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Anti-Hyperuricemic Effects of *Oenanthe javanica* Extracts in Hyperuricemia-Induced Rats

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Background: This study aimed to investigate the effects of *Oenanthe javanica* (OJ) extracts on rats with potassium oxonate (PO)-induced hyperuricemia.
Methods: The effects of OJ extract on rats with PO-induced hyperuricemia-induced were monitored. Changes in the body weight and organ indices of hyperuricemic rats were calculated to detect anti-hyperuricemic effects. Blood samples were collected to observe the effect of reducing serum uric acid concentration. Kidney tissues were stained to observe histopathological changes under a microscope. The activity of xanthine oxidase (XO), which catalyzes xanthine to uric acid in the liver, was assessed to observe the inhibitory effect of XO.
Results: 1. The body weight of hyperuricemic rats showed no considerable differences between the control group and the treatment group. The OJ group had significantly improved liver index, whereas the allopurinol group had improved liver and kidney indices. 2. Serum uric acid levels increased significantly after PO injection, and the OJ and allopurinol groups showed a significant reduction effect. 3. PO injection led to the inflammation of kidney tissues, and OJ improved it significantly. 4. The activity of XO after PO injection was significantly increased, and allopurinol significantly inhibited XO activity in the liver.
Conclusion: In the hyperuricemia rat model, OJ extract reduced uric acid concentration and demonstrated its anti-inflammatory effects. Thus, OJ extracts can be used to lower uric acid levels.

Keywords: Allopurinol; Gout; Hyperuricemia; *Oenanthe*; Uric acid; Xanthine oxidase

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INTRODUCTION

Gout is a chronic, inflammatory arthritic disease caused by persistent elevations in serum uric acid levels (hyperuricemia) resulting in the deposition of monosodium urate (MSU) crystals in the joints, tendons, and other tissues [1]. A typical symptom of gout is severe acute pain in the lower extremity joint known as gout flare, and pain reaches its peak intensity within a short period, usually less than half of a day [2]. According to a study published in 2018, the age-standard prevalence rate of hyperuricemia was 11.4%. Both the prevalence of hyperuricemia and the average uric acid levels were higher in males than in females [3].

To diagnose gout, methods such as observing MSU crystals and tophi under a microscope [4] or using classification criteria were published in 2015 [5]. However, early treatment is not feasible because of the asymptomatic period in the early stages [6]. A major risk factor for gout is hyperuricemia [7], which is generally defined as uric acid level in the blood of <7.0 mg/dL in males and 6.0 mg/dL in females [8]. Hyperuricemia occurs when uric acid is overproduced or insufficiently excreted in the body [9]. Because it is closely related to metabolic syndromes such as hypertension, diabetic mellitus, and dyslipidemia [10], early management of hyperuricemia is necessary.

Based on the 2020 guidelines, allopurinol is strongly recommended as the first-line agent to initiate urate-lowering therapy (ULT), starting at a low-dose (≤100 mg/day) [11]. However, the potential life-threatening events of allopurinol have been reported, such as allopurinol hypersensitivity syndrome, rash (e.g., Stevens–Johnson syndrome, and toxic epidermal necrolysis), eosinophilia, leukocytosis, fever, and even hepatitis or renal failure [12]. Thus, an alternative agent with fewer side effects while controlling serum uric acid concentration and relieving inflammation states is needed.

Oenanthe javanica (OJ), called water dropwort, widely grows in tropical and warm areas of Asia [13]. In Korea, it has been traditionally used to treat various diseases such as hepatitis, jaundice, fever, high blood pressure, abdominal pain, and urinary disorders [14]. Although OJ has been reported to have beneficial effects [15], this study is the first to investigate the effects of OJ administration on hyperuricemia to manage gout.

In this study, the effects of OJ extracts on hyperuricemia and organ indices such as serum uric acid level and renal inflammation were investigated in a potassium oxonate (PO)-induced hyperuricemia rat model and compared with the effects of conventional methods such as allopurinol, a representative xanthine oxidase (XO) inhibitor. Furthermore, this study aimed to investigate whether OJ extracts can inhibit the activation of enzymes that help produce uric acid in the liver.

