Biomedicine & Pharmacotherapy 118 (2019) 109195

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Curcumin attenuates potassium oxonate-induced hyperuricemia and kidney inflammation in mice

Yonger Chen[a,1], Cantao Li[a,1], Shuni Duan[b], Xin Yuan[c], Jian Liang[b,*], Shaozhen Hou[a,*]

[a] School of Pharmaceutical Sciences, Guangzhou University of Chinese Medicine, Guangzhou 510006, Guangdong, China
[b] Guangdong Provincial Key Laboratory of New Drug Development and Research of Chinese Medicine, Mathematical Engineering Academy of Chinese Medicine, Guangzhou University of Chinese Medicine, Guangzhou 510006, Guangdong, China
[c] The Second Affiliated Hospital, Guangzhou University of Chinese Medicine, Guangzhou 510120, China

ARTICLE INFO

Keywords:
Curcumin
Hyperuricemia
XOD
NLRP3 inflammasome

ABSTRACT

Current evidences suggest that hyperuricemia is closely related to the overproduction or underexcretion of uric acid (UA). Curcumin (CUR), a natural polyphenol component extracted from the rhizome of Curcuma longa, has been reported to treat various symptoms such inflammation disease, seems to be efficacious in hyperuricemia. In this study, we aimed to investigate the effect of CUR on hyperuricemia and kidney inflammation in hyperuricemic mice. Administration with CUR (20 or 40 mg/kg) or allopurinol (ALL, 5 mg/kg) was given to mice orally one hour later after the injection of potassium oxonate (PO) (300 mg/kg, i.p.) for 14 days. CUR administration decreased the levels of uric acid (UA), creatinine (CRE) and blood urea nitrogen (BUN) in serum. Meanwhile, treatment with CUR effectively inhibited serum and liver xanthine oxidase (XOD) levels, and further renewed normal antioxidant enzymes activities (SOD, GSH-Px), reduced MDA accumulation in serum. Further studies showed that CUR decreased inflammatory cytokines productions (IL-1β, IL-18) in serum, as well as inhibited PO-induced the activation of NLRP3 inflammasome signaling in the kidney. In conclusion, the study revealed that CUR exhibited anti-hyperuricemic and anti-inflammatory effects through suppressing NLRP3 inflammasome activation in kidney and provided the evidence for treating hyperuricemia and associated renal inflammation.

1. Introduction

Hyperuricemia is a risk factor for diabetes, cardiovascular complications, metabolic syndrome and chronic kidney disease [1,2]. In the past decades, the growth trend of hyperuricemia has been attracted widespread attention. It is well known that hyperuricemia is closely associated with overproduction and underexcretion of uric acid (UA) in patients. During the formation of UA, xanthine oxidase (XOD) is the key enzyme involved in the transformation of xanthine and hypoxanthine into UA [3]. Excessive consumption of purine foods and a lack of genetic enzymes can lead to uricemia and hyperuricemia. Such as allopurinol (ALL) [4], a commonly used drug in clinic, but less than half of patients with hyperuricemia can control their serum UA level and easy to cause side effects (hypersensitivity reaction). In UA excretion, the kidney and the intestine play an important role, that more than 70% of UA excretion through the kidney pathway [5]. However, underexcretion of UA in kidney can lead to kidney inflammatory injury, and further slashed their functions, which in turn worsen the renal dysfunction for UA excretion. It is notable that increasing evidence of many medication for hyperuricemia have side effects.

NLRP3 (NLR family pyrin domain containing3) inflammasome, a danger signal for inflammation, which plays a crucial role in the pathogenesis of renal inflammation [6,7]. Recently, evidences have shown that soluble UA and UA crystals could activate the NLRP3 inflammasome, and then mediate the secretion of IL-1β to trigger congenital immune against danger signals [8]. In addition, the NLRP3 inflammasome can also is activated by oxidative stress [9]. Under oxidative stress, oxidative enzymes can increase ROS levels, and then activated NLRP3 and caspase1, leading to pyroptosis and up-regulating the levels of IL-1β [10]. So, inhibiting the activation of NLRP3 inflammasome and reducing oxidative stress may be feasible strategies for drugs to suppress kidney inflammation.

Curcumin (CUR), a natural hydrophobic polyphenol from the rhizomes of *Curcuma longa*, possesses multiple pharmacologic activities, including anti-inflammatory and anti-oxidant. Previous studies have shown that CUR alleviated inflammation by inhibiting of NLRP3-

* Corresponding authors.
E-mail addresses: lj102601@126.com (J. Liang), hsz0214@gzucm.edu.cn (S. Hou).
[1] These authors contributed equally to this article.

https://doi.org/10.1016/j.biopha.2019.109195
Received 27 May 2019; Received in revised form 29 June 2019; Accepted 2 July 2019

dependent caspase-1 activation and reducing IL-1β secretion in dextran sulfate sodium (DSS)-induced colitis [11]. CUR was also demonstrated to ameliorates monosodium urate (MSU)-induced gouty arthritis [12]. In addition, recently studies also found that CUR could exert obvious bioactivity towards hepatoprotective effect and renoprotective effect through anti-inflammatory and anti-oxidant [13,14]. However, to date, hyperuricemia causes complication, such as renal injury, has become a problem that can't be ignored. Therefore, it is particularly important to search whether some drugs can alleviate hyperuricemia, and also improve the renal injury induced by hyperuricemia.

Based on this, in the present study, we established a hyperuricemia model induced by potassium oxonate (PO) (300 mg/kg), which has been reported to cause obvious kidney injury. We further detected the levels of UA, CRE, BUN, XOD and MDA, SOD, GSH-Px and cytokines to evaluate the therapeutic effects of CUR in hyperuricemic mice. Finally, the effect of CUR on NLRP3 inflammasome was investigated to illustrate its mechanism for improving kidney inflammation.

