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Protective effects of *Sasa quelpaertensis* Leaf Residue Extract against Potassium Oxonate-induced Hyperuricemia in Mice

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Leaves of *Sasa quelpaertensis* Nakai are used in folk medicine for their anti-inflammatory, antipyretic, and diuretic properties. To ensure efficient utilization of *S. quelpaertensis* leaf, we previously reported a preparation method for phytochemical-rich extract (PRE) using the leaf residue, which was produced after hot water extraction. This study was undertaken to evaluate the hypouricemic potential of *S. quelpaertensis* leaf PRE in potassium oxonate (PO)-induced hyperuricemic mice. The administration of PRE significantly reduced serum uric acid (UA), blood urea nitrogen (BUN), and serum creatinine levels and increased urine UA and creatinine levels in the PO-induced hyperuricemic mice. It also reduced liver UA levels and xanthine oxidase (XA) activity. A histological analysis revealed that PRE administration protected against PO-induced liver damage, pointing to anti-inflammatory and cytoprotective effects in PO-induced hyperuricemic mice. We analyzed the transcriptome response to PRE administration in PO-induced hyperuricemic mice using RNA sequencing (RNA-Seq) in kidney tissues. The administration of PRE mainly enriched genes involved in mediating immune and inflammatory responses and the metabolic pathway. A Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis showed that the metabolic pathway, purine metabolism, and antibody biosynthesis were the major pathways altered in the PRE and PO groups. These results suggest a potential role for PRE in the prevention and treatment of hyperuricemia with inflammation.

Key words : Hyperuricemia, potassium oxonate, RNA sequencing, *Sasa quelpaertensis,* uric acid

Introduction

Uric acid (UA) is the terminal product of purine metabolism and is produced from hypoxanthine by xanthine oxidase (XO) in the liver [26]. Serum UA levels are determined by endogenous factors, such as *de novo* purine synthesis, tissue catabolism, and exogenous proteins delivered to the liver [12]. UA excretion is controlled by transporters in the kidneys through renal plasma flow, glomerular filtration, and proximal tubular exchange [8, 21]. An imbalance between UA production and excretion induces hyperuricemia, which is a major causal factor for the development of gout and many other diseases such as obesity, cardiovascular and renal diseases, hypertension, and metabolic syndrome [3, 4].

Allopurinol (an XO inhibitor) is the synthetic drug most widely used to treat hyperuricemia [20]; however, its use can lead to side effects [5]. It is therefore necessary to search for alternative agents with few adverse effects for the treatment and prevention of hyperuricemia. Natural products have become a source for novel pharmaceuticals due to their potent efficacy and reduced side effects, due to the presence of complex bioactive compounds. Many studies have been conducted on natural products for the purpose of treating hyperuricemia [1, 9, 28].

Sasa species are bamboo grasses, which are widely distributed in Asian countries including China, Japan, Korea, and Russia [19]. Their leaves have traditionally been used in folk medicine for their anti-inflammatory, antipyretic, and diuretic properties. *Sasa quelpaertensis* Nakai is a unique genetic resource from Jeju Island, Korea, native to Halla Mountain. Recently, it has been reported that *S. quelpaertensis* leaves possess various health-promoting properties, including anti-inflammatory, anti-cancer, anti-obesity properties [10, 11]. As various applications of *S. quelpaertensis* leaves become known, the leaves are increasingly used as nutrace-

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uticals. We previously reported a procedure for the preparation of a phytochemical-rich extract (PRE) using residue produced by hot water extraction of *S. quelpaertensis* leaves [16]. In the current study, we investigated the hypouricemic effects of PRE in potassium oxonate (PO)-induced hyperuricemic mice. We also analyzed the effects of PRE on transcriptome profiles in kidney tissue by RNA sequencing (RNA-Seq).