MATERIALS AND METHODS

1. Animals

Twenty 7-week-old male Sprague-Dawley rats were obtained from DBL Co., Ltd. (Incheon, Korea). Rats were made to adapt to the experimental conditions in an air-conditioned animal room (temperature, 22 ± 1℃; humidity, 55 ± 5%) and given access to a standard diet and water ad libitum. All experimental procedures described were approved by the Gachon University Center of Animal Care and Use (GIACUC-R2020028).

2. Sample preparation

OJ as natural products were washed with sterile water and dried. The drying yield was 13.99%. Then, 5 g of dried OJ was prepared, added with 1 L of sterile water, and placed into a small circulation extraction device. Reflux extraction was performed for 2 hours at 100℃, and the sample was filtered with paper. The weight of the extraction was recorded, and the extraction yield was 90.64%. The OJ extract was diluted in purified water to a concentration of 10 mg/mL and titrated to pH 7.4 using 0.9% NaCl. The sample was finally filtered to 0.2 μm. The sample was filled into a transparent vial, with 1 mL each and sealed. The sample was sterilized by moist heat at 121℃ for 15 minutes. The vial was labeled with the name of the raw material, date of preparation, and content, for example, OJ, 2022.04.12., 10 mg/mL.

3. Hyperuricemia induction and OJ extract administration

The OJ extract used in this study was provided as a dried powder by JU-HWAN BIOCELL Co., Ltd. (Cheonan, Korea). Then, 250 mg/kg PO, a uricase inhibitor, was intraperitoneally injected into the rats to induce hyperuricemia. Allopurinol (Sigma-Aldrich, St. Louis, MO, USA) was used as the positive control drug. Before the injection, the PO was dissolved in 0.5% carboxymethyl cellulose (CMC; Sigma-Aldrich) and 0.1 M sodium acetate (Sigma-Aldrich).

To investigate the sample effectiveness and molecular mechanisms of OJ, the rats were divided into four groups (n = 5 for each group): saline (sham) group, PO (control) group, PO + 10 mg/kg allopurinol group, and PO + 100

mg/kg OJ group. Samples were dissolved in 0.5% CMC solution and administered orally every day to the rats 1 hour after PO injection for 5 days.

4. Collection of blood and tissue samples

Blood samples were collected after 2 hours of drug administration, and urine samples were collected within 2 hours of utilizing a metabolic cage following sample treatment. After blood and urine collection, tissue (kidney and liver) samples were carefully divided and preserved at −80℃ for further assays. The serum was separated by centrifugation (2,000 g, 15 minutes, 4℃). Serum and urine samples were then used for biochemical analysis.

5. Analysis of uric acid concentrations in serum

The uric acid concentrations from the serum were determined using a commercial uric acid assay kit (Sigma-Aldrich) according to the manufacturer's instructions.

6. In vitro XO activity from the liver

The activity of XO in liver tissues was determined using the XO activity assay kit (Sigma-Aldrich) according to the manufacturer's protocols. The activity of XO was estimated by Epoch2 microplate reader (Biotek, Winooski, VT, USA). The addition of 0.5 mM xanthine as substrate induces an enzyme reaction, and the uric acid concentration was measured every minute for 5 minutes. Allopurinol was used as an XO inhibitor. The hepatic XO activity was standardized by the total protein level.

7. Kidney histopathological examination

Kidney tissues were removed, immediately fixed for 1 day in formalin, and embedded in paraffin. Sections were cut at 6 μm thickness and were stained with hematoxylin and eosin (H&E) reagents. Histopathological changes in the specimens were then observed under a microscope.

8. Statistical analysis

Statistical analysis was conducted using GraphPad Prism® 5.0 (GraphPad Software Inc., San Diego, CA, USA) with the one-way analysis of variance and Dunnett's post hoc test. The significance was verified at $p < 0.05$, and measurements were indicated as mean ± standard error of the mean.