2. Materials and methods

2.1. Reagents

PO and ALL were purchased from Sigma chemicals (St. Louis, MO, US). CUR (HPLC purity > 98%) was purchased from shanghai PureOne Biotechnology Co., Ltd. (Shanghai, China). The uric acid (UA), xanthine oxidase (XOD), creatinine (CRE), blood urea nitrogen (BUN), malondialdehyde (MDA), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) texting kits were provided by Nanjing KeyGEN Biotech. Co., Ltd. (Nanjing, China). Enzyme-linked immunosorbent assay (ELISA) kit of IL-1β was obtained from Thermo Fisher Scientific, and IL-18 ELISA kit was obtained from MEIMIAN (China). RNAiso Plus reagent, PrimeScript™RT reagent kit and SYBR Green PCR Master Mix were provided by TaKaRa (TaKaRa, Japan). Primary antibodies against NLRP3 and caspase1 were produced by Bioss (Beijing, China), ASC was supplied by Cell Signaling Technology (Danvers, USA), IL-1β was purchased from Proteintech (Wuhan, China).

2.2. Animals and treatment

Male Kunming mice (18–22 g) were purchased from the Laboratory Animal Services Center, Guangzhou University of Chinese Medicine (Guangzhou, China) (SYXK 2018-0085). Animals were acclimated for 1 week before the experiments. All animals were allowed to eat a standard diet and drink ad libitum, and adapted to the specific pathogen free (SPF) conditions at 22 ± 2 °C, humidity 60 ± 5% with a fixed 12 h artificial light period. The study was guided and approved by the Animal Ethics Committee of Guangzhou University of Chinese Medicine (No.20180908004).

All mice were randomly divided into 5 groups (n = 8/group): (1) Control group; (2) PO group: hyperuricemic mice were intraperitoneally injected with PO (300 mg/kg); (3) ALL group: hyperuricemic mice treated with ALL (ALL, 5 mg/kg) group; (4) other two groups consisted of mice receiving PO and administrated with CUR(20, 40 mg/kg/day respectively for 14 days). PO was suspended in 0.5% sodium carboxymethylcellulose (CMC-Na) freshly and given to mice by i.p. injection (300 mg/kg) daily for 14 days. Control mice were treated with water (vehicle) accordingly. CUR or ALL was administrated to the mice by oral gavage 1 h after the PO treatment. On the day 15, mice were all sacrificed after being fasted for 12 h and anesthetized by pentobarbital sodium. Then mice blood samples were collected in 2 ml EP tubes followed by the centrifugation (3000 rpm for 10 min at 4 °C) and then stored at -80°C for biochemical assays. Kidney tissues were quickly removed, weighted and divided into two parts, one was fixed in 4% paraformaldehyde for histopathological examination, and the other was stored at -80°C for further biochemical assays.

2.3. Serum and liver biochemical analysis

The levels of UA, XOD, CRE and BUN in the serum and XOD in the liver were detected by using commercial detection kits (Jiancheng Bioengineering Institute, China) according to the instructions of manufacturers.

2.4. Histopathological examination

The kidney tissues from mice were fixed in 4% paraformaldehyde for 24 h and embedded in paraffin. According to standard method, tissue sections (4 μm), were stained with Hematoxylin and Eosin (HE) for histopathological examination. Finally, kidney histological lesions were evaluated with a light microscope (OLYMPUS, Japan) at 200× magnifications. The kidney injury was scored according to previous paper [15].

2.5. Antioxidant activity and cytokine levels

The activities of MDA, SOD and GSH-PX in the serum were detected by using commercial detection kits (Jiancheng Bioengineering Institute, China) and the levels of IL-1β and IL-18 in the serum and kidney were measured using the enzyme-linked immunosorbent assay (ELISA) kits. The detection method was performed according to the instructions of manufacturers.

2.6. Immunohistochemistry (IHC) staining

The paraffin embedded kidney sections of each sample were dewaxed and dehydrated with xylene and gradient concentrations of alcohol. Antigen retrieval was conducted by autoclaving at 120 ℃ for 15 min in citrate buffer (pH 6.0), and then sections were incubated with 3% hydrogen peroxide for 5–10 min to inactivate endogenous catalase. Then, sections were blocked with 10% horse serum. And they were incubated with IL-1β antibody (1:200, Proteintech, Wuhan, China) for overnight at 4 ℃. Then, the sections were incubated with HRP-conjugated secondary antibody (Bioss, Beijing, China) for 1 h at room temperature. Subsequently, the sections were incubated with streptavidin HRP (Bioss, Beijing, China). The expression of IL-1β in kidney were subjected to microscopic (Olympus, Japan) analysis and analyzed by Image J software.

2.7. Gene expression

Total RNA of kidney samples was obtained by using RNAiso Plus reagent (TaKaRa, Janpan) following the manufacturer's protocol. The concentration of protein was measured at Nanodrop 2000c (Thermo Scientific). Then, 1 μg RNA was reverse transcribed to cDNA using a PrimeScript™RT regent kit (TaKaRa, Janpan). The cDNA was amplified by using the SYBR Green PCR Master Mix and specific primers in the CFX96 Real-Time PCR Detection system (Bio-Rad, USA) and these primers were listed as follows: IL-1β forward, 5′-GCCCATCCTCTGTGACTCA-3′; IL-1β reverse, 5′-AGTTGTCTGATTCCAGGTCTCCAT-3′; ASC forward, 5′-AGACATGGGCTTACAGGA-3′; ASC reverse, 5′-CTCCCTCATCTTGTCTTGG-3′; Caspase1 forward, 5′-TATCCAGGAGGGAATATGTG-3′; Caspase1 reverse, 5′-ACAACACCACTCCTTGTTTC-3′; NLRP3 forward, 5′-GTGGTGACCCTCTGTGAGGT-3′; NLRP3 reverse, 5′-TCTTCCTGGAGCGCTTCTAA-3′; β-actin forward, 5′-GGTCATCACTATTGGCAACG-3′; β-actin reverse, 5′-ACGGATGTCAACGTCACACT-3′; RT-PCR was performed in a CFX96 Real-Time PCR Detection system (Bio-Rad, USA) and reaction conditions were performed as follows: 95℃ for 30 s, and then 40 cycles of 95 ℃ for 5 s and 60 ℃ for 30 s. Relative mRNA expressions of NRLP3, ASC, caspase1 and IL-1β were calculated using the $2^{-\triangle\triangle Ct}$ method. The β-actin was used as the housekeeping gene. All target genes were normalized with β-actin.

