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Moshen granule ameliorates membranous nephropathy by regulating NF-κB/Nrf2 pathways via aryl hydrocarbon receptor signalling

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ABSTRACT

Considerable achievements were realized in illuminating underlying pathological mechanisms of patients with idiopathic membranous nephropathy (IMN). Although IMN patients are well diagnosed before they reach renal failure, no currently available drug intervention is effective in halting IMN progression. In this study, we assess Moshen granule (MSG) effect on IMN patients and cationic bovine serum albumin (CBSA)-induced rats. Increasing studies has indicated that activation of aryl hydrocarbon receptor (AHR) was related to oxidative stress and inflammation. We further determine MSG effect on AHR, nuclear factor κB (NF-κB) and nuclear factor erythroid 2-related factor 2 (Nrf2) in the CBSA-induced rats. MSG markedly reduces proteinuria and improves kidney function in both IMN patients and rats induced by CBSA. MSG markedly inhibits increased mRNA expressions of intrarenal *AHR* and its four downstream target genes including *CYP1A1*, *CYP1A2*, *CYP1B1* and *COX-2* compared with untreated CBSA-induced rats. This is accompanied by markedly downregulated protein expressions of *p*-IκBα and NF-κB p65 and its downstream gene products including MCP-1, COX-2, 12-LOX, iNOS, $p47^{phox}$ and $p67^{phox}$, while markedly preserves protein expressions of Nrf2 and its downstream gene products including catalase, HO-1, GCLM, GCLC, MnSOD and NQO1 in the kidney tissues. These data suggests MSG blunts podocyte damage through inhibiting activation of NF-κB/Nrf2 pathway via AHR signaling. This finding may provide a promising therapy for treatment of IMN through oxidative stress and inflammation.

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1. Introduction

Membranous nephropathy (MN) is the cardinal cause of nephrotic syndrome formed by the accumulation of immune complex deposits in region between podocytes and basement membrane in glomerulus, which results in complement activation and proteinuria development [1,2]. In idiopathic membranous nephropathy (IMN), immune complexes are generated by circulating antibodies binding to podocyte antigens: M-type secretory phospholipase A_2 receptor (PLA_2R) and thrombospondin type-1 domain-containing 7A [3]. Patients with IMN are usually diagnosed well by renal biopsy and/or detected by positive anti-phospholipase A_2 receptor ($aPLA_2R$) before they reach to end-stage kidney disease [3,4]. However, no available treatment approaches is effective in suppressing MN progression.

Traditional Chinese medicines (TCM) have been extensively applied to treat chronic kidney disease (CKD) [1,5–7]. In clinic, an earlier study has suggested that *Astragalus membranaceus* improved patient with IMN without immunosuppressant treatment [8]. In addition, treatment with Shenqi particle improved patients with IMN and nephrotic syndrome [9]. Chinese traditional patent medicines, such as Jian pi qu shi and Shulifenxiao, could improve IMN patients who fail to immunosuppressant intervention [10,11]. TCM also could improve immunosuppressant efficacy. Combining *Tripterygium wilfordii* multi-glycosides and prednisone showed effective for IMN. The remission probability was similar efficacy for *Tripterygium wilfordii* multi-glycosides and tacrolimus [12]. Moreover, Wuzhi capsule increased blood FK506 level in patients with IMN [13]. These findings have demonstrated that TCM treat IMN and decrease proteinuria, but their mechanisms remain enigmatic.

The underlying mechanisms of renal lesion in MN are not completely elucidated but oxidative stress and inflammation is involved in immune complex deposits and complement activation-triggered downstream molecular mechanisms. The latest publication identifies a variety of podocyte-specific genes that remarked expressed in glomeruli of MN patients, which is enriched in targets of nuclear factor ƙB (NF-ƙB) [14]. Increased protein expression of intrarenal phosphorylated NF-ƙB p65 was evident in MN serum recipients [15], indicating activation of inflammation pathway. The highlight of disease action mechanisms aims to search new therapeutic agents. Chinese traditional patent medicines, such as Sanqi oral solution and Zhen-wu-tang, ameliorate cationic bovine serum albumin (CBSA)-induced MN through inhibiting NF-ƙB and/or nuclear factor erythroid 2-related factor 2 (Nrf2) pathways in rats [16,17]. A number of isolated compounds, such as resveratrol, curcumin, betulinic acid, isoliquiritin and coumarin glycosides, could improve NF-ƙB and/or Nrf2 pathways in CBSA-induced MN or passive Heymann nephritis (PHN) [18–22].