Materials and Methods

Preparation of PRE

S. quelpaertensis leaves were collected from Mt. Halla on Jeju Island, and washed and dried in a hot air drier at 60℃. The dried leaves were pulverized to 100-200 mesh powder, and extracted for 4 hr with hot water (90℃). After the hot water extract was removed, the remaining residue was extracted to prepare PRE with 70% ethanol for 48 hr at room temperature. PRE was filtered, concentrated, and stored at -70℃ until use.

Animals

All animals were allowed free access to water and standard mouse chow, and were maintained at a regular cycle (12 hr light/dark) under room temperature (23±2℃) and relative humidity (60±5%) conditions. The experimental animals were acclimatized to the environment for 7 days before use in the experiments. All experiments were approved by the Institutional Animal Care and Experimental Committee of Jeju National University (No. 2016-0043).

Induction of hyperuricemia and drug administration

The uricase inhibitor PO was used to induce hyperuricemia in mice [25]. PO (250 mg/kg) was intraperitoneally administered once daily, 1 hr before the administration of the drug, for 7 consecutive days. The group was randomly divided into four groups (n=5 per group). In the normal group, mice were fed only the basic diet without PO treatment. The day after PO was administered, PO-treated mice were divided into three subgroups: the PO group (PO+50 mg saline/kg of body weight, BW), Allo group (PO+5 mg allopurinol/kg of BW), and PRE group (PO+50 mg PRE/kg of BW).

Blood, urine, and tissue sampling

After 6 days of drug administration, urine samples were collected for 24 hr in a metabolic cage and centrifuged. The supernatant was collected and analyzed for UA content. On the 7th day, the mouse was anesthetized with ethyl ether. The blood was centrifuged at 15,000 rpm for 20 minutes to separate the serum. The tissue was extracted, rapidly cooled using liquid nitrogen, and stored at -70℃.

UA, creatinine, and blood urea nitrogen analyses

Levels of serum and urine UA, blood urea nitrogen (BUN), and creatinine were measured using a UA kit (Abnova, Taipei, Taiwan), BUN assay kit (Asan Pharm, Gyeonggi, Korea), and creatinine assay kit (BioAssay Systems, CA, USA), respectively, according to the manufacturers' protocols.

Xanthine oxidase activity assay

Liver tissue was homogenized with 200 mM sodium phosphate buffer (pH 7.5) and centrifuged (3,000× g, 4℃) for 20 minutes. The fat layer was removed and the supernatant centrifuged (12,000× g, 4℃) for 30 min. The supernatant was used as the enzyme solution. We then added the enzyme solution and the same amount of reaction solution (200 mM sodium phosphate buffer at pH 7.5 in 1 mM xanthine and 2 mM EDTA), followed by reaction at 37℃ for 10 minutes, and the absorbance at 295 nm was measured.

Histological analysis

Liver tissues were fixed with paraformaldehyde, washed, dehydrated, and embedded in paraffin. A paraffin block was then prepared and sectioned using a microtome to prepare tissue slices. Serial paraffin sections (5 μm) were stained with hematoxylin and eosin solution, and histological changes were observed with a microscope.

RNA extraction, library preparation, and RNA-Seq

Kidney tissues were homogenized and total RNA was isolated using TRIzol reagent (Invitrogen Corp., Carlsbad, CA, USA). To reduce variation among individuals within experimental groups, total RNA from kidneys of the same group was pooled together in equal amounts to generate a mixed sample. To explore gene expression profiling, RNA-Seq was performed at eBiogen Inc. (Seoul, South Korea). Briefly, RNA quality was assessed using an Agilent 2100 BioAnalyzer with the RNA 6000 Nano Chip (Agilent Technologies, Amstelveen, The Netherlands), and RNA quantification was performed using an ND-2000 Spectrophotometer

