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Short Review

Effects of Natural Substances on Lowering Uric Acid

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Abstract

Uric acid (UA) metabolism, which includes uric acid production controlled by purine metabolism and uric acid excretion controlled by the gastrointestinal tract and kidneys, is the primary way to maintain the concentration of uric acid in the body. Abnormal functionalizing of the metabolism may cause hyperuricemia, gout, kidney injury, and other diseases. Over the last decade, numerous studies have been conducted on the effect of natural products, including active ingredients of medicinal plants, natural compounds, plant and fungal extracts, traditional herbal formulations, microbial products, alkaloids, etc., on the downward regulation of uric acid for treating uric acid related diseases. Based on the potential sources from 2018 to 2022, 16 studies were reviewed and considered relevant to the topic. This paper is a preliminary summary of the effects of active ingredients of plants, the extracts of plants, and traditional herbal formulations on regulating uric acid levels.

Keywords

Uric acid; gout; natural; metabolism

1. Introduction

Uric acid (UA; $C_5H_4N_4O_3$; 7,9-dihydro-1H-purine-2,6,8(3H)-trione) is the end product of purine metabolism in the human body. Energy-consuming processes and dietary intakes in human life produce inosine monophosphates (IMP). Catalyzed by xanthine oxidase, the hypoxanthine part of IMP becomes xanthine and is further catalyzed by xanthine oxidase to form uric acid [1]. Due to the deficiency of uricase, UA cannot be further broken down in the body and can only be excreted through the gastrointestinal tract and urine. Excessive production and insufficient excretion of UA in the human body caused by aging, dietary habits, environment, and social factors may lead to abnormal UA metabolism and then lead to hyperuricemia and later gouty arthritis.

UA enters the body primarily through the purine metabolism and dietary intake, goes from the blood to the kidneys, and then is eliminated in the urine. Serum uric acid (sUA) level reflects the amount of uric acid in the body; a high level of sUA means uric acid is not overall eliminated in the kidneys. Urine uric acid (uUA) level reflects the amount of uric acid metabolism; a high uUA level means a good purine metabolism level and helps reduce the human body's UA level. The low UA level in urine indicates insufficient and attenuated UA metabolism of the human body, which leads to the high UA level in the blood and, thus, the threat of hyperuricemia. Gout is inflammatory arthritis caused by the formation of monosodium urate (MSU) crystals in or around the joints by serum urates [2]. Abnormal UA metabolism is the leading cause of gout, which can be reflected in the persistently high level of sUA and low level of uUA.

Allopurinol and febuxostat are widely recognized and used to reduce the amount of uric acid produced by a patient's body [3, 4]. However, allopurinol may cause fever, rash, hepatitis, and kidney damage [5]. Febuxostat has side effects of rash, nausea, liver function impairment, and increased risk of cardiovascular disease [4]. Given that existing treatment options are not abundant nor personalized and have terrible side effects, developing new drugs with obvious efficacy and few side effects is urgent. Natural products, with their abundance of bioactive compounds, a history of therapeutic reporting, and complex synergistic pathways, are promising options for developing new, highly effective drugs with few side effects. The great value of natural products has led to flourishing research about their effects on various diseases. In 2020, Roberta et al. reported oral cashews' antioxidant and protective effects on ischemia-reperfusion in a rat model [6]. The following year, Roberta et al. reported the protective effect of Hidrox, a water extract containing 40-50% high hydroxytyrosol as a phytochemical in olive oil, against functional impairment side effects in men through an antioxidant mechanism [7].

Natural products are rich in bioactive compounds and exhibit complex synergistic pathways when they appear as formulations, which support their potential value for new drug discovery while increasing the difficulty of in-depth research on their mechanisms. At this time, network pharmacology, as a powerful tool, greatly helps researchers to carry out complex work. Network pharmacology as a drug design method is suitable for analyzing the potential of multi-component, multi-target, multi-pathway synergistic regulation and cure of disease [8]. With the development of research techniques in recent years, the spread of more efficient network analysis methods, and the improvement of databases, the usefulness of network pathology in the comprehensive analysis of the potentially complex relationships between plant formulations and the whole body has been highlighted [9]. The emerging network pathology provides a new and efficient method for predicting natural plant components with uric acid regulation ability.