Cyclooxygenase-2 (*COX-2*) can be generated by transcription factors both NF-ƙB p65 and aryl hydrocarbon receptor (AHR), indicating their interaction in physiopathological condition. AHR is a cytoplasmic ligand-mediated transcription factor that expresses a battery of genes including xenobiotic-metabolizing enzymes, inflammatory cytokines and adhesion molecules. Extensive evidence has indicated that activation of AHR signaling is involved in CKD patients [23–25]. Our previous study has shown increased AHR nuclear transcription in IMN patients [26]. Increasing publications also demonstrated that AHR interplayed with NF-ƙB in CKD [27–29]. However, there are no agents for simultaneously targeting AHR and NF-ƙB pathways. In this study, we determine therapeutic effect of Moshen granule (MSG, a renoprotective Chinese traditional patent medicine) on patients with IMN. We further evaluate MSG effect on CBSA-injected rats and reveal its regulation effect on NF-ƙB and Nrf2 pathways via AHR signaling. Our study will illuminate MSG ameliorate MN by inhibiting NF-ƙB and Nrf2 pathways via AHR signaling.

2. Material and methods

2.1. Reagents and antibodies

Reagents and antibodies, such as bovine serum albumin and primary antibodies, are described in our previous publication [30].

2.2. Patient registration and follow-up

Twenty-nine patients were registered and the detail information was reported in the previous publication [31]. Twenty-nine IMN patients were treated with MSG between 2021 and 2022. Fasting venous blood and 24 h urine were obtained from patients with MN at month 0, 3, 6, 9 and 12 after treatment by MSG (40 g/day). This study was approved by Ethics Committee of First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine (approval number: TYLLK2020K058), and all participants signed informed consent form.

2.3. MN rats treated by MSG

CBSA preparation and animal experiments were described in details in our previous publication [30,31]. All the experiments are approved Committee of Experimental Animal Administration of the University (approval number: 20200713-06). After seven day of adaption period, the rats are divided into three groups (n = 8): controls, MN rats and MN rats treated with MSG. MN rats are induced with CBSA injection described in our previous study [31]. CBSA-induced rats are administered MSG (3.70 g/kg) for 4 continuous weeks described in our previous publication [31]. Serum and renal tissues are obtained for further analysis.

2.4. Biochemical determination

The methods of serum and urine biochemical analyses are described in details in our previous publication [30,31].

2.5. Histopathological determination

Renal cortex sections are performed following hematoxylin-eosin (HE) based on the previous method [32]. Kidney injury is analyzed by using light microscope.

2.6. Quantitative real-time polymerase chain reaction (RT-PCR) analysis

Quantitative RT-PCR is determined as previously described [23]. The specific primers including cytochrome P450 family 1 subfamily A member 1 (*CYP1A1*), cytochrome P450 family 1 subfamily A member 2 (*CYP1A2*), cytochrome P450 family 1 subfamily B member 1 (*CYP1B1*) and *COX-2* are presented in the previous publication [23]. Gene expressions are normalized by β-actin, and the results are analyzed by $2^{-\Delta\Delta Ct}$ relative quantification.

2.7. Immunohistochemistry

Immunohistochemistry was analyzed reported in our previous publication [33]. Renal cortex sections are incubated with primary antibodies, including F4/80, CD3, AHR, NF-ƙB p65, COX-2, Kelch-like ECH-associated protein 1 (Keap1) and heme oxygenase-1 (HO-1) then incubated with a secondary antibody. The analysis is carried out by light microscope.

2.8. Western blotting analysis

Western blotting analysis is determined based on the previous studies [34,35]. The bands are presented by Western quick horseradish peroxidase chemiluminescent substrate. Expressions are normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH). The relative levels are quantified by ImageJ software.

2.9. Statistical analysis

The data are expressed as mean ± SEM. One-way analysis of variance analysis is used for analyzing differences between various experiments when there are more than two groups by using GraphPad Prism software. The statistical significance is set at $P < 0.05$.