2.8. Western blot analysis

Kidney tissues were homogenized in 0.1% phenylmethylsulfonyl fluoride RIPA buffer (Beyotime, China) and centrifuged at 12,000*g* for 10 min at 4 °C. Then the supernatant was collected and protein concentrations were detected by BCA protein assay kit (Beyotime, China). Protein samples and loading buffer were mixed at the ratio of 4:1 and boiled for 6 min. The mixture was separated in 8%–10% SDS-PAGE electrophoretic gel and transferred to PVDF membrane (Bio-Rad, USA) for 1.5 h. The membranes were blocked in 5% non-fat milk dissolved in TBST for 1 h at room temperature and incubated with antibodies against NLRP3(Abcam, USA), ASC (CST, Danvers, USA), caspase1 (Abcam, USA) and IL-1β (Proteintech, Wuhan, China) at a dilution of 1:1000 respectively overnight at 4 ℃. Then, these membranes were incubated with secondary antibody for 1 at room temperature after washing with TBS-Tween for 3 times. The membranes were imaged with ECL kit (Beyotime, China), and densitometric analysis was performed by Image J software (National Institutes of Health, USA).

2.9. Statistical analysis

Data is expressed as means ± S.E.M and all data analysis were using SPSS version 13.0 software. Differences between groups were determined using analysis of variance (ANOVA). When the F ratios were significant, post hoc comparisons were made using the LSD post hoc test. P values < 0.05 was considered statistically significantly.

3. Results

3.1. CUR decreased the levels of UA, CRE and BUN in serum

UA, an important indicator of hyperuricemia, which is produced by the liver and excreted by the kidney. Underexcretion of UA can cause kidneys damage [16]. As shown in Fig. 1A, PO treatment caused a significant elevation in serum level of UA compared with the control group ($P < 0.01$), and CUR at doses of 20, 40 mg/kg also markedly decreased the levels of UA in serum, indicating that CUR could alleviate PO-induced hyperuricemia. CRE and BUN also are important indicators to reflect kidney injury. We found that the levels of CRE and BUN increased significantly in PO group ($P < 0.01$, Fig. 1B–C). ALL or CUR treatment obviously inhibited the elevation of CRE and BUN ($P < 0.05$ or $P < 0.01$) induced by PO, suggesting that CUR could effectively improve PO-induced kidney injury in mice, which has similar effect as compared to ALL.

3.2. CUR decreased the levels of XOD in serum and liver

The key enzyme XOD is closely related to the production of UA [17]. As shown in Fig. 2A–B, the PO group had a significantly higher XOD level in serum and liver as compared to those levels in the control group ($P < 0.01$). However, administration with ALL or CUR could significantly reduce the serum and hepatic levels of XOD ($P < 0.05$ or $P < 0.01$), suggesting that the effect of CUR on reducing the production of UA is closely related to inhibit XOD level.

3.3. CUR improved PO-induced kidney histopathological changes in mice

In clinical trials, the inflammation status and some organizational structure changes were observed as an obvious pathological characteristic of hyperuricemia [18]. The inflammatory cells infiltration and tissue damage of PO-induced hyperuricemia were translated into a histological severity score [15]. Kidney histological changes of control mice and experimental mice were depicted in Fig. 3A–B. The renal tissues in control mice showed a normal morphology with no evidence of inflammation. While PO-treated mice exhibited several characterized histologic alterations, including inconspicuous boundaries between adjacent proximal tubule cells, swelling and proximal tubule necrosis. Compared with PO group, tubulointerstitial and glomerular lesions

