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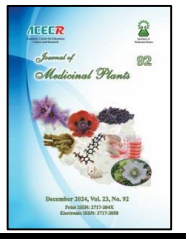

Review Article

Uric acid reducing plants with Xanthine Oxidase inhibitory effects: (A mini review article)

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ABSTRACT

Background: Hyperuricemia is a common metabolic disorder of purines catabolism pathway that is associated with abnormal increases in uric acid levels. It is one of the important risk factors for gout and stress-oxidative related illness such as cancer and cardiovascular diseases. **Objective:** At present, allopurinol is used to treat it and the mechanism of this drug is to inhibit the enzyme xanthine oxidase (XO). In addition to side effects, this drug sometimes interacts with some other drugs. Therefore, the tendency of patients has increased to use medicinal plants for treatment of these diseases as the effectiveness of some plant compounds has been proven in various studies. **Methods:** In this study, uric acid reducing plants which had inhibitory properties on XO were reviewed. To get the comprehensive finding, keywords related to the subject of the study were searched in databases including: Scopus, PubMed, Google Scholar, Science Direct, Magiran and SID. **Results:** Our study showed, in order to inhibit XO enzyme and to be lowered uric acid levels by some plant families including Asteraceae, Malvaceae, Plantaginaceae, Fabaceae, Piperaceae, Moraceae, Asphodelaceae, Lamiaceae, Solanaceae, Anacardiaceae, Apiaceae, Amaryllidaceae, Tiliaceae, Oxalidaceae, Caricaceae, Sapotaceae, Arecaceae, Sapindaceae, Capparaceae, Lauraceae, Bignoniaceae, Polygonaceae, Calophyllaceae, Magnoliaceae, Portulacaceae and Menispermaceae, a specific dose of compounds of natural products in a range of 100 to 5000 mg/Kg is necessary. **Conclusion:** The presences of phenolic compounds, especially polyphenols and flavonoids such as chlorogenic acid and luteolin have been predominantly considered as the most important natural antioxidants inhibiting XO enzyme to treat hyperuricemia.

Abbreviations: UA, Uric acid; XO, Xanthine Oxidase; ICD, International Classification Diseases; ROS, Reactive Oxygen Species; XDH, Xanthine Dehydrogenase; DMC, Dilated Cardiomyopathy; GFR, Glomerular Filtration Rate; CKD, Chronic Kidney Disease; NAFLD, Non-Alcoholic Fatty Liver Disease; MSU, Monosodium Urate; TNF-α, Tumor Necrosis Factor Alpha; NSAIDs, Nonsteroidal Anti-Inflammatory Drugs; CGA, Chlorogenic Acid; T2DM, Type 2 Diabetes Mellitus; PIH, Pregnancy-Induced Hypertension; LBW, Low Birth Weight; SGA, Small for Gestational Age; SUA, Serum uric acid

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1. Introduction

Uric acid (UA) is the end product of purines catabolism and the most important enzyme participating in its formation is xanthine oxidase (XO), which plays an important role in the production of UA [1]. At normal concentrations and under normal physiological conditions, UA prevents lysis of erythrocytes which is done by peroxidation. Also, it is a potent inhibitor of oxygen and hydroxyl radicals [2]. Abnormal increase or decrease of this important parameter causes several diseases. Its increase in diseases such as gout and its abnormal decrease are also associated with diseases such as multiple sclerosis, Parkinson's and Alzheimer's [3]. Serum uric acid (SUA) is also significantly increased in obesity, type 2 diabetes and metabolic syndrome [4]. Observational studies have also shown a relationship between hyperuricemia and increased risks of hypertension, chronic kidney disease, cardiovascular events, metabolic disorders, end-stage renal disease, and death [5]. Therefore, accurate measurement of UA is an important factor in the diagnosis of these diseases, in order to provide appropriate treatment for the health of patients.

Hyperuricemia is also caused by an abnormal increase in serum UA levels. In accordance with disease categories defined by international classification diseases (ICD); in hyperuricemia the UA level will increase and reach more than 7 mg/dL [6]. This disease is caused by disorders of purine metabolism pathway and is one of the important risk factors for gout and oxidative stress diseases [1, 7]. At present, standard management in the control and reduction of injuries of these diseases is the common use of synthetic drugs. Importantly, in the case of gout due to the chronic condition of the disease, side effects of the anti- hyperuricemic drugs such as allopurinol are more common due to long-term use of drugs [8]. Therefore, the tendency of patients has increased to use of medicinal plants in the treatment of these diseases.

Many studies have examined the role of plants or their medicinal products on reduction of uric acid [9]. Some researches have studied the effectiveness of concomitant use of medicinal plants with synthetic drugs or the simultaneous use of several plants which bearing some acceptable results [9-12]. According to the results of researches, some plants due to their important medicinal properties have been considered a suitable option to replace antibiotics and even for the development of natural-based anticancer drugs [13, 14]. Despite numerous studies on the effectiveness of medicinal plants in the treatment of diseases, the impressible of plants in many diseases still needs further studies. Especially, little is known on side effects on patients whom received medicinal plants for their anti – hyperuricemia effects. However, it seems the aforementioned side effects reported by medicinal plants will be lowered in this regards [15]. With respect to the global importance of hyperuricemia and gout diseases that have caused the research to be greatly focused on them**;** in the present study, the therapeutic effects anti-hyperuricemia, anti-gout of some medicinal plants have been reviewed using a series research done in different parts of the world.

2. Materials and methods

In the present study, some species from plant families belonging to Asteraceae, Malvaceae, Plantaginaceae, Fabaceae, Piperaceae, Moraceae, Asphodelaceae, Lamiaceae, Solanaceae, Anacardiaceae, Apiaceae, Amaryllidaceae, Tiliaceae, Oxalidaceae, Caricaceae, Sapotaceae, Arecaceae, Sapindaceae, Capparaceae, Lauraceae, Bignoniaceae, Polygonaceae, Calophyllaceae, Magnoliaceae, Portulacaceae and Menispermaceae, those who have reducing effects of UA or have

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been reported to somehow inhibit XO enzyme and could more natively used in herbal treatments in different countries were reviewed. The plants have also been studied by researchers. Additionally, several experiments were based on their effectiveness *in vitro* and *in vivo*. In order to achieve notable finding among researchers `s studies, a series of principal databases including: Scopus, PubMed, Google Scholar, Science Direct, Magiran and SID, were selected. Then the keywords related to medicinal plants, the relevant parameters of uric acid, xanthine oxidase, hyperuricemia and gout were searched for result analysis. The time interval between the years 2009-2023 was considered for identifying related articles, and the criteria for selecting articles were all original, review, case studies as well as articles presented in scientific congresses.