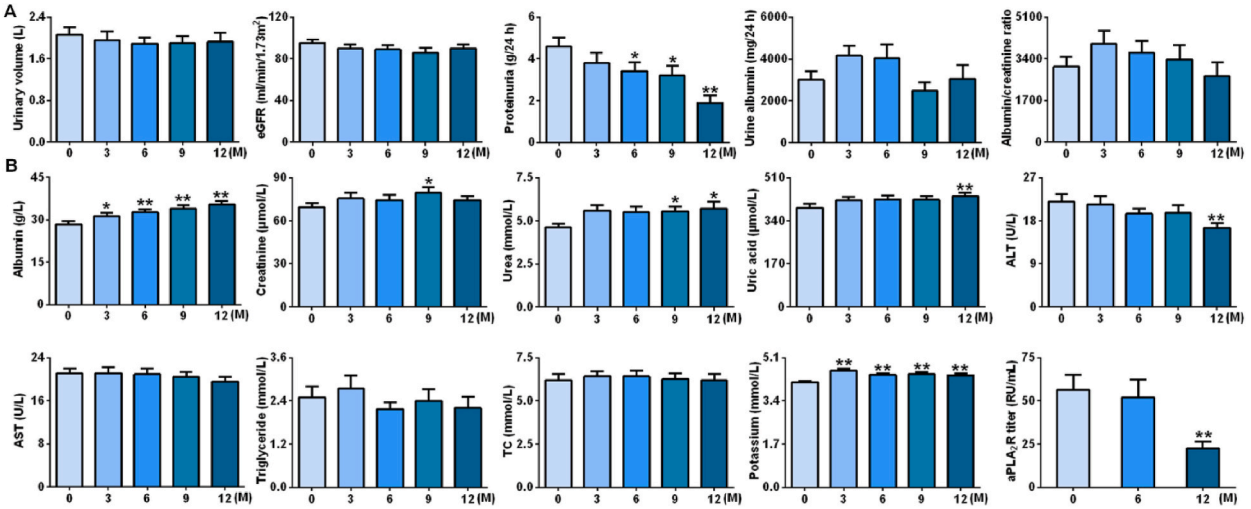

Fig. 1. Treatment with MSG improves renal function in IMN patients. (A) Urine volume, eGFR, proteinuria and albumin levels and albumin/creatinine ratio in IMN patients after MSG treatment at month 0, 3, 6, 9 and 12. (B) Serum levels of albumin, creatinine, urea, uric acid, ALT, AST, triglyceride, TC and potassium as well as $aPLA_2R$ titer in IMN patients after MSG treatment at month 0, 3, 6, 9 and 12. $^*P < 0.05$, $^{**}P < 0.01$ compared to IMN patients before MSG treatment.

3. Results

3.1. Treatment with MSG improves patients with IMN

Proteinuria level is remarked decreased in the IMN patients after MSG treatment at month 6, 9 and 12 compared with pre-treatment stage, (Fig. 1A). There are no significant differences in urine volume, estimated glomerular filtration rate (eGFR), urine albumin and urine albumin/creatinine ratio before and after MSG treatment from 3 to 12 months (Fig. 1A). The levels of albumin and potassium in serum are markedly increased after MSG treatment from 3 to 12 months (Fig. 1B). The levels of creatinine and uric acid in serum are markedly elevated after MSG treatment at month 9 and 12 respectively (Fig. 1B). Moreover, serum urea level is markedly elevated after MSG treatment at month 9 and 12, while serum alanine aminotransferase (ALT) level is markedly reduced after MSG treatment at month 12 (Fig. 1B). Serum aPLA$_2$R titer is markedly reduced after MSG treatment at month 12 (Fig. 1B). In addition, there were no significant differences in serum levels of aspartate aminotransferase (AST), total cholesterol (TC) and triglyceride before and after treatments at months 3, 6, 9 and 12. Collectively, these data suggest that MSG treatment attenuates proteinuria and enhances kidney function for IMN patients.