In the past decade, many studies have been conducted on regulating UA *in vivo* or *in vitro* using natural substances such as plant extracts, herbal formulations, and active herbal ingredients. However, a comprehensive view of the latest natural products with uric acid lowering activity is lacking. As shown in Table 1, this article reviews 16 recent studies reported between 2018 and 2022 on natural plant active ingredients, extracts, or herbal formulations (*in vivo* or *in vitro* experiments) that have been shown to have the ability to directly affect uric acid levels in order to facilitate ongoing investigators to understand the latest results.

Table 1 Active ingredients, extracts, and formulations have been reported to lower UA.

Classification	Ingredient/Herb/ Formulations	Year	Authors	Research method	Result
Active Ingredients	Anthocyanins	2019	X. Qian, et al.	*In vivo.*	sUA ↓, XO activity↓, UA Production↓, UA Excretion↑
	12 compounds from *Clerodendranthus spicatus*	2020	W.D. Chen, et al.	*In vitro. and in vivo.*	UA Excretion↑
	Ursolic acid	2018	E. Abu-Gharbieh, et al.	*In vitro. and in vivo.*	UA↓, XO activity↓
	Two triterpenes from *Alstonia scholaris*	2021	B.Y. Hu, et al.	*In vitro. and in vivo.*	UA↓
Combined Extracts	Mori Ramulus (Chin.Ph.)	2019	J. Yao, et al.	*In vivo.*	sUA↓
	Chrysanthemum indicum and *Cornus officinalis*	2021	O.K. Kim, et al.	*In vivo.*	XO activity↓, XO↓, UA Excretion↑
	Grapefruit	2020	A. Mehmood, et al.	*In vivo.*	sUA ↓, XO activity↓, UA↓
	Persicaria capitata	2021	C.L. Zhang, et al.	*In vivo.*	sUA↓, uUA↑, XO activity↓, XO↓
	Purple potato leaves	2022	R. Sun, et al.	*In vitro. and in vivo.*	UA↓, XO activity↓
	stevia rebaudiana	2022	A. Mehmood, et al.	*In vivo.*	sUA↓
	stevia rebaudiana	2020	A. Mehmood, et al.	*In vivo.*	UA Production↓, UA Excretion↑
	Tea	2022	S. Sang, L. et al.	*In vivo.*	UA↓, XO activity↓
Formulations	Chatuphalatika	2018	V.H. Sato, et al.	*In vitro. and in vivo.*	UA↓, XO activity↓
	Fresh ginseng paste	2022	H. Zhang, et al.	*In vivo.*	UA↓, XO activity↓, XO↓

Selaginella moellendorffii prescription	2019	X.Y. Zhang, et al.	*In vitro. and in vivo.*	UA↓
Simiao Powder	2022	H. Xu, et al.	*In vivo.*	sUA ↓, XO activity↓
Yokuininto	2019	S.H. Lee, et al.	*In vivo.*	sUA ↓, XO activity↓, UA Production↓, UA Excretion↑

2. Active Ingredients from Natural Plants on Lowering UA Levels

Research has shown that studying specific natural plant active compounds with UA-lowering effects is essential in developing new and highly effective drugs for controlling and treating gout-related symptoms.

Back in 2018, the study of the *Tribulus arabicus* extraction by Abu-Gharbieh et al. [3] indicated that the ursolic acid in the fraction of the hexane fraction is the active ingredient in the alcohol extract, which has a good effect on the reduction of UA. This study confirmed that ethanol extract of *Tribulus arabicus* exhibited a dose-dependent UA reduction in hyperuricemia BALB/c male mice induced by potassium oxalate (PO). In contrast, n-hexane fractions of the ethanol extract showed extremely significant ($p < 0.001$) UA reduction activity in both low-dose and high-dose groups. Ursolic acid therapy also showed a significant ability ($p < 0.001$) to reduce uric acid levels across both low and high doses. It is further demonstrated that ursolic acid is the main component of n-hexane that inhibits activity through xanthine oxidase (XO). According to the simulation results of the docking engine FRED (FRED 3.2.0.2 OEDocking software), ursolic acid plays an inhibitory role by docking XO active sites with a unique binding mode. Unlike traditional Febuxosta, and Allopurinol, which were combined with bulk solvent and molybdate cofactor channel into the deep inlet to exert their effect, like a plug, ursolic acid blocks the entrance of bulk solvent channel to the distal end of molybdate cofactor site, like a lip. The researchers also highlight the possibility of enhancing the specificity of XO inhibitors by expanding the interaction between ursolic acid and specific residues (Leu-648 and ph-649), where there is less selective pressure. Overall, the potential of ursolic acid as a uric acid lowering agent can be confirmed.