3. Results

3.1. The role of free radicals and increasing uric acid

3.1.1. Xanthine oxidase and ROS

With characterizing the role of reactive oxygen species (ROS) in the creation of diseases, many efforts have been made to neutralize their destructive effects on the body. ROS is produced in the body by two major systems - NADPH oxidase and Xanthine oxidase (XO) [16]. Xanthine oxidase / Xanthine dehydrogenase Liver is a key enzyme in the catabolism pathway of purines, which catalyzes the oxidation reaction of hypoxanthine to xanthine and xanthine to UA [17]. The active form of the enzyme under physiological conditions is xanthine dehydrogenase (XDH). But, in pathological conditions, XDH is converted to XO at the same time as ATP decomposes into adenine and xanthine. Xanthine oxidase along with the production of UA leads to the production of superoxide and peroxide free radicals. Thus, XO is an important biological source for the generation of free radicals and ROS, which leads to oxidative damage, to living tissues [18]. Figure 1 shows the mechanism of action of the XO enzyme in the production of UA and some diseases caused by its increase.

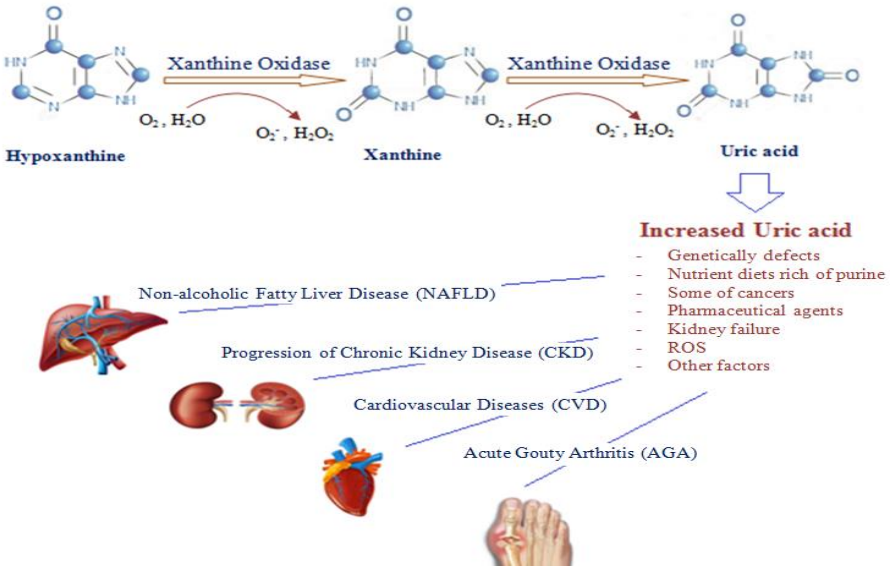

Fig. 1. The role of XO in the conversion of hypoxanthine to xanthine and eventually the formation of UA is shown. Overproduction or deficiency of UA excretion may lead to diseases such as hyperuricemia, gout, cardiovascular and kidney disease (Researcher made image).

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3.1.2. The role of uric acid and XO in cardiovascular diseases

Many studies have examined UA levels and their relationship with cardiovascular disease. Some studies have shown that hyperuricemia is related with systolic and diastolic function in patients with dilated cardiomyopathy (DMC) [16]. Therefore, inhibition of XO is very important in the treatment progress of heart disease. In myocardial ischemia status, which leads to the destruction of adenosine nucleotides and conversion of xanthine to hypoxanthine, XO causes the production of free radicals by acting on these two chemical parameters. Therefore, drugs with antioxidant properties are used to inhibit this enzyme [19].

3.1.3. Increased uric acid levels in kidney disease

Since the UA is excreted by the kidneys, some studies have shown that an excessive increase in UA levels is associated with a significant reduction in glomerular filtration rate (GFR) and a high risk of renal failure. Hyperuricemia, especially in patients without proteinuria, is a potential factor in the progression of chronic kidney disease (CKD) [20]. In a research has shown that controlling UA levels in the normal range in patients with type 2 diabetes mellitus and the use of serum UA -lowering drugs can be effective in controlling the progression of diabetic nephropathy [21]. Hyperuricemia is considered as a possible risk factor in the development of CKD, and based on the research of Rashid et al.'s (2022), the combined prevalence of hyperuricemia in patients with CKD is globally reported to be 43.6% [22]. Hyperuricemia leads to poor prognosis and increased complications of diabetes, including diabetic neuropathy, retinopathy, and nephropathy, as well as increased complications and mortality in type 2 diabetes mellitus (T2DM) patients [23]. A systematic review and meta-analysis of the high prevalence of hyperuricemia among T2DM patients in Africa showed the highest prevalence in Central Africa at 33.72 % and in men more than (28.20 %) than in women (28.02 %) [24]. Uric acid stones are also the most common urinary stones after calcium oxalate sources and are more seen in men than women [25].

3.1.4. Uric acid in non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is associated with several factors such as diabetes, insulin resistance, hyperlipidemia, hypertension, obesity and hyperuricemia. Uric acid stimulates fat accumulation, hepatic steatosis and hepatitis, which are important factors in the pathogenesis of NAFLD [26]. Evidence suggests that high UA is often associated with the development or progression of NAFLD. However, in some cases it can be considered as a simple and non-invasive method to follow patients with lean-NAFLD. Therefore; it prevents liver biopsy as an invasive approach with surgery problems and high costs [27].

3.1.5. High uric acid and adverse pregnancy complications

It is important to predict the level of uric acid in order to prevent adverse pregnancy complications and reduce its consequences. High uric acid in mothers with hyperuricemia can be transferred to the fetus through blood circulation [28]. The results of the meta-analysis study of Ten et al.'s (2023) on the relationship between hyperuricemia and its consequences for the mother and fetus in pregnant women, showed that; hyperuricemia is positively associated with pregnancy-induced hypertension (PIH), low birth weight (LBW), small for gestational age (SGA) and premature delivery [29].