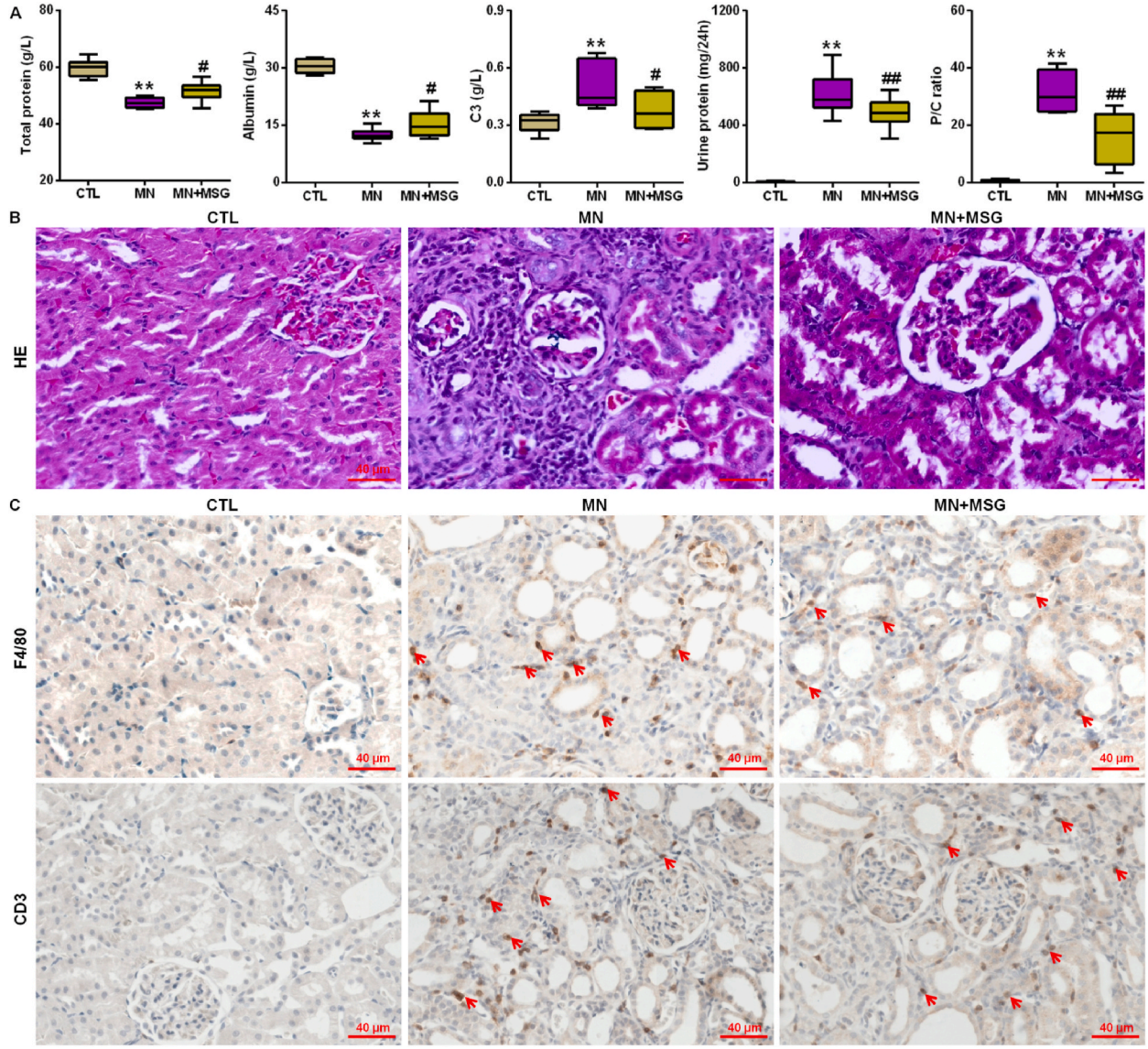

Fig. 2. Treatment with MSG improves renal function and inflammation in CBSA-injected rats. (A) Total protein, albumin and C3 in serum and urinary P/C ratio in healthy control and MN rats with or without MSG. (B) Images of HE stainings of renal tissues in healthy control and MN rats with or without MSG. (C) Immunohistochemical results with intrarenal anti-F4/80 and anti-CD3 antibodies in healthy control and MN rats with or without MSG. $^{*}P < 0.05$, $^{**}P < 0.01$ compared to healthy control rats (n = 6); $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ compared to MN rats (n = 6).

3.2. MSG treatment retards renal lesion and inhibits inflammation response in the CBSA-injected rats

To understand mechanism of MSG, we assessed the pharmacological role of MSG on the CBSA-injected rats. Treatment with MSG markedly increases serum levels of total protein and albumin in CBSA-injected rats compared with untreated CBSA-injected rats (Fig. 2A). In addition, treatment with MSG markedly decreases serum complement 3 (C3) level in the CBSA-injected rats compared with untreated CBSA-injected rats (Fig. 2A). By comparison, MSG treatment markedly decreases proteinuria level and urine protein/creatinine (P/C) ratio in the CBSA-injected rats compared with untreated CBSA-injected rats (Fig. 2A). Compared with the control rats, the rats with CBSA-injected MN show a severely renal parenchymal inflammatory cell infiltration around glomeruli that demonstrate activation of inflammation, while MSG treatment ameliorates intrarenal inflammation response (Fig. 2B). Immunohistochemical staining further shows a marked significant infiltration of F4/80-positive macrophages and CD3-positive T cells in the kidney tissues of the CBSA-injected rats (Fig. 2C), indicating that interstitial infiltration of inflammatory cells is one of subepithelium-like immune-complex deposits and complement activation-induced pathological features in IMN.

3.3. MSG inhibits activation of AHR signaling in the CBSA-injected rats

MSG treatment significant preserves the expression of podocyte-specific proteins including podocin, nephrin, podocalyxin and synaptopodin in glomeruli of CBSA-induced rats compared with untreated CBSA-induced rats (Fig. 3A and B). COX-2 is an important target gene of *AHR*, pointing out that AHR signaling is implicated in oxidative stress and inflammation. Compared with healthy control rats, CBSA-injected MN rats show a remarked increase in mRNA expressions of *AHR* and its four target genes including *CYP1A1*, *CYP1A2*, *CYP1B1* and *COX-2* in the kidney tissues (Fig. 3C), which is accompanied by protein expressions of downregulated cytoplasm