In 2021, Hu et al. [10] isolated two triterpenoids from the leaves of *Alstonia scholaris* that demonstrated strong UA regulation *in vitro* and *in vivo*. These two triterpenes have rearranged structures with 6/6/6/7/5 and 6/6/5/6/6/6 ring systems [10]. Based on the results of the determination of uric acid level induced by MSU *in vitro* and the determination of serum uric acid value by phosphotungstic acid method in a mouse hyperuricemia model established with potassium oxyate, Hu et al. indicated that it has an effective regulatory effect on UA. Its mechanism needs further study.

In the study of Chen et al. [11] on *Clerodendranthus spicatus* (kidney tea), a traditional Chinese functional food, for the treatment of gout, they found that the ethyl acetate extract of kidney tea could control the development of gout. Among the 32 compounds isolated, 12 compounds could reduce UA by promoting the excretion of UA at the dose of 10 μg/ml [11]. According to the positive results obtained from the determination of uric acid level induced by MSU *in vitro* and the comparison results with positive drugs in MSU-induced HK-2 cells, the urinary efficacy of orthosiphol N, A, B, and α-amyrin in 12 compounds had a more substantial uricosuric effect than

benzbromarone [11]. In further pharmacological experiments, compound 15 also showed significant control over UA levels in mice. These compounds show great potential as novel anti-gout drugs supporting urea excretion through intuitive numerical measurements *in vivo* and *in vitro* experiments, but the exploration of their mechanisms of action is yet to occur.

In 2019, the effect of the natural flavonoids anthocyanin on the sUA levels in the liver showed that anthocyanins significantly reduced the level of sUA in mice with high yeast, creatinine, and PO by inhibiting the formation of UA and promoting UA from the kidney system [12]. The study showed that anthocyanine regulates sUA by inhibiting the activity of XO and regulating the expression of the renal UA traceable protein to promote UA excretion.

Over the past five years, researchers have actively sought natural products with UA level regulation by discovering new compounds and studying ways to validate known compounds' ability to lower UA and mechanisms of action. Furthermore, this will be the direction of the work of researchers in this field for some time to come. Both report the extracted new compounds and their properties from herbal medicines and examine their basic properties. Continue to delve deeper into the mechanisms of action of these substances reported to have a role in uric acid regulation.

3. Combined Extracts of Natural Plant on Lowering UA Levels

Some studies have explored the chemicals in the plant extract. However, they have not yet demonstrated the specific principle of the chemical's lowering effect on uric acid, as mentioned in the previous module of this article.

In 2019, Yao et al. demonstrated that 60% ethanol extracts of the mulberry branch significantly ($p < 0.001$) reduced sUA levels in a PO-induced hyperuricemia mouse model in Kunming mice [13]. Moreover, they further isolated three organic compounds from morus branch extract by using the HPLC-MS method, namely Scopolin, moriramulosid A (umbelliferone-6-β-d-apiofuranosyl-(1→6)-β-d-Glucopyranoside), and moriramulosid B (6-[[6-O-(6-deoxy-α-L-Mannopyranosyl)-β-d-glucopyranosyl]oxy]-2h-1-benzopran-1-one) [13]. The latter two coumarin glycosides (moriramulosid A and B) were newly discovered in morus branch extract in this study. Moreover, the interaction or individual action of the three organic compounds in mulberry branch extract in the function of UA reduction needs further exploration.

In a study by Sun et al. 2020, they extracted by adsorbed 20% ethanol, then resin with AB-8 macroporous and purified with the methanol extracted the polyphenols (containing chlorogenic acid, seven caffeoylquinic acid derivatives, 3,4,5-tricaffeoylquinic acid, and coffee-based hexose) from purple potato leaves [14]. Quercetin, hypericin, quercetin-3-ohexoside, caffeic acid, rhamnetin, rutin, and luteolin-7-O-glucoside were identified as the main phenolic substance, of which chlorogenic acid (88.3%) was identified [14]. Furthermore, while they did not separate the subclasses further and study which substances have anti-UA effects, they used polyphenols from purple potato leaves (PSPLP), containing ten phenolic acids and six flavonoids, to treat potassium oxalate and yeast cream induced male Institute of Cancer Research (ICR) Mouse animal model of hyperuricemia. The PSPLP effectively ($p<0.05$) inhibited sUA levels in hyperuricemia mice [14]. It is speculated that chlorogenic acid in alcohol extracts containing polyphenols is the primary substance that interferes with abnormal UA metabolism and reduces UA secretion by interacting with XO to prevent substrates from being catalyzed. However, further research aims to clarify the unique compound identity of PSPLP reducing sUA, and its mechanism of action is desiderated.