RESULTS

1. Effects of OJ on the body weight and kidney and liver indices

To confirm the effects of OJ on the prevention of hyperuricemia, OJ was administered for 5 days. PO-induced hyperuricemia rats were monitored daily for body weight changes and any signs of injury or physical changes. As a result, the body weight between the intervention group and the control group is almost similar, showing no significant difference (Fig. 1A).

The organ index (organ-to-body ratio) was calculated in the kidney and liver of PO-induced hyperuricemia rats. The kidney index was significantly lower in the allopurinol group than in the control group. The liver index was significantly improved in both the allopurinol and OJ groups compared with the PO group (Fig. 1B, C).

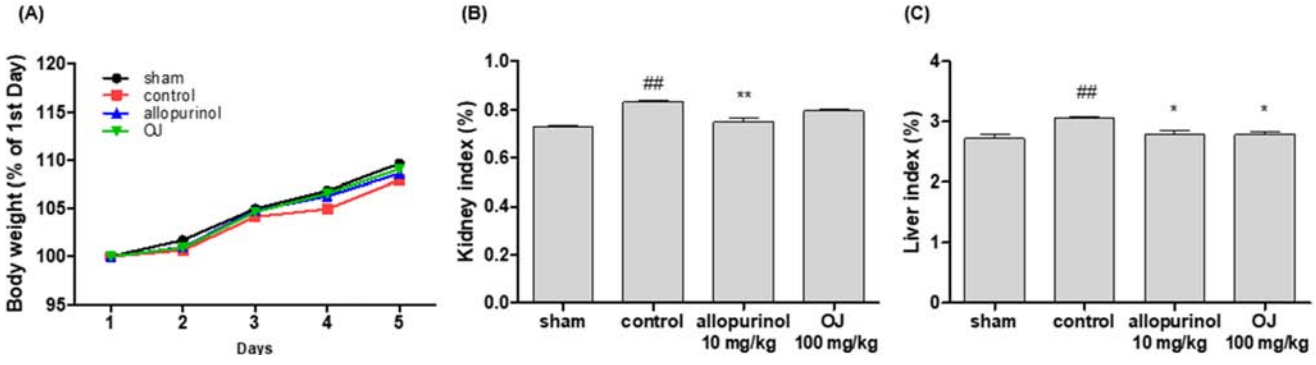

Fig. 1. Effects of *Oenanthe javanica* (OJ) on controlling the hyperuricemia. (A) Body weights of the saline group (sham), potassium oxonate (PO) group (control), PO + allopurinol group, and OJ group each from day 1 to 5. (B, C) Effect of OJ on kidney and liver index in PO rats. $^{\#\#}p < 0.01$ compared to sham group, $^{*}p < 0.05$, $^{**}p < 0.01$ compared to control group. Sham, saline-injected group; control, PO-injected group; allopurinol, PO + 10 mg/kg allopurinol administrated group; OJ, PO + 100 mg/kg OJ administrated group.

2. Effects of OJ on serum uric acid levels

PO was injected for 5 days to determine whether OJ can decrease serum uric acid concentration. During this period, PO-injected hyperuricemic rats showed significantly increasing serum uric acid levels compared with the control rats (Fig. 2). In the meantime, allopurinol (positive control) and OJ 100 mg/kg significantly decreased the uric acid level in PO-injected hyperuricemic rats.

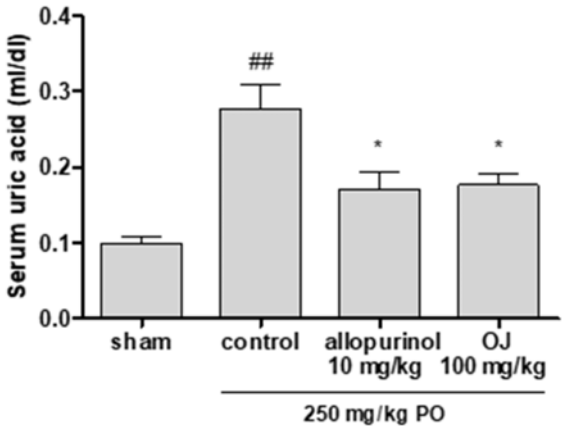

Fig. 2. Effects of *Oenanthe javanica* (OJ) on serum uric acid in hyperuricemic rats. $^{\#\#}p < 0.01$ compared with the sham group, $^{*}p < 0.05$ compared with the control group. Sham, saline-injected group; control, potassium oxonate (PO)-injected group; allopurinol, PO + 10 mg/kg allopurinol group; OJ, PO + 100 mg/kg OJ group.