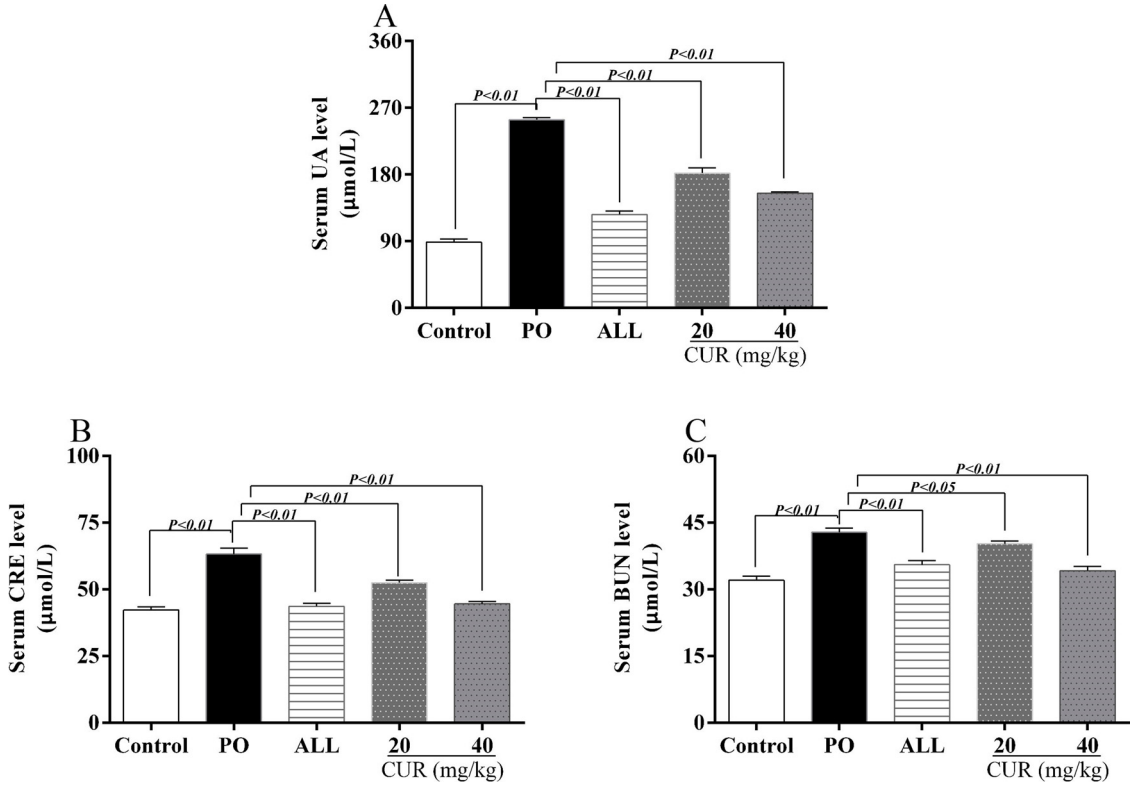

Fig. 1. Eff ;ects of CUR on hyperuricemia and kidney injury in hyperuricemic mice. (A) The level of serum UA. (B) The level of serum CRE. (C) The level of serum BUN. Data are showed as mean ± S.E.M of 6–8 mice in each group.

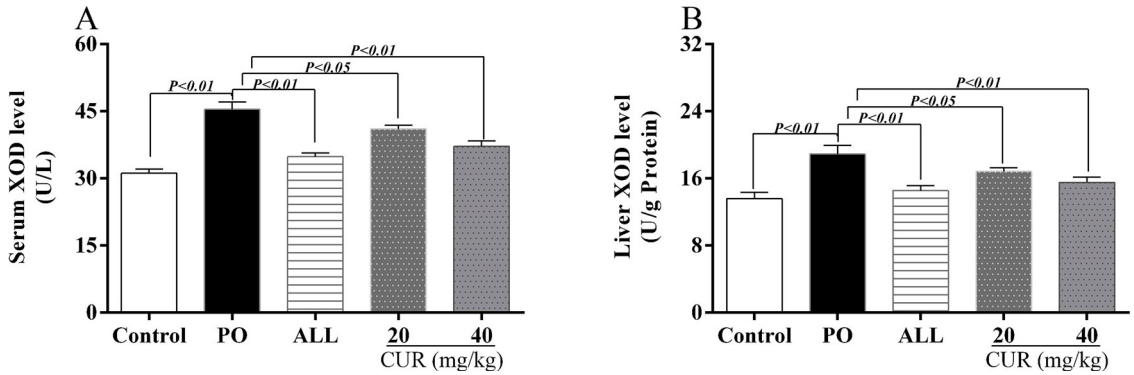

Fig. 2. Eff ;ect of CUR on the level of XOD in serum and liver. (A) The level of XOD in serum. (B) The level of XOD in liver. Data are showed as mean ± S.E.M of 6–8 mice in each group.

were ameliorated in the low-dose treatment group (CUR 20 mg/kg) or the positive control group (ALL, 5 mg/kg) treated groups, and with regulated proximal tubule cells and the cytoplasm were relatively clear. High-dose CUR (40 mg/kg) treatment alleviated PO-induced pathological lesions.

3.4. CUR inhibited the production of cytokines in serum and kidney tissues and the oxidative stress injury in serum in hyperuricemic mice

After pathological observation of kidney, we further investigated the levels of inflammatory cytokines IL-1β and IL-18 in serum and renal tissue in PO-induced hyperuricemic mice. As shown in Fig. 4A–D, the PO group significantly elevated the levels of IL-1β and IL-18 in both serum and kidney compared to control mice ($P < 0.01$). CUR (20, 40 mg/kg) and ALL (5 mg/kg) treatment significantly reversed the elevations of IL-1β and IL-18 in serum and kidney tissues ($P < 0.01$), indicating that CUR could inhibit the inflammatory response to protect against the kidney damage induced by PO. Moreover, we analyzed the levels of prominent antioxidant enzymes (SOD and GSH-Px), MDA in serum. As shown in Fig. 4E–G, compare to control group, the levels of SOD and GSH-Px in PO group were remarkably lower in serum ($P < 0.01$), and the MDA level was significantly increased in PO group ($P < 0.01$). However, administration with ALL or CUR could significantly increase the levels of SOD and GSH-Px ($P < 0.05$ or $P < 0.01$) and reduce the level of MDA ($P < 0.05$), suggesting that CUR may reduce oxidative stress in PO-induced hyperuricemic mice. In addition, the expression of inflammatory cytokine IL-1β in kidney also indicated that the positive staining of IL-1β was significantly increased in PO-induced hyperuricemic mice (Fig. 4H–I). Treatment with CUR (20, 40 mg/kg) and ALL (5 mg/kg) could markedly reduce expression of IL-1β.