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3.1.6. Hyperuricemia and gout

Gout is an inflammatory disorder caused by excessive accumulation of urate in body tissues and the formation of monosodium urate (MSU) crystals in joint tissues [30]. MSU crystals stimulate the immune system by producing and releasing a number of inflammatory mediators such as interleukins, kinins, and tumor necrosis factor alpha (TNF-α). Some of these mediators are chemotactic and potentiate the inflammatory response and leading to the infiltration of neutrophils and the subsequent release of oxygen free radicals, lysosomal enzymes, prostaglandin-E2, leukotrienes, and interleukin-1 [31]. By activating acute inflammatory reactions, these crystals can cause permanent tissue damage that characterized by joint cartilage damage, geodetic and erosive lesions, marginal osteophytosis, and chronic inflammation of the synovial membrane [32]. One of the clinical manifestations and the most important symptom of this disease is recurrent attacks, accompanied by acute inflammation of the joints, their warmth, pain and swelling [33] (Fig. 2). If hyperuricemia to continue, MSU crystalline deposits reduce the body's chronic inflammatory responses and in this way it may lead to chronic joint damage, kidney stone formation, kidney failure, and cardiovascular problems [34].

3.2. XO inhibitors drugs

Xanthine oxidase is considered an important enzyme in the pathology of hyperuricemia and gout by producing UA in the body. Therefore, its inhibition can have potential effects on controlling UA biosynthesis and the treatment of these diseases, as well as diseases caused by an increase in this enzyme [35]. Currently, one of the most important inhibitors of XO enzyme is allopurinol, which is used to treat diseases such as hyperuricemia and gout. And the action mechanism of allopurinol in inhibiting the enzyme xanthine oxidase has been shown in figure 3 [36]. Allopurinol is an oral drug and completely dose-dependent, that may interact with other drugs or inactivate them, such as azathioprine, mercaptopurine, ampicillin, warfarin, and theophylline [37]. It also has side effects such as allergic reactions, kidney poisoning, and toxic effects on the liver [8].

Treatment of gout is aimed at relieving acute attacks and preventing recurrence, and includes the use of anti-inflammatory drugs to relieve symptoms, inhibiting the final stages of UA biosynthesis in chronic gout as well as modifying eating behaviors [38]. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as colchicine are also used in this disease with other mechanisms (such as reduced leukocyte motility). This drug also has side effects such as neuropathy and myopathy [1].

3.3. Treatment based on herbal

Increasing use of herbs in treatment of many diseases and the acceptable results obtained from herbal remedies indicate the important role of plants and their compounds. It is believed that natural resources and plant extracts can be used to treat many diseases [39, 40]. Traditional medicinal plants that have been used in experimental studies to improve hyperuricemia, as an alternative treatment in various experiments, have shown certain effects in reducing hyperuricemia [5]. Active compounds stored in plant organs, which are often produced and stored by plants as secondary metabolites, can exert their therapeutic effects on various organs of the human body [41]. Research on some medicinal plants as inhibitors of the XO enzyme has shown that they can be a suitable alternative to common synthetic drugs [42, 43]. Some of the research on UA -lowering and XO-inhibiting plants that have been studied by researchers in different countries, have been brought in Table 1.

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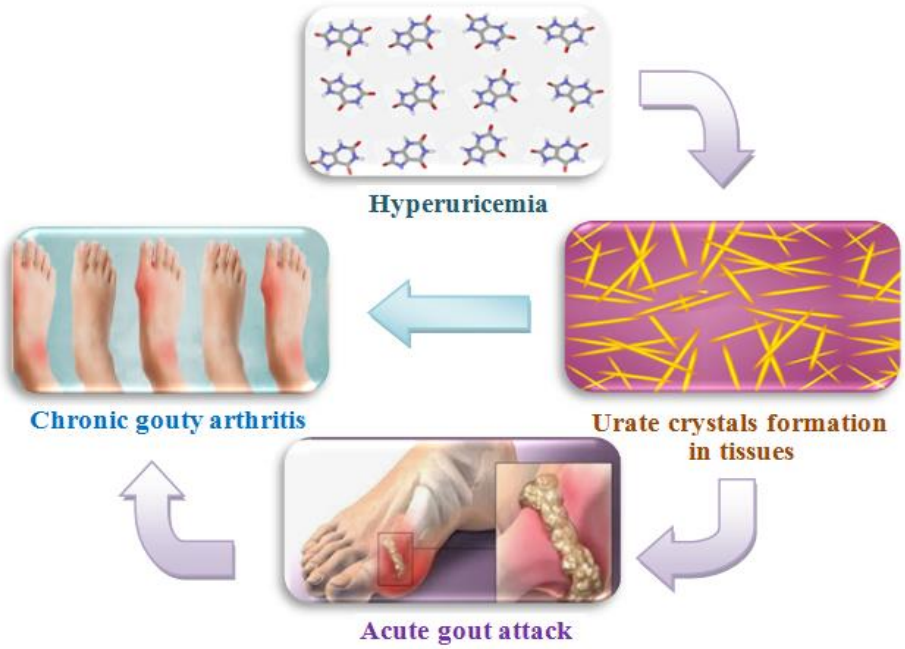

Fig. 2. In gout disease, abnormal increases in UA levels over a long period of time cause urate crystals to form in the tissues. The disease sometimes presents with severe inflammation and in some cases may be asymptomatic and chronic (Researcher made image)

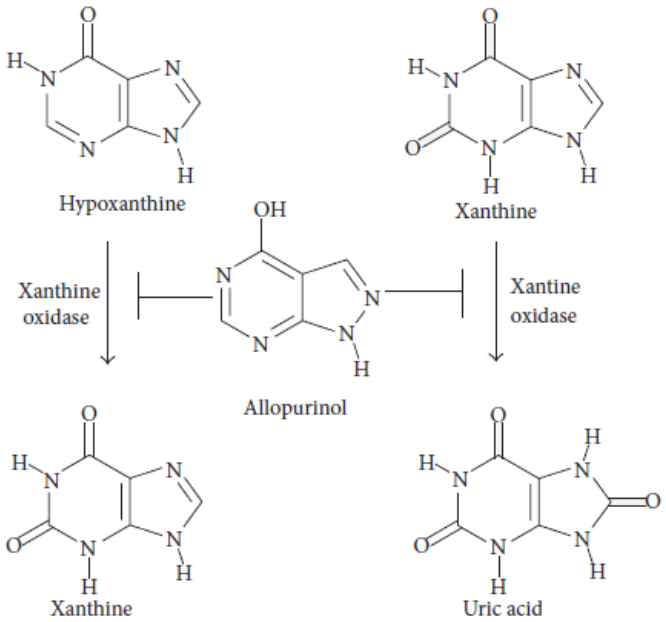

Fig. 3. Inhibition of xanthine oxidase by allopurinol [36]

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Table 1. The previous studies carried out on the effect of some plants species on xanthine oxidase activity in hyperuricemia