(Thermo Inc., Wilmington, DE, USA). For control and test RNAs, a library was constructed using the QuantSeq 3′ mRNA-Seq Library Prep Kit (Lexogen, Inc., Vienna, Austria) according to the manufacturer's instructions. High-throughput sequencing was performed as single-end 75 sequencing using NextSeq 500 (Illumina, Inc., San Diego, CA, USA). QuantSeq 3′ mRNA-Seq reads were aligned using Bowtie2 [15]; Bowtie2 indices were either generated from the genome assembly sequence or representative transcript sequences for alignment to the genome and transcriptome. The alignment file was used to assemble transcripts, estimate their abundances, and detect differential gene expression. Differentially expressed genes (DEGs) were determined based on counts from unique and multiple alignments using coverage in BEDTools [22]. The RT (read count) data were processed based on the quantile–quantile normalization method using EdgeR within the R software environment (R Development Core Team, 2016) using Bioconductor [7]. Gene classification was based on searches performed using the DAVID (http://david.abcc.ncifcrf.gov/) and Medline databases (http://www.ncbi. nlm.nih.gov/).

Statistical analysis

Statistical analysis was performed using (SPSS for Windows software (ver. 12.0; SPSS Inc., Chicago, IL, USA). All data are expressed as means ± standard error (SE). Statistical differences between groups were examined using one-way analysis of variance (ANOVA) test. Differences were considered statistically significant at a level of $p<0.05$.

Results

PRE modulated UA levels in PO-induced hyperuricemic mice

The hypouricemic potential of PRE was assessed by measuring serum and urine UA levels in each experimental group. Serum UA levels were significantly higher in the PO-administrated group than in the normal group, indicating that hyperuricemia was induced appropriately by PO treatment (Fig. 1A). Serum UA levels in the PRE group were lower than those in the PO group, which served as a negative control, but were similar to those of the Allo group, which served as a positive control. This result suggests that PRE effectively suppressed UA production in the body. In contrast, urine UA levels were higher in the PRE and Allo groups than in the PO group (Fig. 1B), suggesting that PRE may promote the secretion of UA. These results indicate that PRE may improve PO-induced hyperuricemia by regulating UA levels throughout the body.

PRE modulated BUN and creatinine levels in PO-induced hyperuricemic mice

To evaluate whether PRE administration affected kidney function in PO-induced hyperuricemic mice, we measured BUN and serum and urine creatinine levels in each experimental group. As shown in Fig. 2, BUN levels in the PRE group were significantly lower than those in the PO group, and were similar to those in the normal and Allo groups. Additionally, we measured creatinine levels, which