From 2020 to 2022, Mehmood's team conducted ongoing work on regulating UA levels in hyperuricemia mice with stevia residue extract. In 2020, Mehmood et al. presented that Stevia residue extracts dissolved in CMC-Na aqueous solution could significantly reduce UA production and increase UA excretion in hyperuricemia mice through interaction with the uric acid transporter (URAT1) [15]. In 2022, Mehmood's team further found that stevia residue extract affects UA levels in the body through the regulation of matrix metalloproteinases [16]. Through their ongoing research on the UA regulation of stevia residue extracts, the mode of action of stevia extracts has been further explained through new technological means.

In addition, a 2020 study conducted by Mehmood's team [17], focused on the effects of grapefruit juice (GFJ) on mice with PO-induced hyperuricemia. Based on animal experiments, they found that grapefruit juice significantly reduced the UA level while effectively inhibiting XO activity, thereby regulating other levels of hyperuricemia and gout. Further analysis showed that GFJ increased renal uric acid excretion and decreased UA production by decreasing the expression of renal URAT1 and glucose transporter 9 (GLUT9) and increasing ATP Binding Cassette Subfamily G Member 2 (Junior Blood Group) (ABCG2) mRNA levels. Along with the study of Mehmood's team's analysis and research on the index detection, histopathology, and immunohistochemistry of PO-induced Kunming mice model and obtained the results that grapefruit juice reduced UA level and other related indicators regulated the expression of related genes, further research should focus on the anti-high UA active ingredients in grapefruit juice and their mechanism of action. In addition, although this study does not explicitly suggest the reported effect of grapefruit juice on the expression of genes associated with UA regulation, it may be explained more deeply by epigenetics.

In 2021, Kim et al. found *Chrysanthemum indicum* and *Cornus officinalis* extracts to reduce sUA levels by increasing the amount of UA [18]. At the same time, the combined use of *Chrysanthemum indicum* and *Cornus officinalis* showed better low UA activity than separately [18]. The *in vitro* cell experiments demonstrated that reducing UA in wild *Chrysanthemum indicum* and *Cornus officinalis* extracts inhibited XO activity and the mRNA of xanthine dehydrogenase. The use of epigenetic tools may be able to explain further the effects of wild chrysanthemum and dogwood extracts on gene expression in subsequent studies.

In 2021, Zhang et al. [19] found that water extract and alcohol extract of *Persicaria capitata* showed the ability to significantly reduce sUA and increase uUA levels in the hyperuricemia mouse model. They also indicated that *Persicaria capitata* extract regulates UA levels *in vivo* by inhibiting XO activity and expression and down-regulating the mRNA and protein expression of GLUT9 and URAT1 [19]. Although the active ingredients in the crude extract were not examined in this study, the mechanism of UA regulation of *Persicaria capitata* extract was explored by epigenetic means.

Sang et al. [20] studied the UA lowering effects of various teas, including green tea, yellow tea, black tea, white tea, red tea, and cyan tea, on rat models. According to the measured results, except for green tea, all tea administration groups showed significant down-regulation of UA ($P < 0.01$), and black tea and yellow tea had perfect UA lowering ability ($P < 0.0001$) [20]. The yellow tea showed a good comprehensive effect comparable to benzbromarone treatment and Traditional Chinese Medicine (TCM) Simiao San treatment in more comprehensive indicators. Sang's team used network pharmacology tools to analyze yellow tea's active ingredients and targets. Through the Protein-protein interaction (PPI) network constructed by the STRING database, yellow tea obtained a compound target network of 35 targets and ten active compounds associated with hyperuricemia [20]. Molecular complex assays further identify key targets, including inflammasome, peroxisome

proliferator-activated receptor-α, interleukin-1β (IL-1β), interleukin-6 (IL-6), and so on [20]. This is a good example and attempts to apply network pharmacological tools to analyze the active ingredients of a specific natural product extract and the corresponding therapeutic targets for the target disease, symptom, or efficacy.