Scientific name	Family	Distribution area	Organ of plant/solvent used for extract or form of treatment	Important Compounds*	In vivo/In vitro	Results	Reference
Chrysanthemum indicum L.	Asteraceae	East Asia and northeastern Europe. The native range of this species is Himalaya to China to N. Indo-China, Korea, and Japan.	Flower/ 100 g of flower powder that enriched with luteolin (10 mg),	Polyphenols, Flavonoids, Luteolin, Triterpene alcohol, Octulosonic acid derivatives	two groups of 20 Japanese men with different levels of uric acid	The results showed that uric acid serum levels decreased in the first group (6.18 to 5.98 mg/dL) compared to the second group (5.91 to 6.09 mg/dL). Therefore luteolin may be able to prevent gout by controlling uric acid.	[44, 45]
Sida rhombifolia L.	Malvaceae	Eastern and western hemispheres/ Plains areas between Noor and west of Chalus in Iran	Leaves/indistinct	Flavonoids, Alkaloids, Saponins, Phenols, Steroids, Tannins	two groups of 20 gouty arthritis patients with high uric acid	The results showed a decrease in the level of serum uric acid of the group treated with herbal extract (8.65 to 6.68mg/dL) compared to the placebo group (8.85 to 8.86 mg/dL)	[45-47]
Plantago psyllium L.	Plantaginaceae	Different areas of the Mediterranean, North Africa and Southwest Asia/Large parts of Iran	Seeds/ 5 g of seeds with allopurinol drug (100 mg / daily)	Flavonoids, Luteolin, Polyphenols, Polysaccharides, Glycosides, Terpenoids, Coumarins	a case of hyperurice mia	This research showed that Psyllium along with allopurinol can be synergistically decreasing the increased serum level of uric acid, in patient of hyperuricemia. (9.70 ± 0.30 to 5.60 ± 0.26 mg/dL).	[15, 45, 47]
Tephrosia purpurea (L.) Pers.	Fabaceae	It is widespread in tropical, subtropical and dry regions of the world/in Baluchistan, Iran (Sarbaz, Rask, Chabahar).	Root/ methanol	Phenolic compound, Flavonoids, Coumarins, Tannins,	in vitro	The result of this research has shown that at concentrations of 25-100 µg / mL, the lowest and highest inhibition of XO by the extract was 40.00 ± 2.6 % and 99.00 ± 1.2 %, respectively.	[45, 47, 48]
Siegesbeckia orientalis L.	Asteraceae	It has a broad distribution in Africa and Asia, but has been widely naturalized outside this range.	Aerial parts/crude ethanol (CEE)	Phenolic compound, Kaempferol, Quercitrin, Chlorogenic acid, Caffeic acid	male Wistar rats (140 ± 10 g)	The CEE at dose of 600 mg/kg orally, displayed anti-hyperuricemic activity and reduce uric acid levels.	[38, 45]
Piper betle L.,	Piperaceae,	It grows in South and East Asia like India and Indonesia.	Leaves/ ethanol	Flavonoids, Phenolic compound, Tannin, Phenols	male white rats	The both leaves of betel and breadfruit extracts by oral doses 332 mg/200g BW and 500mg/200g BW respectively, have significant reduction effect on uric acid levels in white male rats.	[45, 49]
Artocarpus altilis(Parks.) Fosb.	Moraceae	It grows in Southeast Asia and most of the Pacific Islands.	Leaves/ ethanol				

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Table 1. The previous studies carried out on the effect of some plants species on xanthine oxidase activity in hyperuricemia (Continue)

Scientific name	Family	Distribution area	Organ of plant/solvent used for extract or form of treatment	Important Compounds*	In vivo/In vitro	Results	Reference
Aloe barbadensis Miller	Asphodelaceae	South-East Arabian Peninsula in the Hajar mountains in north-eastern Oman and eastern U.A.E.	Gel/ ethanol	Polyphenols, Glycoproteins, Polysaccharides, Phytoestrogen, Anthraquinones	female Wistar rats (200-220 g)	The mean serum uric acid concentration at a dose of 1200 mg/kg extract compared with control group was significantly reduced after 35 days.	[45, 50]
Vicia faba L., *Lotus edulis* L.	Fabaceae	It is now widespread in Europe, North Africa, Central Asia, China, South America, the USA, Canada and Australia. Widespread in southern Europe, North Africa and Southwest Asia	Aerial parts of plants /methanol	Kaempferol, Quercetin, Flavonoids, Phenolic compounds	in vitro	The results showed that these two plants have were potent inhibitors of xanthine oxidase with IC_{50} values range from 40–135 mg/mL and 55–260 mg/mL, respectively.	[45, 51]
Teucrium polium L.	Lamiaceae	Mediterranean countries, southwestern Asia, Europe, and North Africa/ Distribution in Iran: Gorgan, Azerbaijan, Kurdistan, Hamedan, Isfahan, Bakhtiari, Fars, Lorestan, Khuzestan, Khorasan, Kerman, Tehran, Semnan	Leaves and flowering branches/ methanol	Flavonoids, Phenolic compound, Anthocyanins, Alkaloids, Coumarins,	in vitro	The results of this study show that T. polium extracts from different habitat have had various inhibitory effects on XO activity. Ramian region samples show the highest inhibitory effect on the enzyme activity (91.45 + 6.623 %).	[45, 47, 52]
Physalis alkekengi L.	Solanaceae	Southern Europe to South Asia and Northeast Asia/ Distribution in Iran: organ, Mazandaran, Gilan, Azerbaijan, Kermanshah	Aerial parts/methanol	Phenolic compound, Flavonoids, Carotenoids, Anthocyanins, Luteolin, Quercitrin	in vitro	The results this research suggested that extracts from different parts of Physalis alkekengi at various phonological stages in 0.3 mg/ml concentration had high inhibitory effects on XO activity (45 to 86.86%).	[45, 47, 53]
Rhus coriaria L.	Anacardiaceae	Eastern Mediterranean, Crimea, Caucasus/ Distribution in Iran: Mazandaran, Azerbaijan, Hamedan, Bakhtaran, Isfahan, Bakhtiari, Fars, Tehran, Khorasan	Fruits/hydroalcoholic (ethanol)	Flavonoids, Phenolic acids	male mice (25-30 g)	The results showed that extract of this plant decreased uric acid level in a dose-dependent manner (at 250, 500 and 1000 mg/kg concentrations).	[45, 47, 54]

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Table 1. The previous studies carried out on the effect of some plants species on xanthine oxidase activity in hyperuricemia (Continue)