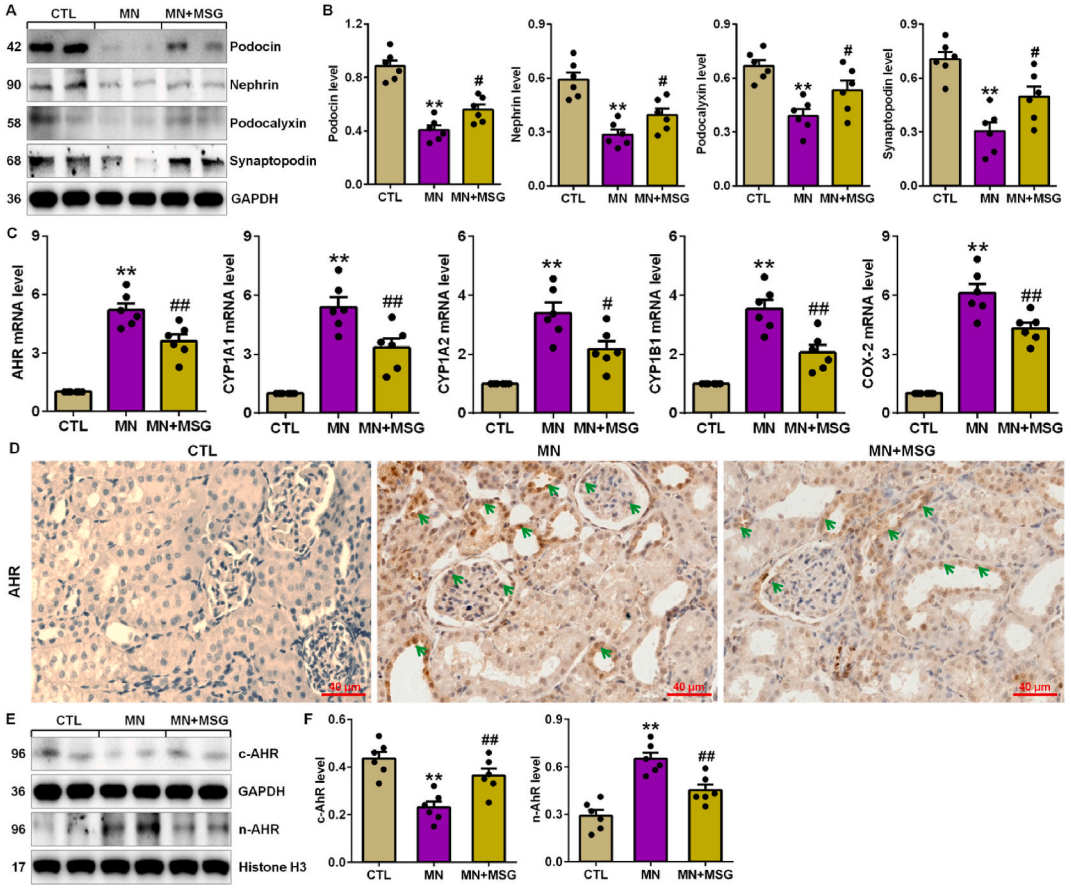

Fig. 3. Treatment with MSG inhibits activation of AHR signaling in the CBSA-injected rats. (A) Podocyte-specific protein expression in the glomeruli of healthy control and MN rats with or without MSG. (B) Podocyte-specific protein levels in the glomeruli of healthy control and MN rats with or without MSG. (C) mRNA levels of intrarenal *AHR* and its target genes, including *CYP1A1*, *CYP1A2*, *CYP1B1* and *COX-2* in healthy control and MN rats with or without MSG. (D) Immunohistochemical analysis with intrarenal anti-AHR antibody in healthy control and MN rats with or without MSG. (E) Intrarenal cytoplasm and nuclei AHR protein expression in the kidney tissues of healthy control and MN rats with or without MSG. (F) Intrarenal cytoplasm and nuclei AHR protein levels in healthy control and MN rats with or without MSG. $^{*}P < 0.05$, $^{**}P < 0.01$ compared to healthy control rats (n = 6); $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ compared to MN rats (n = 6).

AHR while upregulated nuclei AHR in kidney tissues (Fig. 3D and E). However, MSG treatment markedly inhibited CBSA-induced AHR expression at both mRNA and protein levels in MN rats. Moreover, immunohistochemical staining shows that MSG treatment markedly inhibits nuclear translocation of AHR in the CBSA-induced rats (Fig. 3F). These results indicate MSG inhibits activation of AHR signaling in MN.

3.4. MSG inhibits activation of IκB/NF-κB pathway in the CBSA-injected rats

To further explore the underlying antiinflammatory mechanism of MSG, we first examined whether MSG affected IκB/NF-κB and Keap1/Nrf2 pathways in the CBSA-injected rats. As presented in Fig. 4A and B, MSG treatment markedly downregulates protein expressions of intrarenal phosphorylated inhibitor of kappa B alpha (*p*-IκBα) and nuclear p65 levels, which is accompanied by a marked decrease in protein expressions of COX-2, monocyte chemotactic protein-1 (MCP-1), inducible nitric oxide synthase (iNOS), 12-lipoxygenase (12-LOX) and nicotinamide adenine dinucleotide phosphate oxidase subunits ($p47^{phox}$ and $p67^{phox}$) in the CBSA-induced rats. In addition, immunohistochemical staining shows that MSG treatment markedly inhibits nuclear translocation of p65 and cytoplasm COX-2 expression in the CBSA-induced rats (Fig. 4C).