3.5. CUR improved kidney inflammation by suppressing the NLRP3 inflammasome activation in hyperuricemic mice

In the above results, CUR could reduce the expression levels of inflammatory cytokines IL-1β and IL-18 in PO-induced hyperuricemia mice, both of which are downstream products of NLRP3 inflammatory

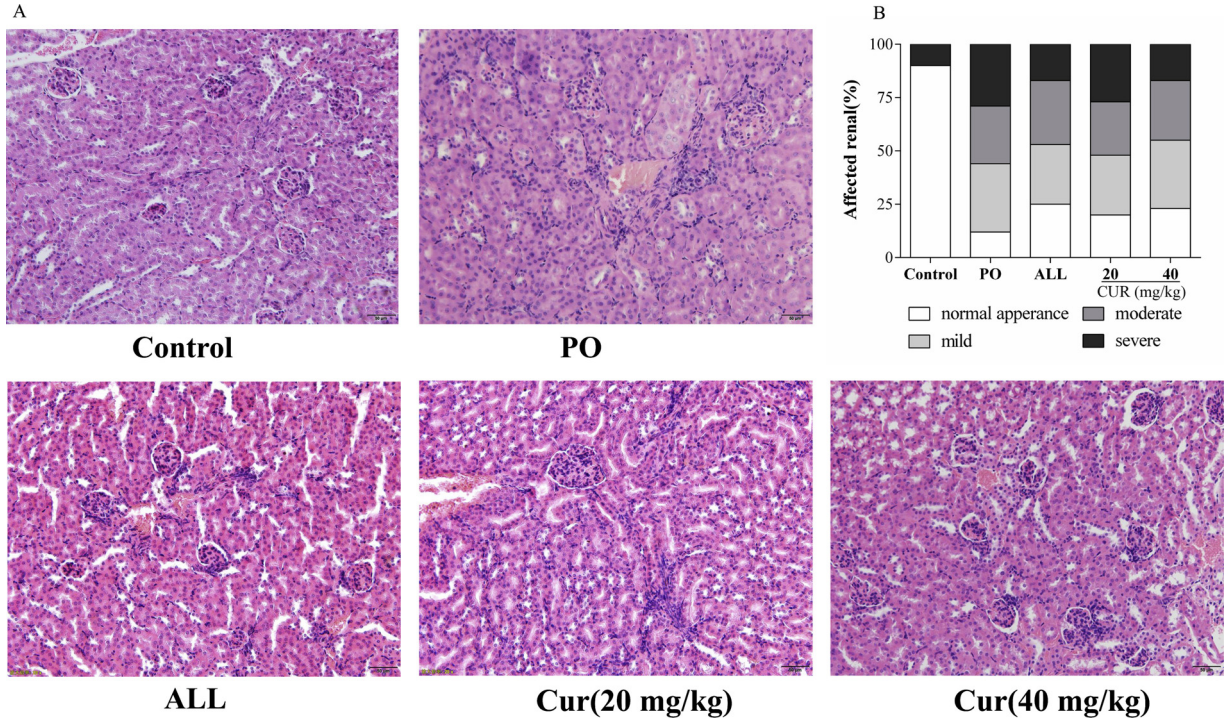

Fig. 3. Eff ;ect of CUR on kidney pathological changes for PO-induced hyperuricemic mice. (A) The representative pictures of kidney histopathology (200×). (B) Affected renal (%) (n = 3).

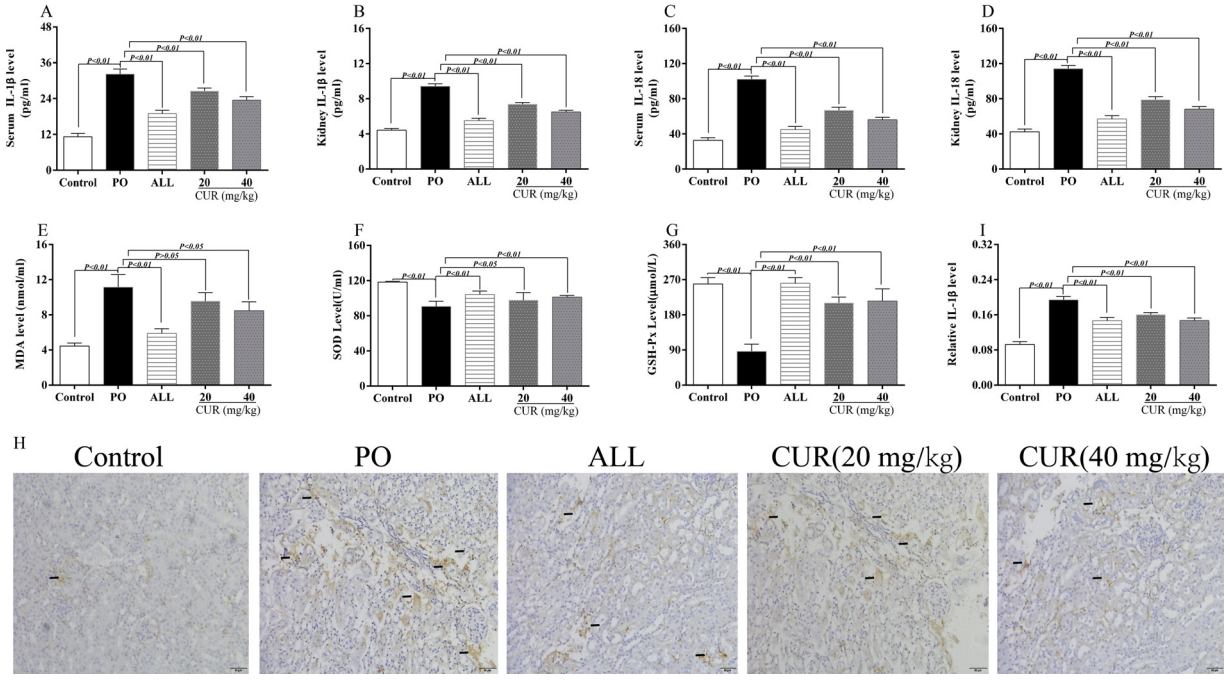

Fig. 4. Eff ;ects of CUR on the levels of pro-inflammatory cytokines. (A) The level of IL-1β in serum. (B) The level of IL-1β in kidney. (C) The level of IL-18 in serum. (D) The level of IL-18 in kidney. (E) The level of MDA in serum. (F) The level of SOD in serum. (G)The level of GSH-Px in serum (H) The representative IHC pictures of IL-1β in kidney (200×). (I) The expression of IL-1β in kidney (n = 3). Data are showed as mean ± S.E.M of 6–8 mice in each group.