Scientific name	Family	Distribution area	Organ of plant/solvent used for extract or form of treatment	Important Compounds*	In vivo/In vitro	Results	Reference
Lycium arabicum Schweinf. ex Boiss.	Solanaceae	The genus has a disjunct distribution around the globe.	Leaves/methanol (CrE), chloroform (ChE), ethyl acetate (EaE), aqueous (AqE)	Phenolic compound, Quercitrin, Phenolic acids, Catechin, Flavonoids	adult male mice (25 - 30 g)	The results of this study showed that EaE was the most potent inhibitor of uric acid formation (IC_{50} = 0.017 ± 0.001 mg/mL) and it reduced serum uric acid level in hyperuricemic mice (4.71 ± 0.29 to 1.78 ± 0.11 mg/L).	[45, 55]
Apium graveolens L.*var. Dulce* (celery),	Apiaceae,	The temperate and Mediterranean areas of North Africa, Europe, and Asia/ Distribution in Iran: Mazandaran, Gilan, Lorestan, Hormozgan, Khorasan, Semnan	Leaves of plants/ aqueous, methanol	Flavonoids, Coumarins, Saponins, Carotenoids, Chlorophyll, Ascorbic acid	male albino rats (160-205 g)	The study found that ethanolic extracts were more active than aqueous in terms of the inhibitory effect of XO. Oral administration of celery, leek, parsley (5 g/kg), and molokhia (4.8 g/Kg) showed a significant decrease in uric acid.	[32, 45, 47]
Allium porrum L. (leek),	Amaryllidaceae	Leek is found in the Mediterranean region and the Near East. Leek is not found in the wild. It is cultivated in many countries including Iran.					
Petroselinum crispum (Mill.) Fuss (parsley),	Apiaceae,	This plant is native to Greece, Morocco and former Yugoslavia. In Europe and other parts of the world and Iran, it is widely cultivated as a plant and vegetable.					
Corchorus olitorius L. (molokhia)	Tiliaceae	It probably grows wild or as a crop in any country in tropical Africa.					
Averrhoa carambola L.,	Oxalidaceae,	This plant is native to Sri Lanka, India and Indonesia.	Different parts of plants / aqueous, methanol and ethanol	Phenolic compound, Tocopherols, Alkaloids, Flavonoids, Coumarins,	in vitro	The results shown that an aqueous extract of *Carica papaya* mature leaves has promising activity to inhibit XO up to 75.68 ± 0.1%.	[45, 56]
Carica papaya L.,	Caricaceae,	Native to tropical America, papaya originates from southern Mexico and Central America. Papaya cultivation is now, spanning Hawaii, Central Africa, India, and Australia.					
Manilkara zapota L.,	Sapotaceae,	It is an evergreen tree native to southern Mexico and Central America.					
Salacca zalacca(Gaertn.) Voss.,	Arecaceae,	It is a species of palm tree native to Java and Sumatra in Indonesia.					
Dimocarpus longan subsp. *malesianus* Leenh.	Sapindaceae	The longan is believed to originate from the mountain range between Myanmar and southern China. Other reported origins include Indonesia, India, Sri Lanka, upper Myanmar, north Thailand, Cambodia, north Vietnam and New Guinea.					

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Table 1. The previous studies carried out on the effect of some plants species on xanthine oxidase activity in hyperuricemia (Continue)

Scientific name	Family	Distribution area	Organ of plant/solvent used for extract or form of treatment	Important Compounds*	In vivo/In vitro	Results	Reference
Hibiscus sabdariffa L.	Malvaceae	This plant is native to Africa and entered Iran as a migrant species and is also cultivated in Sistan and Baluchistan and Khuzestan provinces.	Flower/ aqueous	Flavonoids, Anthocyanins, Polyphenols	male Sprague–Dawley rats (150 ± 20 g)	The serum uric acid levels of hyperuricemic rats, in compare by control with high doses of 5% this extract were lowered significantly by 0.9 and 1.0 mg/dL in 2 and 5 weeks.	[45, 47, 57]
Capparis spinosa L.,	Capparaceae,	This plant is native to the Mediterranean and is used in Cyprus, Italy, Greece, North Africa and some parts of Asia. In Iran, it grows in the provinces of Ardabil, Ilam, Fars, Bushehr, Kermanshah, Khuzestan, Kohgiluyeh and Boyer Ahmad, Yazd, Sistan and Baluchistan, Kerman.	Aerial parts/ aqueous	Flavonoids, Coumarins, Polyphenols, Anthocyanins,	in vitro	The results showed that , *Mentha longifolia* and Phaseolus vulgaris with 72% and 27% inhibition effects on XO at concentration of 3 mg/mL, have had strong and moderate effects in comparison with the control group, and the another plants had no inhibition effect .	[45, 47, 58]
Cichorium intybus L.,	Asteraceae,	The main origin of this plant is Central Europe, Western and Central Asia and North Africa, and it is widely distributed in different regions of Iran.	Aerial parts/ aqueous				
Mentha longifolia (L.) Hadson.	Lamiaceae,	Distribution: Europe to Asia, Iran, Turkmenistan, Afghanistan/In Iran: Azerbaijan, Mazandaran, Hamadan, Fars, Kerman, Tehran, Yazd.	Aerial parts/ aqueous				
Phaseolus vulgaris L.,	Fabaceae,	This species is native to tropical America and from there it was taken to Egypt and India and then to Europe or other places in the world. / In Iran, it is mainly cultivated in the provinces of Central Province, Lorestan, Fars and Zanjan.	Fruit/ aqueous				
Cinnamomum zeylanicum Blume	Lauraceae,	Is native to India, Sri Lanka, Bangladesh and Myanmar.	Bark/ aqueous				
Trigonella foenum-graecum L.,	Fabaceae	Distribution: Iran, Afghanistan, Iraq, Pakistan, Mediterranean region, Turkey, Syria, Caucasus, Arabia, Ethiopia/In Iran: Azerbaijan, Isfahan, Fars, Lorestan, Tehran, Kerman, Semnan, Sistan, Khorasan	Aerial parts/ aqueous				

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Table 1. The previous studies carried out on the effect of some plants species on xanthine oxidase activity in hyperuricemia (Continue)