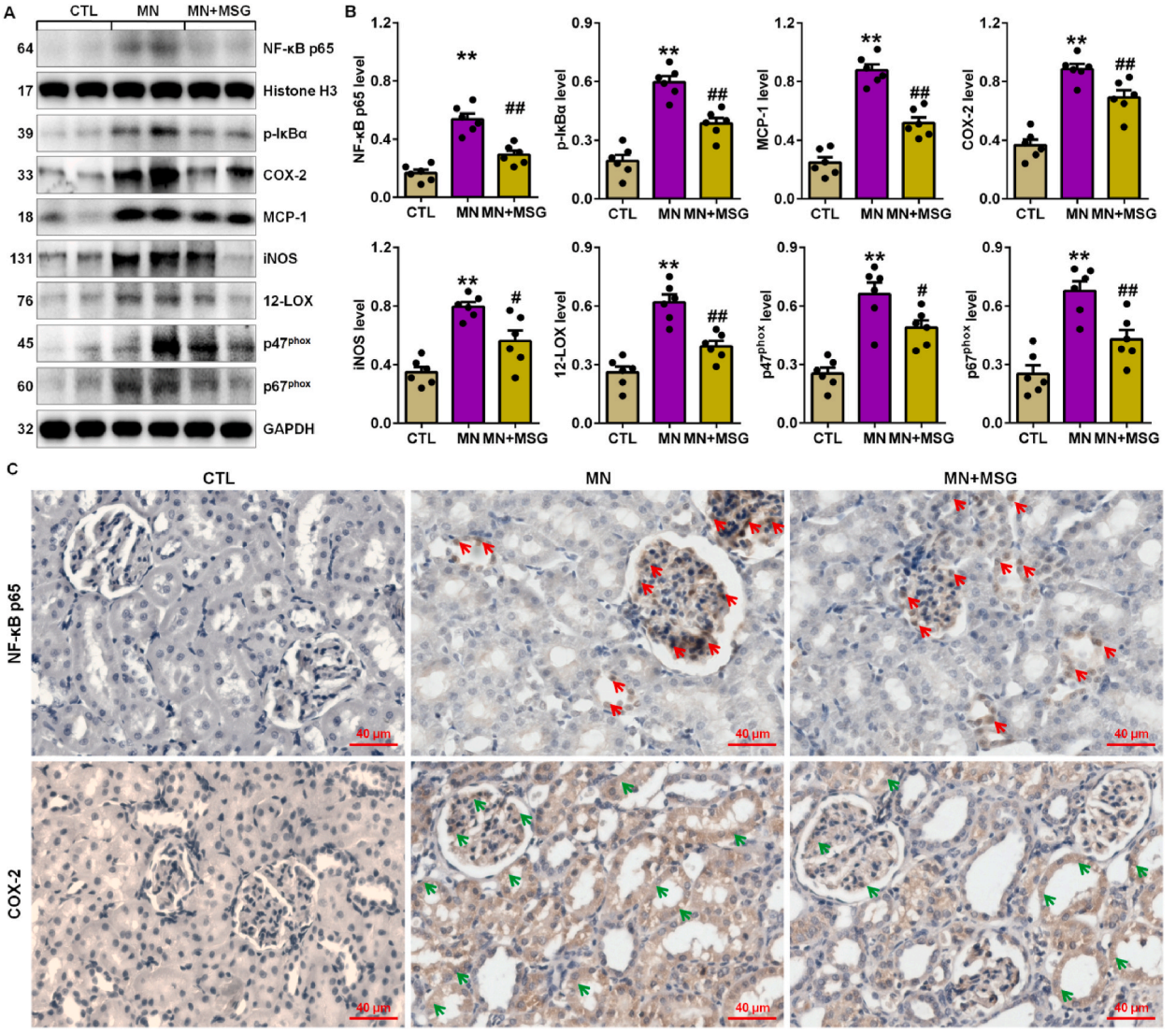

Fig. 4. MSG inhibits activation of IκB/NF-κB pathway in the CBSA-injected rats. (A) Protein expression of intrarenal *p*-IκBα and nuclear translocation of p65 and its gene products including COX-2, iNOS, MCP-1, 12-LOX, $p47^{phox}$ and $p67^{phox}$ in healthy control and MN rats with or without MSG. (B) Protein levels of intrarenal *p*-IκBα, NF-κB p65, COX-2, iNOS, MCP-1, 12-LOX, $p47^{phox}$ and $p67^{phox}$ in healthy control and MN rats with or without MSG. (C) Immunohistochemical results with intrarenal anti-p65 and COX-2 antibodies in healthy control and MN rats with or without MSG. $^{*}P < 0.05$, $^{**}P < 0.01$ compared to healthy control rats (n = 6); $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ compared to MN rats (n = 6).