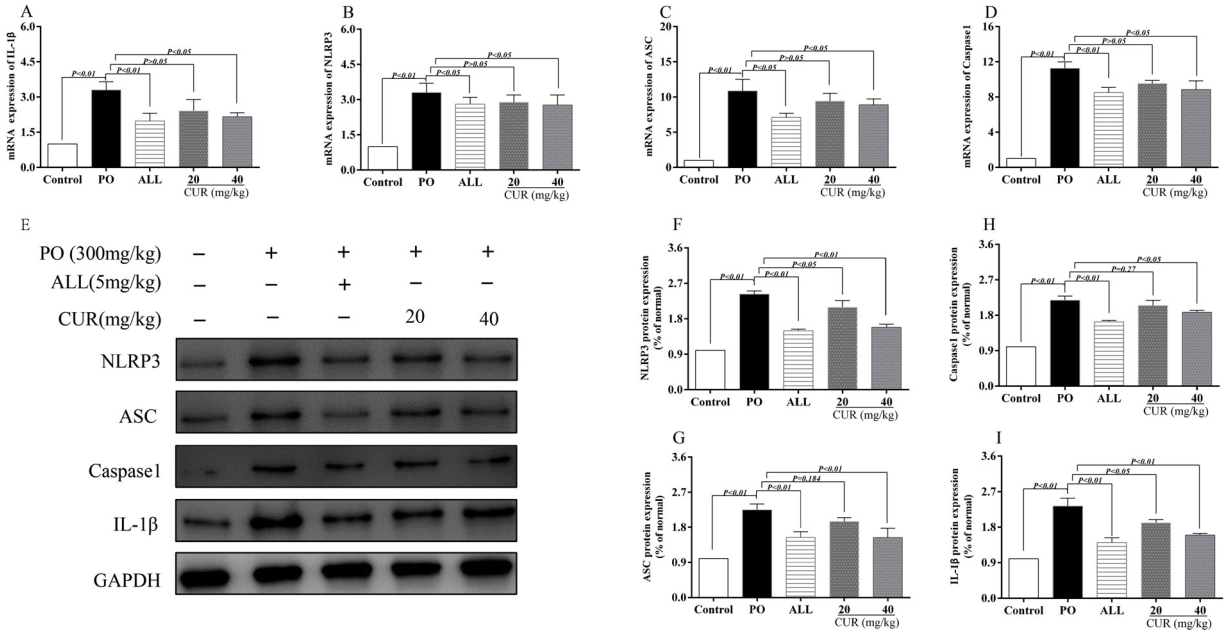

Fig. 5. Eff ;ects of CUR and ALL on NLRP3 inflammasome signaling pathways expressions in PO-induced hyperuricemic mice. The mRNA expression of IL-1β (A), NLRP3 (B), ASC (C) and caspase1 (D) in kidney tissue were detected by RT-PCR. The protein expressions of NLRP3, ASC, caspase1 and IL-1β(E) were detected by Western blot in kidney tissue. The protein expressions of NLRP3 (F), ASC (G), caspase1 (H) and IL-1β (I) were quantitated by Image software. Data are showed as mean ± S.E.M of 3–5 mice in each group.

pathway [19]. On this basis, we further investigated the effect of CUR on NLRP3 inflammasome signal pathway. We found that the mRNA expressions of IL-1β, NLRP3, ASC and caspase1 were significantly increased in the kidney tissues after PO treatment compared to the control group (Fig. 5A–D). Interesting, CUR treatment could dose-dependently reduce the mRNA expressions of IL-1β, NLRP3, ASC and caspase1 (Fig. 5A–D). Next, we explored the effect of CUR on regulating the protein expressions of NLRP3 inflammasome signal pathway. Consistent with the results of mRNA, the protein levels of NLRP3, ASC, caspase1 and IL-1β in kidney tissues of PO-induced hyperuricemic mice were dose-dependently reduced after treatment with CUR (Fig. 5E–I), suggesting that CUR could inhibit the activation of NLRP3 inflammasome to reduce kidney inflammation.

4. Discussion

The increasing trend of hyperuricemia has been noted in the past decades. Patients with hyperuricemia have higher levels of UA, which

affected kidney excretion and then caused kidney damage. Although ALL has been frequently used for patients with hyperuricemia, less than half of them could achieve of goal of controlling their serum UA levels. Hence, there is no doubt that more effective anti-hyperuricemic medicines with fewer side effects are needed. CUR, as a natural polyphenol compound, has been demonstrated for its anti-inflammatory in various disorders. In the present study, we confirmed that CUR can alleviate hyperuricemia and promote nephroprotective effects in PO-induced hyperuricemic mice.

It has been now widely accepted that UA level is the representative hallmark of hyperuricemia [20]. Hyperuricemia occurs when UA is overproduced or under excreted due to disorders of the modulating system of UA [21,22]. CRE and BUN levels are the most important biochemical indexes to detect abnormal renal function [23]. The present study revealed that CUR reduced UA, CRE and BUN levels in serum, indicating that CUR could alleviate PO-induced hyperuricemia, which might be a therapeutic strategy in renal injury.

XOD is a key enzyme involved in conversion of xanthine and hypoxanthine to UA [24]. The higher XOD activity can lead to excessive synthesis of UA [25]. Treatment with CUR (20, 40 mg/kg) could significantly inhibit XOD activities in serum and the liver, suggesting that the effect of CUR on decreasing UA might be due to the inhibitory effect on XOD level.