Scientific name	Family	Distribution area	Organ of plant/solvent used for extract or form of treatment	Important Compounds*	In vivo/In vitro	Results	Reference
Tabebuia roseoalba (Ridl.) Sandwith	Bignoniaceae	This plant is a Brazilian forest species and also is widely distributed in Paraguay, Bolivia and Peru.	Leaves/ aqueous	Chlorogenic acid, Caffeic acid	male albino Swiss mice (25–30 g)	This research showed that the aqueous extract of studied plant in concentration of 500 mg/kg weight body and with inhibition liver XO activity greater than 45%, has anti-hyperuricemic and anti-gout effects.	[45, 59]
Adenanthera pavonina L.	Fabaceae,	The tree has also been introduced in the following countries of the Americas: Brazil, Costa Rica, Honduras, Cuba, Jamaica, Puerto Rico, Trinidad, Tobago, Venezuela, and the United States, especially in southern Florida.	Leaves of plants/ methanol	Alkaloids, Cardiac glycosides, Flavonoids, Phenolic compounds, Saponins, Steroids, Tannins, Terpenoids	in vitro	Among the plants studied in this research, *Blumea balsamifera* have had the highest percent of XO inhibition (79.67%), and followed by Mimosa pudica with 62.36%. Mimosa pudica showed the lowest IC_{50} of 32.8 µg/mL.	[45, 47, 60]
Antigonon leptopus Hook. & Arn.,	Polygonaceae,	A. leptopus is native to the Pacific and Atlantic coastal plains of Mexico. It is widely introduced in the south and eastern United States, the West Indies, South America, and the Old World tropics of Asia and Africa.					
Blumea balsamifera (L.) DC.,	Asteraceae,	Species from the genus Blumea are distributed across tropical Asia, Africa, and Oceania.					
Calophyllum inophyllum L.,	Calophyllaceae,	Plants of this genus are mainly distributed in Asia and some of its species in Africa, America, Australia and Pacific Islands.					
Cassia alata L.,	Fabaceae,	It is an invasive species in Austronesia distributed in ranges from India to America.					
Cassia fistula L.,	Fabaceae,	The species is native to the Indian subcontinent and adjacent regions of Southeast Asia./ It is planted in the south of Iran, such as Baluchistan.					
Gliricidia sepium (Jacq.) Kunth.,	Fabaceae,	The native range of this species is Mexico to Colombia.					
Michelia alba,	Magnoliaceae,	Native to tropical and subtropical south and southeast Asia, including southern China.					

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Table 1. The previous studies carried out on the effect of some plants species on xanthine oxidase activity in hyperuricemia (Continue)

Scientific name	Family	Distribution area	Organ of plant/solvent used for extract or form of treatment	Important Compounds*	In vivo/In vitro	Results	Reference
Mimosa pudica L.,	Fabaceae,	Mimosa pudica is native to the tropical Americas. It can also be found in Asian countries such as Singapore, Bangladesh, Thailand, India, Nepal, Indonesia, Taiwan, Malaysia, the Philippines, Vietnam, Cambodia, Laos, Japan, and Sri Lanka.					
Portulaca oleracea L.,	Portulacaceae,	Dispersion: Iraq, Azerbaijan, Iran, Turkmenistan, Afghanistan, Pakistan./In Iran: Mazandaran, Fars, Yazd, Isfahan, Bakhtiari, Kurdistan					
Pogostemon cablin Benth.,	Lamiaceae,	It is native to the island region of Southeast Asia, including Sri Lanka, Indonesia, the Malay Peninsula, New Guinea, and the Philippines. It is also found in many parts of North East India, and is now extensively cultivated in tropical climates around the world.					
Solanum torvum Sw.,	Solanaceae,	The native range of this species is Mexico to N. South America, Caribbean, E. Brazil.					
Tinospora rumphii Borel.,	Menispermaceae,	Tinospora sp. is found in tropical and sub-tropical parts of Asia, Africa and Australia.					
Vitex negundo L.	Lamiaceae	Vitex negundo is native to tropical Eastern and Southern Africa and Asia. Countries it is indigenous to include Afghanistan, Bangladesh, Bhutan, Cambodia, China, India, Indonesia, Japan, Korea, Kenya, Madagascar, Malaysia, Mozambique, Myanmar, Nepal, Pakistan, the Philippines, Sri Lanka, Taiwan, Tanzania, Thailand, and Vietnam.					
Salvia syriaca L.	Lamiaceae	58 species of Sylvia have been identified in different parts of Iran, 17 of which are unique to Iran.	Aerial parts/ethanol	Flavonoids, Tannins, Phenolic compound, Sesquiterpenes, Monoterpenes, Thymol	male Wistar rats (200-250 g)	Oral treatment of alcoholic plant extract with doses of 100 and 200 mg / kg body weight showed a significant decrease in blood uric acid levels in healthy and diabetic rats ($P < 0.001$).	[45, 47, 61]
Chrysanthemum indicum L.,	Asteraceae,	East Asia and northeastern Europe. The native range of this species is Himalaya to China to N. Indo-China, Korea, and Japan.	Flower/ ethanol	Chlorogenic acid, Coumarin, Cinnamaldehyde,	in vitro, male Sprague–Dawley rats (7 weeks)	The results of this study suggested that the combination of these both plants, with 23.2±0.4, 94.3±3.2, and 101.0±0.2% had inhibited XO activity at concentrations of 100, 250 and 500 μg/mL, respectively.	[10, 45]
Cinnamomum cassia Presl.	Lauraceae	This plant is distributed in China, India, Vietnam, Indonesia and other countries.	Bark/ ethanol				
Sparattosperma leucanthum (Vell.) K.Schum.	Bignoniaceae	Its native range is Southern Tropical America.	Leaves/ethyl acetate (SLE), methanol (SLM), water (SLW)	Flavonoids, Saponins, Triterpene, Steroids	male albino Swiss mice (25-30 g)	SLW, at the dose of 125 mg/kg; orally, SLM and SLE on all doses tested (125, 250 and 500 mg/kg) have capable to reduce hyperuricemia.	[45, 62]

*The "Most Important Compounds" column in this table contains the plant compounds that they have been cited more in each study.

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4. Discussion

As the data shown in the table 1, much research has been done to reduce UA levels and find XO inhibitors were developed by using natural sources. In order to investigate the effects of *Chrysanthemum indicum* L. (CI) and *Sida rhombifolia* L. plants on different groups of herbal volunteers, Hirano et al. [44] and Marpaung and Siregar [46] respectively showed; herbal therapies with these two used medicinal plants in volunteer group had a significant reduction in UA levels compared to the control group. In the chemical structure of these selected plants, compounds such as flavonoids and polyphenols present and are of special importance.