3. Effects of OJ on renal inflammation

To investigate the anti-inflammatory effect of OJ on hyperuricemia rats, kidney sections were observed under a microscope at 200× magnification through H&E staining. PO-injected hyperuricemic rats demonstrated histological changes such as mild tubular dilation, vacuolar degeneration of the tubular epithelial cell, swelling, and infiltration of inflammatory cells (Fig. 3). By contrast, OJ administration in hyperuricemic rats improved these renal histopathological changes. This finding indicates that OJ alleviated inflammatory conditions and improved the function of the hyperuricemic kidney tissues of rats.

4. Effects of OJ on XO activity

XO contributes to uric acid production in the liver and is involved in purine metabolism. Therefore, the assay of XO activity in the serum and liver was conducted to determine whether OJ can inhibit hyperuricemia. The XO activity in the liver was significantly increased in the PO group (Fig. 4). Allopurinol, an XO inhibitor, significantly decreased the XO activity in the serum and liver. Although OJ reduced XO activity and uric acid production,

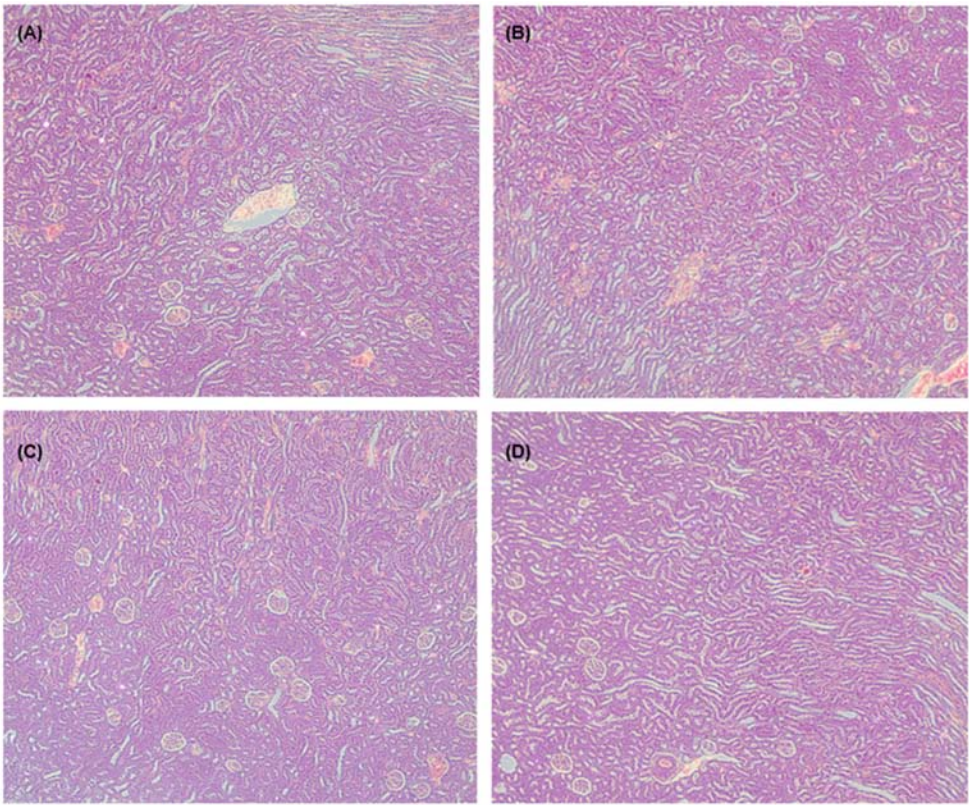

Fig. 3. Effects of *Oenanthe javanica* (OJ) on renal inflammation in rats with potassium oxonate (PO)-induced hyperuricemia: renal histopathological changes. (A) Sham, (B) control, (C) allopurinol, and (D) OJ. Sham, saline group; control, PO group; allopurinol, PO + 10 mg/kg allopurinol group; OJ, PO + 100 mg/kg OJ group. H&E stain, ×200.