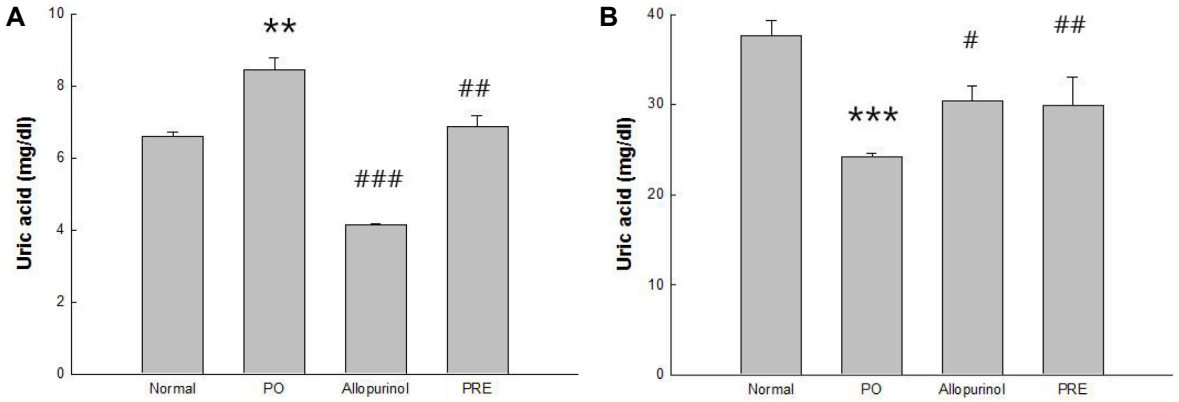

Fig. 1. Administration of *Sasa quelpaertensis* leaf phytochemical-rich extract (PRE) modulated uric acid (UA) levels in potassium oxonate (PO)-induced hyperuricemic mice. (A) Serum UA; (B) urine UA. Results represent means ± standard error of the mean (SEM; n=4). Normal, normal group; Negative, PO group (PO+50 mg saline/kg of body weight, BW); Allo, allopurinol group (PO+5 mg allopurinol/kg of BW); PRE, PO + PRE group (50 mg PRE/kg of BW). *$p<0.05$ vs. Normal group, **$p<0.01$ vs. Normal group, ***$p<0.001$ vs. Normal group, #$p<0.05$ vs. Negative group, ##$p<0.01$ vs. Negative group, ###$p<0.001$ vs. Negative group.

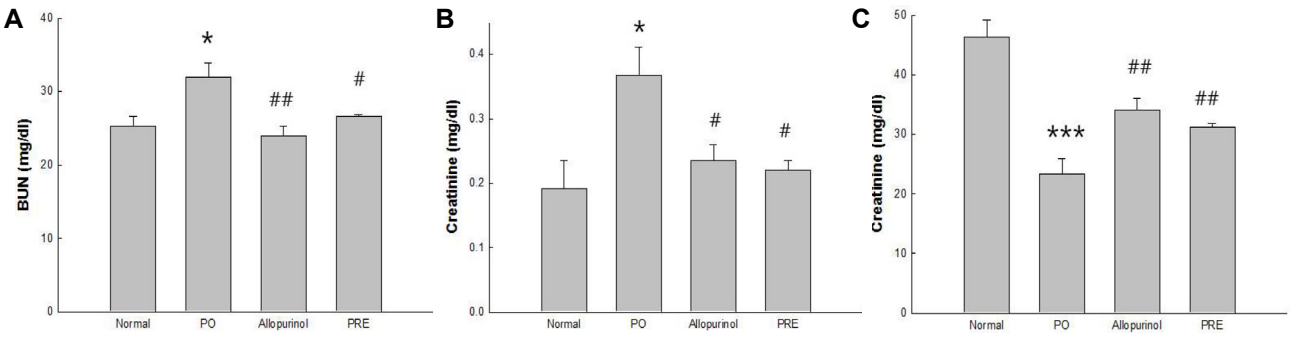

Fig. 2. PRE administration modulated blood urea nitrogen (BUN) and creatinine levels in PO-induced hyperuricemic mice. (A) Serum BUN; (B) serum creatinine; (C) urine creatinine. Results represent means ± SEM (n=4). *p<0.05 vs. Normal group, **p<0.01 vs. Normal group, ***p<0.001 vs. Normal group, #p<0.05 vs. Negative group, ##p<0.01 vs. Negative group.

are related to the glomerular filtration rate, in the serum and urine of the experimental animals. Serum creatinine levels were significantly higher in the PO group, and significantly lower in the PRE group (Fig. 2B). Conversely, urine creatinine levels were significantly higher in the PRE group than in the PO group (Fig. 2C). These results indicate that PRE may improve kidney function in PO-induced hyperuricemic mice.

PRE restored liver damage in PO-induced hyperuricemic mice

We next investigated whether PRE administration could restore PO-induced liver damage by measuring the amount of UA and XO activity in the liver tissues of each experimental group. The amounts of UA were significantly higher in the PO group than in the normal group. However, the amount of UA in PRE group livers was lower than that in PO group livers (Fig. 3A). Consistent with the amounts of UA detected in liver tissues, XO activity, which is a major factor in UA production, was highest in the PO group (Fig. 3B). XO activities of PRE groups were reduced by 41% compared to those of PO group. These data suggest that PRE administration may improve liver function by restoring PO-induced liver damage. These results were confirmed by

