administration of apigenin at doses of 50 and 100 mg/kg/day decreased uric acid production.[38] Meanwhile, in in vitro testing, apigenin can inhibit the xanthine oxidase enzyme at concentration of 0.64 ± 0.14 µM and 2.63 ± 0.69 µM.[39, 40]

Betulinic acid

Betulinic acid, also known as ((3β)-3-Hydroxy-lup-20(29)-en-28-oic acid), is a pentacyclic triterpenoid that is naturally found in the bark of many plant species, especially white birch (*Betula pubescens*).[41] Betulinic acid has been proven to have several pharmacological activities such as antidiabetic, antidyslipidemia, anti-inflammatory, antiviral, anticancer, anti-parasitic, and anti-infective.[42] In studies using a hyperuricemia mouse

model, giving betulinic acid to mice by mouth at a dose of 50 mg/kg/day is found to lower their acid production. Meanwhile, in in vitro testing, betulinic acid can inhibit the xanthine oxidase enzyme at a concentration of 121.10 ± 4.57 μM.[43]

CONCLUSION

All of these isolates have been scientifically proven to have antihyperuricemia activity, where each compound has a different mechanism of action in inhibiting the increase in uric acid. However, further research must be carried out to determine the effectiveness of this compound as an antihyperuricemia medication so that it can be used in the treatment of new gouty arthritis, which has now shown adverse side effects.

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