3.5. MSG inhibits impairment of Keap1/Nrf2 pathways in the CBSA-injected rats

By contrast, MSG treatment markedly inhibits Keap1 protein expression while preserves protein expression of nuclear Nrf2 and its downstream target gene products including HO-1, catalase, glutamate-cysteine ligase modifier subunit (GCLM), glutamate-cysteine ligase catalytic subunit (GCLC), manganese superoxide dismutase (MnSOD) and nicotinamide adenine dinucleotide phosphate quinone dehydrogenase 1 (NQO1) in renal tissues of CBSA-induced rats compared with CBSA-induced rats (Fig. 5A and B). Immunohistochemical staining shows markedly decreased Keap1 expression and increased HO-1 expression in renal tissues of the CBSA-induced rats (Fig. 5C). Taken together, these data demonstrate that MSG can improve the dysregulation of IκB/NF-κB and Keap1/Nrf2 pathways in the CBSA-induced MN rats.

4. Discussion

MN is a unique glomerular damage that is the most common cause of adult nephrotic syndrome. MN is first treated by some supportive therapies including diuretics, renin-angiotensin system inhibitors/blockers and lipid-lowering agents to only improve edema, blood pressure and other complications. Conventional immunosuppressive agents including steroids, cyclosporine A, tacrolimus and cyclophosphamide are effective for the treatment of IMN patients, but their use cause severely side effects. TCM have been selected as an important therapy for treating glomerular-related diseases including MN [1,3], glomerulonephritis [36,37], diabetes [38–40] and diabetic kidney disease (DKD) [41,42]. Our present study suggests that MSG treatment decreases proteinuria and improves renal function in both patients with IMN and CBSA-induced MN rats, which are accompanied by preserving protein expression of nephrin, podocin, podocalyxin and synaptopodin (Fig. 6).

Our current study suggest MSG inhibits intrarenal mRNA expressions of *AHR* and its target genes including *CYP1A1*, *CYP1A2*, *CYP1B1* and *COX-2* in the CBSA-induced rats, which is accompanied by inhibiting nuclear translocation of AHR in the renal tissues of