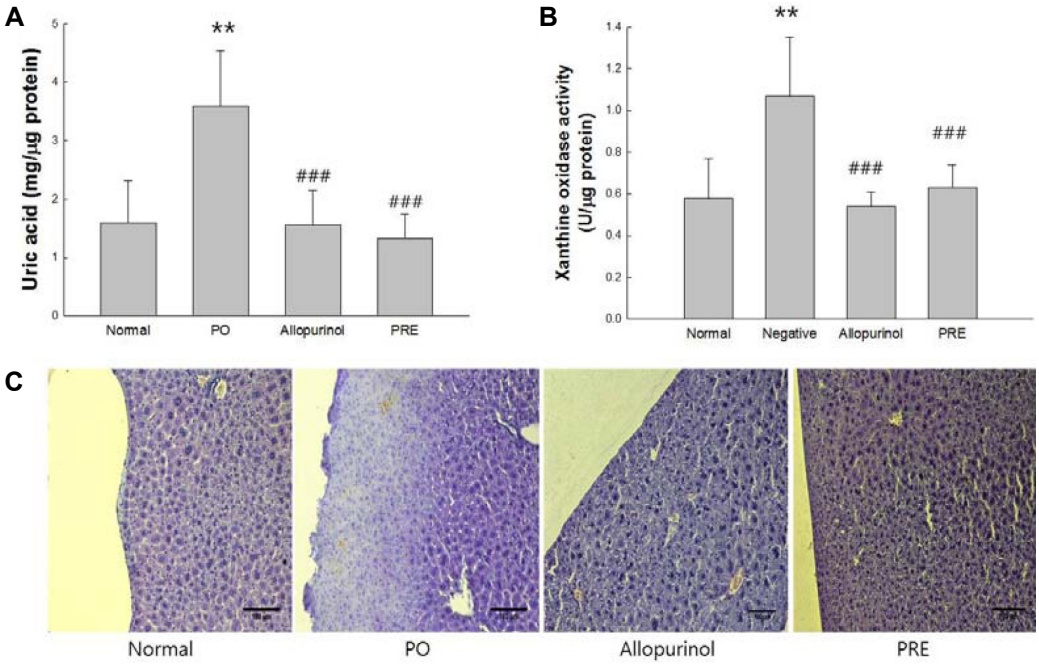

Fig. 3. PRE administration restored PO-induced liver damage. (A) UA; (B) xanthine oxidase levels in livers from each experimental group. (C) Hematoxylin and eosin staining of hepatic paraffin sections at ×200 magnification. Results represent means ± SEM (n=4). **p<0.01 vs. Normal group, ##p<0.01 vs. Allopurinol group, ###p<0.001 vs. Negative group.

histology of the liver tissue. As shown in Fig. 3C, PRE administration improved PO-induced liver damage. These results indicate that PRE may improve hyperuricemia by inhibiting XO activity, thus reducing UA production and protecting liver tissue from destruction by excessive UA.

PRE modulated transcriptome profiles in PO-induced hyperuricemic mice

To obtain a global view of the transcriptome response to PRE administration in PO-induced mice, we performed comparative RNA-Seq analyses of kidney transcriptomes. To identify DEGs in kidneys from the PO and PRE groups, we compared gene expression data from each group using the ExDEGA software (eBiogen). A total of 856 DEGs (456 upregulated, 384 downregulated) were detected in the kidneys of PRE versus PO groups. Gene ontology (GO) analysis was performed to determine the DEG signatures. This analysis revealed that enriched genes were mainly involved in the regulation of transcription, DNA templates, the innate immune response, the inflammatory response, and immune system processes (in order of the number of counted DEGs; $p<0.05$; Table 1). Pathway analysis using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database showed that 10 pathways were significantly enriched in the identified DEGs ($p<0.05$; Table 2). These genes were mainly involved in complement and coagulation cascades, metabolic pathways, fat digestion and absorption, acute myeloid leukemia, ascorbate and aldarate metabolism, purine metabolism, and drug metabolism.