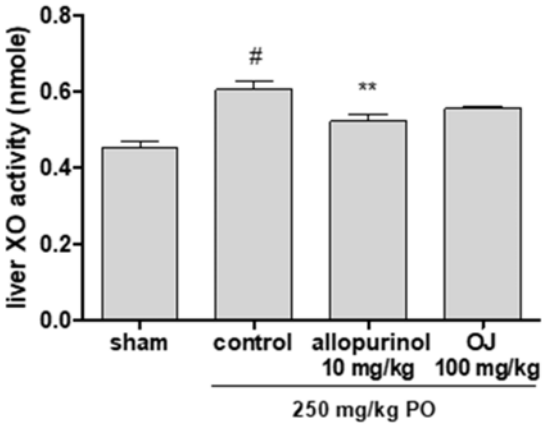

Fig. 4. Effects of *Oenanthe javanica* (OJ) on liver xanthine oxidase activity in rats with potassium oxonate (PO)-induced hyperuricemia. $^{\#}p < 0.05$ compared with the sham group, $^{**}p < 0.01$ compared with the control group. Sham, saline group; control, PO group; allopurinol, PO + 10 mg/kg allopurinol group; OJ, PO + 100 mg/kg OJ group.

it was not significant.

DISCUSSION

Gout is one of the common conditions of inflammatory arthritis [1]. It can be classified into four types according to clinical features: asymptomatic hyperuricemia, acute gouty arthritis, intermittent gout, and chronic gout nodule with tophi [16]. Once a gout flare occurs, it can recur when serum uric acid levels are poorly controlled [2]. In a gout epidemiological study in Korea, the prevalence of gout was gradually increasing from 0.39% in 2002 to 2.01% in 2015, which was predicted to be 1.66% in 2025. Specifically, the prevalence rate was the highest in the 60s in 2002, and in 2015, it changed to the 70s, suggesting that patients with gout have been continuously receiving gout treatment and that gout should be managed from a long-term perspective rather than as a temporary acute disease [17]. Furthermore, gout is associated with various comorbidities such as hypertension, cardiovascular diseases, and stroke. In addition, hyperuricemia affects the kidney directly, which implies that lowering serum uric acid levels can prevent kidney disease and protect its function [18].

Corticosteroids, non-steroidal anti-inflammatory drugs, and low-dose colchicines are recommended for the treatment of gout flares. If a gout flare occurs frequently, starting a ULT is recommended in consideration of costs, advantages and disadvantages, side effects, and underlying diseases [19]. In addition, the 2020 guidelines strongly recommended initiating ULT if nodular gout and radiographic damage appears. Allopurinol (an XO inhibitor) is primarily recommended (100 mg/day) and even suggested at a lower dose to patients with chronic kidney disease [11]. Infrequently, allopurinol can cause various side effects, ranging from mild hypersensitivity to severe skin adverse reactions, such as Stevens–Johnson syndrome/toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and hypersensitivity syndrome. It can also lead to leukocytosis, fever, hepatitis, and progressive renal failure [20]. A study in the United States reported that it is cost-effective to perform preliminary tests on HLA-B*5801 before taking allopurinol, especially in Asian and African-Americans, to avoid adverse effects [21]. Although the application of optimal allopurinol dose is an important factor in gout management, determining the appropriate dose and selecting high-risk groups that require drug treatment remains unclear [22].

Current treatments for hyperuricemia and gout are not sufficient considering their risk and effectiveness. Thus, additional alternative medications should be devised to improve gout flare and control uric acid serum levels, and herbal medicines can be an alternative.