Our previous research showed that flavonoid compounds such as luteolin in psyllium seeds (*Plantago psyllium* L.) with the concomitant use of allopurinol by synergistic creating effects were able to inhibit the XO enzyme and reduce elevated UA levels in patient with hyperuricemia [15]. Our subsequent studies on other patient of hyperuricemia also showed that this plant alone can inhibit the XO and reduce blood UA level [63]. Psyllium is a medicinal plant that has been used in traditional Iranian medicine in the treatment of gastrointestinal diseases and inflammation of the kidneys and bladder; and due to the presence of high levels of phenolic compounds in this plant, as a result, it has strong antioxidant properties [64].

The study results of Lee et al. [10] have also shown that the use of combination two plants of *Cinnamomum cassia* Presl. (CC) and CI were able together enhance anti-hyperuricemic properties *in vivo* by creating synergistic effects. These two plants have been used to treat hyperuricemia and gout in traditional Chinese and Korean medicine. The mixture of two plants and their compounds inhibited XO activity *in vitro.* The most important components in CI extract, namely chlorogenic acid (CGA) and 3,4-dicaffeoylquinic acid, as well as coumarin, cinnamaldehyde, *trans*-cinnamic acid, and *o*-methoxycinnamaldehydein CC extract, have been reported to be responsible for the inhibitory effects on XO.

The study results of Apaya and Chichioco-Hernandez [60] on a number of species of Philippine medicinal plants showed that some of these plants have a higher potential to inhibit the XO enzyme. The most important compounds that were known to be effective in their research were included with flavonoids, phenolic compounds, Tannins, alkaloids and terpenoids. The results of Limos Lima [62] and Eidi [61] *in vivo* experiments on extracts of *Sparattosperma leucanthum* (Vell.) K.Schum. and *Salvia syriaca* L., respectively, showed that these extracts reduce the serum level of UA in laboratory animals in a certain dose. The best known components of these plants in these studies were flavonoids, tannins, phenolic compounds and terpenes.

In the research of Faizal et al. [49], Das et al. [54], Trabsa et al. [55]and Kuo et al. [57], which were performed on plants of different families, reported a significant decrease in UA levels after the use of plant extracts. The most important compounds in these plants were included with flavonoids, phenolic compounds and phenolic acid. In the research of Nguyen et al. [38] and Ferraz-Filha et al. [59] plant extracts also reduced UA in specific doses. The most important plant compounds in these two studies were CGA and caffeic acid.

In other studies, plant extracts have reduced UA levels and inhibited XO enzyme. The most important compounds in these researches were polyphenols, flavonoids, coumarins, anthocyanins and phenolic compounds [32, 50-53, 56, 58].

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Researches on the potential of herbal treatments in the treatment of hyperuricemia in other countries have also reported promising results. Research on the effectiveness of Chinese herbal medicines shows that they have promising clinical effects compared to western medical treatments in patients with high serum uric acid levels [65]. The results of the research of Dong et al.'s (2023) showed that the ethanolic extract of Amomum villosum Lour. is able to treat hyperuricemia by reducing the production of uric acid by inhibiting xanthine oxidase and increasing the excretion of uric acid by regulating the urate transporter. Also, the extract showed a special protective effect on liver and kidney damage caused by hyperuricemia [66].

In the study of Cheng-yuan and Jian-gang (2023), common medicinal and edible plants with uric acid-reducing effects were investigated. Their results showed that different bioactive components of uric acid reduction mechanisms in the potential role of medicinal and edible plants are divided into five categories: flavonoids, phenolic acids, alkaloids, polysaccharides and saponins. These active ingredients show the positive effects of reducing uric acid by inhibiting uric acid production, increasing uric acid excretion and improving inflammation [67].

Some of these plants have been used in the traditional medicine of many lands as a decoction, infusion with water – soluble form containing biologically active compounds and sometimes these herbs could be used as nutrition [32, 52-54, 56, 63] However , most extracts were also prepared with both of water or alcohol in laboratory studies done by this kind of herbs.

4.1. Determining the effective dose in studies

In reviewed studies, it has been shown that plant compounds in certain doses inhibit XO or reduce UA levels (25-100 µg/mL [48], 600 mg/kg [38], 332- 500 mg/200g [49], 1200 mg/kg [50], 40-135 & 55-260 mg/mL [51], 0.3 mg/mL [53], 250-1000 mg/kg [54], 5 & 4.8 g/kg [32], 3 mg/mL [58], 500 mg/kg [59], 125-500 mg/kg [62], 100-500 µg/mL [10], 100-200 mg/kg [61]). The necessity to determine the effective dose in the treatment and effectiveness of all drugs and herbal compounds is very important. In addition to identifying and determining the amount of drug used, this issue also distinguishes the therapeutic dose from the toxic dose [68]. Although no toxic dose was determined in the mentioned studies, knowing these doses about some drugs and herbal compounds such as glycosides which the distance between their therapeutic and toxic doses are very close [69]. Obviously, this type of study especially in human studies would be very necessary and important.

4.2. Summary of research conducted

Among the findings of researchers, flavonoids are the apex of many propounded compounds with XO enzyme inhibitory action [49, 51, 70-72]. The potential role of compounds with antioxidant properties such as phenolic compounds and flavonoids in the inhibition of XO enzyme is very important and decisive. Phenolic compounds, especially flavonoids, are very important in human health due to their high antioxidant capacity. They may act as terminators of free radical chain reactions [73]. Flavonoids are found in foods of plant origin and based on their structural differences; they are divided into subgroups of chalcones, flavanones, flavones flavanonols, flavonols, isoflavones, catechins and anthocyanidins [71] (Fig. 4).

A few valuable effects such as antiviral, anti-allergic, anti-platelet, anti-tumour, antioxidant, and anti-inflammatory, have been reported for flavonoids and attention to these compounds is

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increasing because they can be beneficial to human health [14, 74]. By inhibiting XO, flavonoids inhibit the production of active superoxide radicals, thereby blocking one of the main sources of free radical production and tissue damage. Also, flavonoids inhibit the release of toxic oxidants and the formation of oxygen-derived free radicals by reducing the number of immobile leukocytes and inhibiting the degranulation of neutrophils [75]. Flavonoids can bind to the active site of the enzyme and inhibit its activity due to the structural similarity with XO enzyme substrates, [72]. Using structural molecular modelling, it has been shown that among the flavonoids; apigenin the strongest XO inhibitor, has a stronger interaction to the active site of the enzyme [53].

Other compounds mentioned in the chemical structure of the plants studied in the present research were included of coumarins, tannins, catechins, anthocyanins, phenolic compounds, chlorogenic acid, caffeic acid and cinnamaldehyde (Fig. 5) [76-78].