Before extracting and isolating the active molecules in natural products, evaluate and experimentally demonstrate the UA lowering ability of a plant or natural product extract when its medicinal value has not been clearly reported and rigorously demonstrated. These reports provide clues and a basis for subsequent studies to understand the UA regulation function of single phytochemicals derived from natural products. In addition, many studies [17, 18] have focused on the differences and effects of gene expression in different dosed therapies but have not explored their epigenetic modalities in more depth. Using epigenetic tools to study the changes in silencing and active regions of its genes has important implications for human understanding of the effects of lifestyle and diet on UA metabolism. On the other hand, through network pharmacology and non-targeted metabolomics studies, Sang et al. [20] and we have the opportunity to more efficiently map the effective active ingredients, targets, and associated signaling pathways. This points the way for further research to facilitate the screening of potentially valuable drug candidates.

4. Herbal Formulations on Lowering UA Levels

According to the traditional preparation formula of certain local plants, various plants could reduce UA levels and treat gout. The study by Sato et al. 2018 [21] proved that chatuphalatika (CTPT) (a Thai herbal formula for traditional gout treatment) has a significant inhibition of UA, including the fruits of the herbs, such as *Phyllanthus emblica*, *Terminalia belerica*, *Terminalia chebula* and the fruit of *Terminalia arjuna*. Oral treatment with 250 mg/kg and 500 mg/kg CTPT aqueous extract decreased the sUA level of hyperuricemia mice induced by potassium oxalate. Among them, the oral dose of 1000 mg/kg CTPT aqueous extract group showed a significant reduction *in vivo* sUA level ($P < 0.05$) [21]. They are *in vitro* determination of sUA by HPLC using sUA calibration curves and also supported the reduction of sUA by quantitative sUA CTPT extract [21]. This may be related to the typical reversible inhibition of non-competitive enzymatic responses shown by inhibiting XO activity. Moreover, further investigations into how CTPT acts on regulating serum urea acid *in vivo* and the specific role of its components are expected.

In traditional Japanese medicine and therapy, Kampo medicine, Yokuininto is a combination drug for the treatment of osteoarthritis or rheumatoid arthritis that usually includes *Coicis Semen*, *Angelicae Sinensis*, *Atractylodis Macrocephalae*, *Ephedrae Herba*, *Cinnamomi Cortex*, *Paeoniae Radix*, and *Glycyrrhizae Radix*. In 2019, Lee et al. studied the effect of Yokuininto on gout attack and kidney injury [22]. The experiment on the UA lowering effect of the Yokuininto by PO-induced high sUA state in Male ICR mice was conducted [22]. They found that the extract of Yokuininto at a dose of 300 mg/kg drastically reduced the sUA level by about 44% in the PO-induced mouse model [22]. At the same time, they further studied the transport characteristics of the extract of Yokuininto and found that the extract actively entered cells and played a role in enhancing urate secretion and inhibiting urate reabsorption through the organic anion transporter 3 (OAT3) [22]. In general, the study of Lee et al. has shown that Yokuininto reduces sUA by inhibiting the catalytic activity of XO to inhibit UA production directly.

Selaginella moellendorffii prescription (SMP), a combination of *Selaginella moellendorffii* (SM), *Smilacis glare* (SGR), and *Plantaginis Semen* (PS) for the treatment of gout and hyperuricemia, has been around for thousands of years. A significant inhibitory effect on sUA levels has been reported [23]. In a study by Zhang et al. [23], the optimal compatibility ratio of SM, SGR, and PS in SMP was explored. In the Kunming mice's PO-induced hyperuricemia mouse model, Blood Urea Nitrogen showed a significant ($P < 0.05$) reduction in the group that gavaged SMP. However, the mass fraction of SM:SGR:PS in the formula 3:1:1 group showed highly significant ($P < 0.01$) reductions in Blood Urea Nitrogen and UA [23]. This experiment even decreased the sUA level below the normal control group, which indicated the potential of SMP for treating gout. The results also showed that SM played the most critical role in SMP, while SGR and PS assisted and enhanced its regulatory effect. However, further studies need to clarify the identity and mechanism of the active ingredients in the water extracts of SM that play the role of UA regulation.

Zhang et al. used network pharmacology and molecular docking methods to analyze 25 related targets and five active compounds of food ginseng paste (FGP, containing *Radix ginseng*, and *Ziziphus jujube*) and hyperuricemia [24]. PPI analysis showed that TNF-α, IL-1β, and VEGFA were the core pathways of ginseng extract. Based on the molecular docking verification results, The main active compounds in FGP ((20R)-ginsenoside Rg3, ginsenoside Rg5, ginsenoside Rh4, oleanolic acid, and kaempferol) are associated with crucial targets of hyperuricemia (TNF-α, IL-1β, Vascular Endothelial Growth Factor A (VEGFA), and XO) bind stably and have good UA inhibitory activity. In animal experiments, FGP did show the ability to reduce sUA and significantly inhibit XO activity and liver XO level ($p < 0.05$) [24]. However, more experimental verification of the results of molecular docking verification is the goal of further work.