Discussion

Recently, morbidity due to hyperuricemia has rapidly increased worldwide in all age groups. Therefore, there is a growing demand for natural hypouricemic agents that have fewer side effects than therapeutic drugs in current use. In the current study, we investigated the hypouricemic activities of *S. quelpaertensis* leaves using PRE, an ethanol extract of residue produced by hot water extraction, in PO-induced hyperuricemic mice. PO has been shown to induce a significant elevation of XO activity and the amount of UA amount in mouse livers, and to impair renal function [2]. We found that PRE decreased serum UA levels in PO-induced hyperuricemic mice and was effective in reducing liver UA levels in hyperuricemic mice. PRE also significantly inhibited liver XO. Thus, it seems likely that PRE reduced serum UA levels by inhibiting liver XO activity. XO is an enzyme that generates superoxide radicals with xanthine as a substrate to generate UA; i.e., it acts as an oxidizing agent [2, 29]. Since PRE has exhibited antioxidant and XO inhibition activities *in vitro*, PRE may exert a similar function to that of allopurinol.

The glomerular filtration rate is an indicator of kidney function. When kidney function deteriorates and the excretion capacity of waste products decreases, the blood creatinine level increases and urinary excretion decreases [6, 30]. PRE appears to have the potential to restore kidney function; this activity was affected by PO-induced hyperuricemia in the current study, because PRE controlled BUN and crea-

Table 1. Gene ontology (GO) analysis of differentially expressed genes (DEGs) in PRE versus PO groups

Biological process	Count	*p*-Value
Glucose homeostasis	15	0.0001
Cholesterol metabolic process	11	0.0012
Blood coagulation	10	0.0023
Negative regulation of transcription from RNA polymerase II promoter	41	0.0026
Protein phosphorylation	34	0.0030
Regulation of cell proliferation	17	0.0054
Phosphorylation	34	0.0075
Regulation of transcription, DNA-templated	98	0.0152
Lipid metabolic process	26	0.0165
Heart development	17	0.0192
Negative regulation of peptidase activity	10	0.0198
Innate immune response	23	0.0217
Inflammatory response	20	0.0297
Axon guidance	11	0.0336

Significant GO terms (biological processes) associated with the identified DEGs. Count: number of genes in set with annotation. *p*-Value: Modified Fisher Extract *p*-Value.

Table 2. Pathway analysis of differentially expressed genes (DEGs) in PRE versus PO groups

KEGG-Pathway	Count	*p*-Value
Complement and coagulation cascades	10	0.0001
Metabolic pathways	60	0.0018
Fat digestion and absorption	6	0.0069
Acute myeloid leukemia	7	0.0087
Ascorbate and aldarate metabolism	5	0.0101
Purine metabolism	13	0.0125
Drug metabolism - cytochrome P450	7	0.0188
Drug metabolism - other enzymes	6	0.0231
Retinol metabolism	8	0.0239
African trypanosomiasis	5	0.0249
Vascular smooth muscle contraction	9	0.0515
Hematopoietic cell lineage	7	0.0526
Axon guidance	9	0.0555
Platelet activation	9	0.0597
Steroid hormone biosynthesis	7	0.0601
N-Glycan biosynthesis	5	0.0715
Chemical carcinogenesis	7	0.0750
Staphylococcus aureus infection	5	0.0758
Glutamatergic synapse	8	0.0764
Biosynthesis of antibiotics	12	0.0836

Significant pathway associated with the identified DEGs. Count: number of genes in set with annotation. *p*-Value: Modified Fisher Extract *p*-Value.

tinine levels, which are critical renal function indicators. There is evidence that excess UA is associated with kidney disease, cardiovascular disease, and metabolic disease [30, 18]. It has been reported that liver injury increases XO activity in the liver and serum and may be involved in organismal defenses [24]. Taken together, the results of the current study indicate that PRE restored PO-induced liver damage, and subsequently reduced XO activity and liver UA levels. The data analysis in the present study indicated that PRE exhibited hypouricemic activities in PO-induced hyperuricemic mice through UA production and increasing UA excretion.