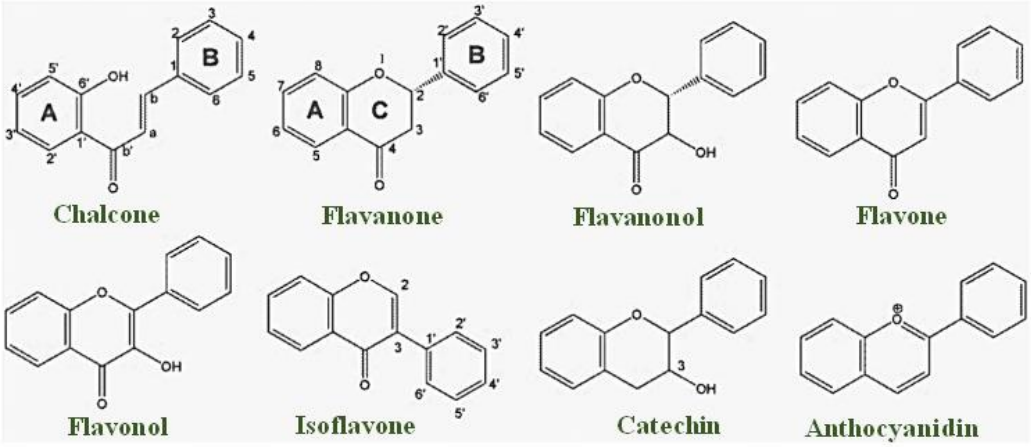

Fig.4. Classification of flavonoids based on their chemical structure [59]

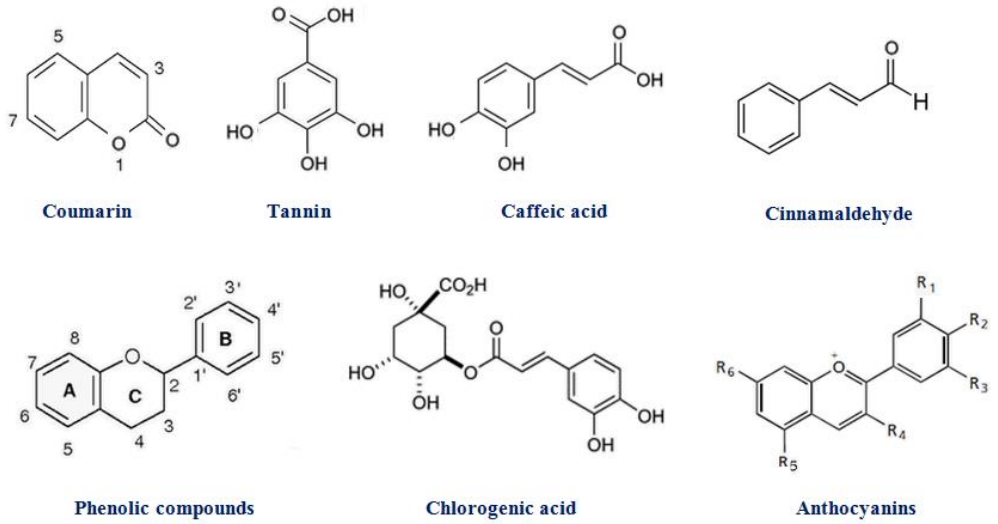

Fig. 5. The chemical structure of some of the plant compounds discussed in this study [64-66]

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Generally, phenolic compounds, especially polyphenols and flavonoids are the most important natural antioxidants that found in many plants [64]. Chlorogenic acid is one of the phenolic compounds and a derivative of caffeic acid that has anti-tumour and anti-inflammatory properties and is present in a variety of plant species [70]. Laboratory research has shown that CGA and caffeic acid are antioxidants that are also role in the prevention of type 2 diabetes and cardiovascular disease. They also have antiviral, antibacterial and antifungal properties, with very low toxicity and uncomplicated effects [79]. Chlorogenic acid significantly reduces serum UA levels by inhibiting XO enzyme activity. In addition, CGA improves the symptoms of inflammation caused by MSU crystals by inhibiting the production of proinflammatory cytokines including interleukin-1β (IL-1β), interleukin-6 (IL-6) and TNF-α [80].

Anthocyanins also have antioxidant and anti-inflammatory activities and are found in berries, fruits, flowers and leaves [81]. Regarding the mechanism of action of their activity, some studies have shown that the replacement of hydroxyl (OH) with sugars in the structure of anthocyanins can inhibit the activity of XO in relation to aglucone anthocyanins. Also, steric interactions reduce the inhibitory effect on XO [76]. Cinnamaldehyde protective mechanisms reduce UA levels by inhibiting XO activity and suppressing inflammatory signaling cascade; IL-6 / JAK1 / STAT3; and also it reduces inflammation by increasing antioxidant defense and decreasing pro-inflammatory cytokines [82]. Coumarins are also natural products found in plants with a wide range of biological activities and act as scavengers of free radicals and absorption of harmful ROS [83]. The results of a systematic in vitro study on eighteen coumarin derivatives to evaluate the ability protect of cells against oxidative stress from XO; identified 6,7-dihydroxylated coumarin as the most effective inhibitors of XO [77].

5. Conclusion

The selection of suitable medicinal plants for use in pharmacy, and the screening of their extracts to identify and introduce safe and newer drugs for the treatment of various diseases, especially gout, are of particular importance. In this study, the effect of several plant extracts used in different countries to inhibit xanthine oxidase enzyme and reduce uric acid levels in the treatment of gout and hyperuricemia was reviewed. The evaluation of these studies was based on specific doses of compounds from natural products that have high potential in terms of antioxidant properties and can confront with various pathological conditions caused by free radicals in these diseases. The most important compounds that received special attention in all studies were the role of flavonoids in inhibiting the xanthine oxidase. The results of all these studies indicate the key role of plants and the effectiveness of their compounds, especially flavonoids, in the health, immunity and treatment of hyperuricemia and gout. It is also very important to determine therapeutic doses in the consumption of herbal compounds and to maintain the balance of the presence of uric acid in the body.

Suggestion for future research

Despite the extensive research that has been done on the effectiveness and replacement of medicinal plants and herbal medicines so far, but regarding the safety of this type of treatment, and determining the appropriate dose, as well as the simultaneous use of both modern and traditional treatments, the need for further investigation and research seems necessary.

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Author contributions

G A-R searched for the articles, and wrote the first draft. M A contributed to the study process. A E-N designed the study and contributed to the writing process and analysis, and as a study supervisor, he provided the final manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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