In 2022, Xu et al. used network pharmacological means to analyze the TCM Simiao Powder (SmP, consisting of *Atractylodes Lancea*, *Phellodendri Chinrnsis Cortex*, *Cyathulae Radix*, *Coicis Semen*), Twenty of the active ingredients were thought to interact with 19 targets of gout [25]. The four potentially active compounds of Simiao San (quercetin, beta-sitosterol, stigmasterol, wogonin) had high binding energy with the amino acid residues of the target IL-6, PTGS1, PPARG, BCL2, and had good regulatory ability [25]. Animal results show that SmP has almost the same significant function as allopurinol in lowering UA ($P < 0.001$) but shows fewer side effects and renal function regulation [25]. Through the flexible use of a wealth of advanced analytical means and tools, Xu et al. efficiently analyzed the active ingredients with targeted regulatory effects in SmP and conducted further verification. However, there are still many results obtained from digital analysis that need to be further studied.

There are abundant resources of indigenous formulations worldwide that are potential solutions to many of humanity's most troubling diseases. The work to validate these traditional medical formulations is extensive and needs to be continuously perfected. In the past, demonstrating the efficacy of each ingredient in a formula and finding the most effective ingredient and corresponding target was a tedious and complex task, let alone sorting out the mechanism of action. However, evolving technology provides increasingly sophisticated database resources and electronic data analysis tools to help us quickly get reference answers to these questions. This makes the process of formulation research and the search for natural ingredients with medicinal value and even the potential for new drugs more efficient. This suggests that researchers can flexibly apply these digital tools to help in future studies.

5. Conclusion

As people's standard of living has changed over the past few decades, the ability and willingness to obtain and consume purine-rich foods have increased. The prevalence of abnormal UA metabolism and related diseases has increased rapidly globally and has become an influential metabolic disease.

In this review, three types of natural products have been found and proven to have the regulating effect of UA in recent years, specifically with: 1) single compounds, 2) plant extracts, and 3) herbal formulations. Two compounds in *Alstonia scholaris*, ursolic acid, *Clerodendranthus spicatus* ethyl acetate extract of 12 organic compounds, and Anthocyanins are organic compounds with powerful UA regulation from natural plants. The researchers demonstrated the low UA activity of *Morus alba* and *Ipomoea batatas* leaf extracts, and the main components in the extracts were further explored. Crude extracts of *Stevia rebaudiana*, *Citrus paradise*, *Chrysanthemum indicum*, *Cornus officinalis*, *Persicaria capitata*, and tea have been shown to have good uric-lowering activity. The urate-lowering effects of Chatuphalatika (CTPT) from Thailand, Yokuininto from traditional Japanese therapeutic formula, Selaginella moellendorffii prescription (SMP), food ginseng paste (FGP), and Simiao Powder (SmP) from traditional Chinese medicine have been studied and demonstrated.

This study focuses on a review of natural ingredients that have been directly demonstrated to have the ability to regulate UA. In contrast, other factors that affect UA levels *in vivo*, such as xanthine oxidase activity, xanthine dehydrogenase activity, and URAT1, need to be summarized in further work. Over the past decade, research on the effects and regulation of natural components on regulating the UA levels in humans has grown steadily rather than exploded, and studies involving the UA regulatory capacity of more natural components have emerged that require more thorough review.

The scientific verification of the urate-regulating effects of plants, herbs, or formulations from various cultural traditions is ongoing. Exploring the mechanisms of action for the urate-regulating effects of various natural ingredients needs further extensive and in-depth research. Epigenetic methods have enabled researchers to efficiently explore the underlying mechanisms of UA regulation by natural plant components. More researchers are beginning to experiment and use emerging tools, including network pharmacology and molecular docking analysis, to efficiently explore the effects and value of natural ingredients, especially in the study of complex formulations. These studies positively impact the process of discovering and developing new and effective gout drugs.

Author Contributions

Hehe Zhang took the primary responsibility on literature review, data analysis, and manuscript writing. Ruihan Xu did auxiliary work on data analysis and manuscript revision. Dr. Shasha Zheng was the correspondence and guided the project.

Competing Interests

The authors have declared that no competing interests exist.

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