Genome-wide association studies were consistent with the fact that about 90% of patients suffer from the underexcretion type in hyperuricemia [26]. The kidney plays an important role in UA excretion, with more than half of urate excretion through the renal pathway [27]. Meanwhile, histological examinations of renal tissues exhibited severe inflammatory cell infiltration in PO-treated mice, while these characteristics effectively attenuated by CUR or ALL. We further detected the levels of inflammatory cytokines in serum and kidney. Our results also confirmed that CUR significant reversed the elevated production of pro-inflammatory cytokines in serum and renal tissues, demonstrating that the nephroprotective effects of CUR might be due to its anti-inflammatory effect, which is similar to previous studies [28,29].

It has been reported that increased expressions of IL-1β and IL-18 is closely associated with activation of the NLRP3 inflammatory pathway. The previous studies also found that UA could induce activation of caspase 1 and release of IL-1β [30]. Moreover, hyperuricemia-induced NLRP3 activation in macrophages is used as the contributors to the progression of diabetic nephropathy [32]. In addition, accumulating evidence have demonstrated that oxidative stress can increased oxidative enzyme to induce the increase of ROS, which could activate NLRP3 inflammasome signal pathway to up-regulate the expressions of pro-inflammatory cytokines [10]. In this study, we found that CUR could reduce oxidative stress and inhibit the expressions of pro-inflammatory cytokines IL-1β and IL-18, suggesting that CUR may be regulate NLRP3 inflammasome signal pathway to alleviate kidney injury in PO-induced hyperuricemic model mice. Further studies also evidence that CUR could significantly inhibit the activation of NLRP3 inflammasome signal pathway.

5. Conclusions

In conclusion, our findings confirmed that CUR could decrease the UA level in PO-induced hyperuricemia model and ameliorate renal damage. Further studies showed that the therapeutic effect of CUR on alleviating renal injury and inflammation were closely related to the inhibition on NLRP3 inflammasome activation in hyperuricemic mice. Thus, our results suggest that CUR might be used as a new potential drug or supplement in protecting against hyperuricemia-caused renal injury.

Declaration of Competing Interest

All authors declare no conflicts of interest in this study.

Acknowledgements

This work was supported by the Guangdong Province Universities and Colleges the Special Funds from Central Finance of China in Support of the Development of Local Colleges and University (No. A1-AFD018181Z3961, No. A1-AFD01515A03, No. A1-AFD016151Z3207), National Natural Science Foundation of China (No. 81673668), Science and Technology Project Scheme of Guangdong Province China (No. 2015B020234008), Natural Science Foundation of Guangdong Province China (2014A030304059, No. 2017A030313657).