In recent years, the goal of clinical gout treatment has been to reduce serum UA levels and the inflammatory response, because UA crystallization within joints and tissues can drive an inflammatory response. The leaves of *Sasa* species have various health-promoting properties, including antioxidant, anti-inflammatory, anti-cancer, and anti-obesity effects [10, 11, 13, 14, 23]. PRE is a mixture of phytonutrients including polysaccharides, amino acids, and polyphenols, including tricin and *p*-coumaric acid, which have higher antioxidant and anti-inflammatory activities [16]. *p*-Coumaric acid, a major compound in *S. quelpaertensis* extracts, has the potential to prevent or improve insulin resistance and type 2 diabetes by modulating glucose and lipid metabolism [27]. Thus, PRE is expected to exhibit beneficial activities against metabolic diseases, such as hyperuricemia, obesity, cardiovascular and renal diseases, and hypertension [3, 4].

To elucidate the molecular mechanism underlying PRE hypouricemia action, we further investigated the transcriptome response to PRE administration using RNA-Seq. GO and KEGG pathway analyses revealed that PRE regulated the expression of genes involved in transcription regulation, DNA templates, glucose homeostasis, the innate immune response, the inflammatory response, and immune system processes. These results are consistent with those of our previous studies, which demonstrated that PRE played an important role in lipid metabolism and glucose regulation by influencing the metabolic processes associated with the AMPK signaling pathway [11, 27]. It has also been demonstrated the PRE is involved in the regulation of inflammatory responses and immune system processes by inhibiting NF-κB activity [10]. Therefore, PRE may improve PO-induced hyperuricemia in part by regulating immune response and inflammatory signaling in hyperuricemic mice. The transcriptome data and identified genes obtained in this study will serve as a molecular basis for understanding the mechanisms through which PRE improves PO-induced hyperuricemia.

In summary, we examined the hypouricemia effects of PRE in hyperuricemia mice. These actions may be attributed to the synergistic effects of UA production inhibition and uricosuric activities of PRE. PRE administration in PO-induced hyperuricemic mice mainly enriched genes for immune and inflammatory response mediation and the metabolic pathway. These results suggest that PRE has potential applications in the prevention and treatment of hyperuricemia with inflammation.

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초록 : 생쥐에서 제주조릿대 잎 잔사 추출물의 고요산 혈증 저감 효과

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조릿대 잎은 항염, 해열, 이뇨작용 등의 약리효과를 가지고 있어 예로부터 전통의약에서 사용되어 왔다. 본 연구팀은 열수 추출한 후 남는 잔사로부터 식물화합물을 다량으로 함유한 잔사 추출물(PRE)을 제조하는 방법을 보고 바 있다. 본 연구는PRE의 고요산 혈증 저감소재로서 활용 가능성을 평가하기 위하여 수행하였다. Potassium oxonate (PO)로 유도한 고요산 혈증 생쥐 모델에서 PRE는 혈액 내의 요산, 요소 질소, 크레아틴 농도는 감소시켰고, 오줌 내의 요산과 크레아틴 농도는 증가하였다. 또한, PRE 투여한 고용산 혈증 생쥐에서 간 내 요산 농도와 xanthine oxidase 활성이 대조군에 비해 감소하였고, PRE는 PO에 의해 유도된 간 조직의 상해를 보호하였다. 이 결과는 PO로 유도된 고요산 혈증 생쥐에서 PRE는 항염증 및 세포보호 작용에 기인하는 것으로 판단된다. 부가적으로 PRE에 의한 신장조직에서 transcriptome의 반응 변화를 RNA 서열분석법으로 분석하였다. PRE는 주로 면역반응, 염증반응 및 대사과정에 관여하는 유전자의 발현에 영향을 미치는 것으로 나타났다. 본 연구 결과는 염증을 동반하는 고요산 혈증을 개선하는 소재로서의 PRE의 활용 가능성을 제시해 준다.