Uric acid is a product of complicated purine metabolic processes. When purine is converted to hypoxanthine, XO enzyme oxidized hypoxanthine to xanthine, which is then catalyzed from xanthine to uric acid [23]. Supersaturated uric acid in the blood forms MSU crystals, which are associated with the mechanism of damage and can stimulate innate immune pathways, resulting in gout flares [23], chronic inflammation, and structural deformation [2]. It is caused by increased purine intake, excessive action of uric acid-degrading enzymes, and changes in renal excretion [24]. Although the production and metabolism of uric acid involve a complex process of controlling liver production and excretion in the kidneys and intestines [25], several studies have reported treating hyperuricemia using herbal medicines such as *Alpinia oxyphylla* [26], *Aster glehni* leaves [27], and liquiritigenin [28].

OJ, a herbal medicine, has been widely consumed as dietary and medicinal product, called “Minari.” It has been traditionally used in Korea for jaundice, fever, hypertension, abdominal pain, polydipsia diseases, overcoming alcohol hangovers, leukorrhea, mumps, urinary difficulties of infections, and inflammatory conditions [15]. Phytochemical studies have shown that OJ contains biphenyls [29], flavonoids [30], and polyphenols [31]. Moreover, OJ has therapeutic characteristics including

hepatoprotective [32], anti-inflammatory [33], and antiviral effects [34]. OJ is known to eliminate reactive free radicals, reinforce the endogenous antioxidant system, and inhibit pro-inflammatory mediators [32].

PO, a competitive uricase inhibitor, produces hyperuricemia in rats [35]. In animal studies, the body weight and organ index are used to identify pathological changes [36] or toxication in organs [37]. The organ index can be a primary indicator of comparing the intervention group and the control group in the absence of morphological changes [28]. In this study, PO showed a significant increase in both kidney and liver indices. Moreover, allopurinol significantly improved both kidney and liver indices, whereas OJ significantly improved the liver index only.

In a previous study, PO was used to determine the anti-hyperuricemic effect of test compounds [24]. Likewise, in the present study, PO showed significant elevation in serum uric acid levels, whereas both allopurinol and OJ significantly lower the uric acid levels. Consequently, OJ suggests a potential as an alternative ULT agent.

The kidneys eliminate approximately two-thirds and the gastrointestinal tract eliminates one-third of the uric acid load [25]. Uric acid is filtered, reabsorbed, and secreted in the proximal tubule. Chronically higher uric acid level causes kidney impairment [38], activates inflammasome factors [39], and induce histopathological changes [40]. In this study, pathological changes in kidney tissues in hyperuricemic rats were observed through H&E staining and microscopy. The results show that OJ significantly improved the inflammatory condition of kidney tissues. This suggests the possibility of treating inflammatory diseases accompanying hyperuricemia.

XO inhibitors such as allopurinol and febuxostat have been developed for the long-term treatment of gout [41]. Therefore, XO inhibitors might be good candidates for the treatment of gout by decreasing uric acid levels [32]. In this study, whether OJ functions as an XO inhibitor was determined by evaluating the XO activity in the liver and serum. As a result, allopurinol significantly inhibited the XO activity, whereas OJ slightly decreased it. OJ showed some inhibitory activity against XO, although weaker than allopurinol, confirming its potential as an XO inhibitor.

CONCLUSION

OJ significantly improved the hepatic injury in hyperuricemia without toxicity, reducing uric acid levels and changing histological conditions of the inflamed kidney. Therefore, OJ presents a strong potential for reducing uric acid levels and inflammation simultaneously. OJ could be a safe alternative in the treatment of hyperuricemia and gout. However, further studies through clinical applications are needed.

AUTHOR CONTRIBUTIONS

Conceptualization: WJL, HSS. Data curation: WJL. Formal analysis: HSS. Investigation: HSS. Methodology: WJL, HSS. Project administration: WJL, HSS. Resources: WJL. Software: HSS. Supervision: HSS. Validation: WJL. Visualization: WJL. Writing – original draft: WJL, HSS. Writing – review & editing: All authors.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

FUNDING

None.

ETHICAL STATEMENT

All experimental procedures described were approved by the Gachon University Center of Animal Care and Use (GIACUC-R2020028).

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