References

[1] M. Jin, F. Yang, I. Yang, Y. Yin, J.J. Luo, H. Wang, X.F. Yang, Uric acid, hyperuricemia and vascular diseases, Front Biosci. 17 (1) (2012) 656–669.
[2] R. Liu, C. Han, D. Wu, X. Xia, J. Gu, H. Guan, Z. Shan, W. Teng, Prevalence of hyperuricemia and gout in mainland China from 2000 to 2014: a systematic review and meta-analysis, Biomed Res. Int. 2015 (2015) 1–12.
[3] J. Maiuolo, F. Oppedisano, S. Gratteri, C. Muscoli, V. Mollace, Regulation of uric acid metabolism and excretion, Int. J. Cardiol. 213 (2016) 8–14.
[4] P. Pacher, A. Nivorozhkin, C. Szabó, Therapeutic effects of xanthine oxidase inhibitors: renaissance half a century after the discovery of allopurinol, Pharmacol. Rev. 58 (1) (2006) 87–114.
[5] M.S. Lipkowitz, Regulation of uric acid excretion by the kidney, Curr. Rheumatol. Rep. 14 (2) (2012) 179–188.
[6] R. Zhou, A.S. Yazdi, P. Menu, J. Tschopp, A role for mitochondria in NLRP3 inflammasome activation, Nature 469 (7329) (2011) 221–225.
[7] A. Chang, K. Ko, M.R. Clark, The emerging role of the inflammasome in kidney diseases, Curr. Opin. Nephrol. Hypertens. 23 (3) (2014) 204–210.
[8] J. Xiao, X.L. Zhang, C. Fu, R. Han, W. Chen, Y. Lu, Z. Ye, Soluble uric acid increases NLRP3 inflammasome and interleukin-1β expression in human primary renal proximal tubule epithelial cells through the toll-like receptor 4-mediated pathway, Int. J. Mol. Med. 35 (5) (2015) 1347–1354.
[9] S. Wang, X. Zhao, S. Yang, B. Chen, J. Shi, Salidroside alleviates high glucose-induced oxidative stress and extracellular matrix accumulation in rat glomerular mesangial cells by the TXNIP-NLRP3 inflammasome pathway, Chem. Biol. Interact. 278 (2017) 48–53.
[10] A. Sharma, M. Tate, G. Mathew, J.E. Vince, R.H. Ritchie, J.B. de Haan, Oxidative stress and NLRP3-inflammasome activity as significant drivers of diabetic cardiovascular complications: therapeutic implications, Front. Physiol. 9 (2018) 114.
[11] Z. Gong, S. Zhao, J. Zhou, J. Yan, L. Wang, X. Du, H. Li, Y. Chen, W. Cai, J. Wu, Curcumin alleviates DSS-induced colitis via inhibiting NLRP3 inflammsome activation and IL-1β production, Mol. Immunol. 104 (2018) 11–19.
[12] X. Li, D.Q. Xu, D.Y. Sun, T. Zhang, X. He, D.M. Xiao, Curcumin ameliorates monosodium urate-induced gouty arthritis through Nod-like receptor 3 inflammasome mediation via inhibiting nuclear factor-kappa B signaling, J. Cell. Biochem. 120 (4) (2019) 6718–6728.
[13] H. Khan, H. Ullah, S.M. Nabavi, Mechanistic insights of hepatoprotective effects of curcumin: therapeutic updates and future prospects, Food Chem. Toxicol. 124 (2019) 182–191.
[14] X. Sun, Y. Liu, C. Li, X. Wang, R. Zhu, C. Liu, H. Liu, L. Wang, R. Ma, M. Fu, D. Zhang, Y. Li, Recent advances of curcumin in the prevention and treatment of renal fibrosis, Biomed Res. Int. 2017 (2017) 2418671.
[15] D.F. Dai, K. Sasaki, M.Y. Lin, K.D. Smith, R.F. Nicosia, C.E. Alpers, B. Najafian, Interstitial eosinophilic aggregates in diabetic nephropathy: allergy or not? Nephrol. Dial. Transplant. 30 (8) (2015) 1370–1376.
[16] S. Pilemann-Lyberg, T.W. Hansen, N. Tofte, S.A. Winther, S. Theilade, T.S. Ahluwalia, P. Rossing, Uric acid is an independent risk factor for decline in kidney function, Diabetes Care (2019) dc182173.
[17] Y. Isaka, Y. Takabatake, A. Takahashi, T. Saitoh, T. Yoshimori, Hyperuricemia-induced inflammasome and kidney diseases, Nephrol. Dial. Transplant. 31 (6) (2016) 890–896.
[18] M.K. Gupta, J.A. Singh, Cardiovascular disease in gout and the protective effect of treatments including urate-lowering therapy, Drugs (2019) 1–11.
[19] P.A. Ruiz, B. Morón, H.M. Becker, S. Lang, G. Rogler, Titanium dioxide nanoparticles exacerbate dss-induced colitis: role of the NLRP3 inflammasome, Gut 66 (7) (2016) 1216–1224.
[20] K. Ichida, H. Matsuo, T. Takada, A. Nakayama, K. Murakami, T. Shimizu, Y. Yamanashi, H. Kasuga, H. Nakashima, T. Nakamura, Y. Takada, Y. Kawamura, H. Inoue, Decreased extra-renal urate excretion is a common cause of hyperuricemia, Nat. Commun. 3 (2012) 764.
[21] S.Y. Kim, J.P. Guevara, K.M. Kim, H.K. Choi, D.A. Albert, Hyperuricemia and coronary heart disease: a systematic review and meta-analysis, Arthritis Care Res. 62 (2) (2010) 170–180.
[22] A.L. Gaffo, D.R.J. Jacobs, C.E. Lewis, T.R. Mikuls, K.G. Saag, Association between being african-american, serum urate levels and the risk of developing hyperuricemia: findings from the coronary artery risk development in young adult cohort, Arthritis Res. Ther. 14 (1) (2012) R4.
[23] N. Wang, P. Li, J. Pan, M. Wang, M. Long, J. Zang, S. Yang, Bacillus velezensis A2 fermentation exerts a protective effect on renal injury induced by zearalenone in mice, Sci. Rep. 8 (1) (2018) 13646.
[24] Y.P. Si, J.W. Park, S. Jung, G.S. Hwang, E. Goh, H.J. Lee, Layer-by-layer

electrochemical biosensors configuring xanthine oxidase and carbon nanotubes/graphene complexes for hypoxanthine and uric acid in human serum solutions, Biosens. Bioelectron. 121 (2018) 265–271.
[25] X. Zhao, J.X. Zhu, S.F. Mo, Y. Pan, L.D. Kong, Effects of cassia oil on serum and hepatic uric acid levels in oxonate-induced mice and xanthine dehydrogenase and xanthine oxidase activities in mouse liver, J. Ethnopharmacol. 103 (3) (2006) 357–365.
[26] K. Ichida, What lies behind serum urate concentration? Insights from genetic and genomic studies, Genome Med. 1 (12) (2009) 118.
[27] M.S. Lipkowitz, Regulation of uric acid excretion by the kidney, Curr. Rheumatol. Rep. 14 (2) (2012) 179–188.
[28] L. Wen, W.J. Guo, Y.C. Zhu, S. Peng, W. Zheng, C. Zhang, F.L. Shao, Y.Y. Zhu, N. Hang, L.D. Kong, X.B. Meng, Q. Xu, Y. Sun, Targeting peroxiredoxin 1 by a curcumin analogue, AI-44, inhibits NLRP3 inflammasome activation and attenuates lipopolysaccharide-induced sepsis in mice, J. Immunol. 201 (8) (2018) 2403–2413.
[29] A. Bugyei-Twum, A. Abadeh, K. Thai, Y. Zhang, M. Mitchell, G. Kabir, K.A. Connelly, Suppression of NLRP3 inflammasome activation ameliorates chronic kidney disease-induced cardiac fibrosis and diastolic dysfunction, Sci. Rep. 6 (1) (2016) 39551.
[30] S.A. Nicholas, V.V. Bubnov, I.M. Yasinska, V.V. Sumbayev, Involvement of xanthine oxidase and hypoxia-inducible factor 1 in Toll-like receptor 7/8-mediated activation of caspase 1 and interleukin-1β, Cell. Mol. Life Sci. 68 (1) (2011) 151–158.
[32] S.M. Kim, S.H. Lee, Y.G. Kim, S.Y. Kim, J.W. Seo, Y.W. Choi, D.J. Kim, K.H. Jeong, T.W. Lee, C.G. Ihm, K.Y. Won, J.Y. Moon, Hyperuricemia-induced NLRP3 activation of macrophages contributes to the progression of diabetic nephropathy, Am. J. Physiol. Renal Physiol. 308 (9) (2015) F993–F1003.