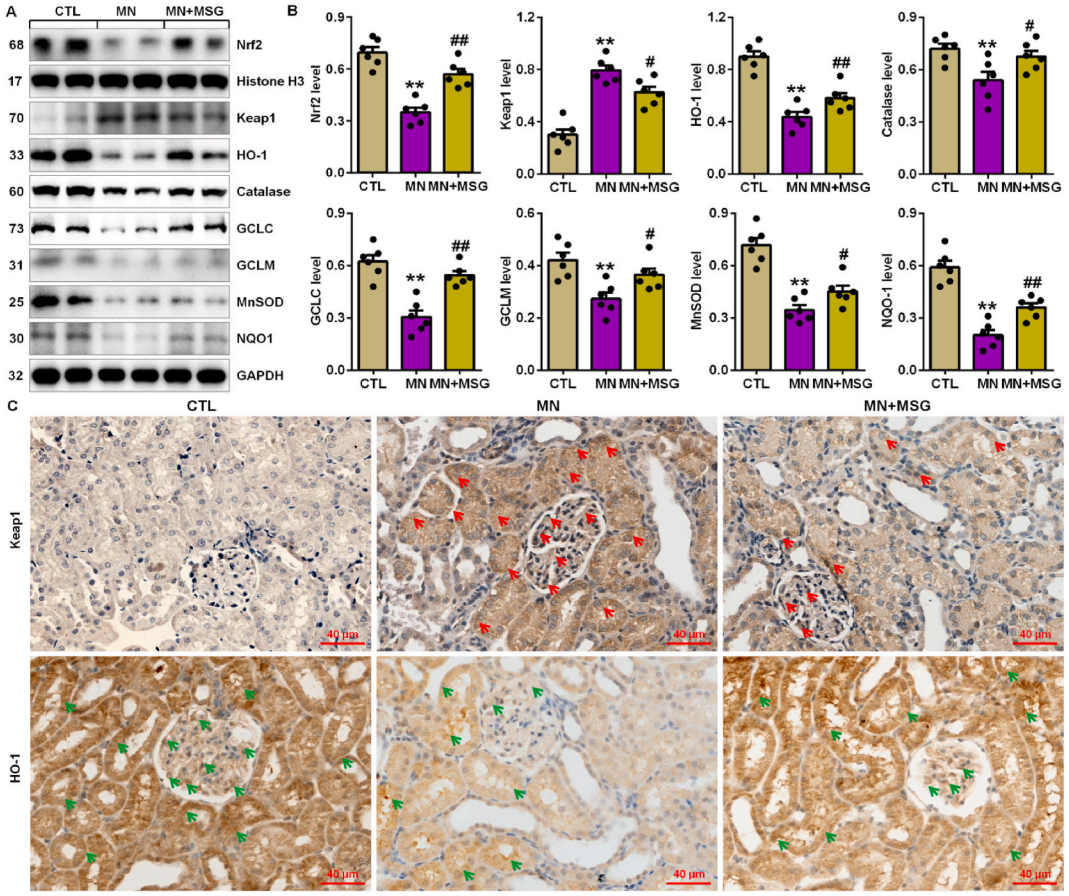

Fig. 5. MSG improves impairment of Keap1/Nrf2 pathway in the CBSA-injected rats. (A) Protein expression of intrarenal nuclear translocation of Nrf2 and its repressor, Keap1, and its downstream gene products including HO-1, catalase, GCLM, GCLC, MnSOD and NQO1 in healthy control and MN rats with or without MSG. (B) Protein levels of intrarenal Nrf2, Keap1, HO-1, catalase, GCLM, GCLC, MnSOD, and NQO1 in healthy control and MN rats with or without MSG. (C) Immunohistochemical analysis with intrarenal anti-Keap1 and HO-1 antibodies in healthy control and MN rats with or without MSG. $^{*}P < 0.05$, $^{**}P < 0.01$ compared with healthy control rats (n = 6); $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ compared to MN rats (n = 6).

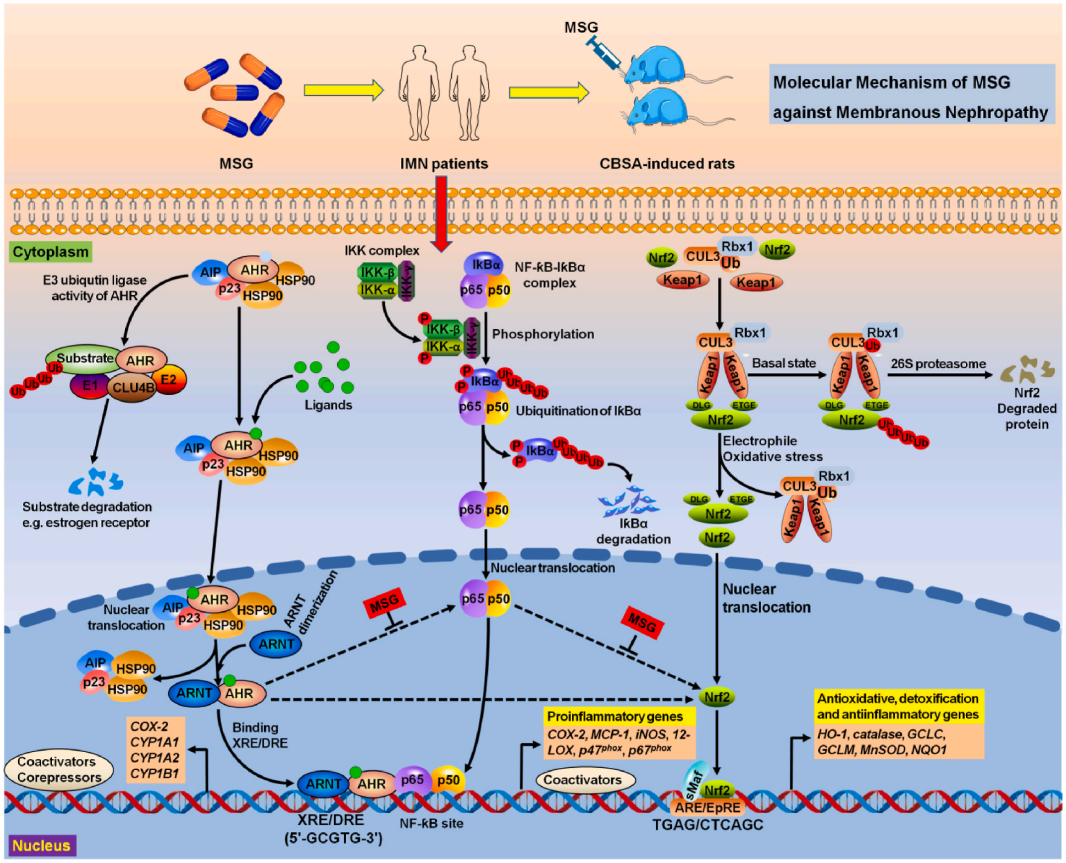

Fig. 6. Molecular mechanism of MSG against MN. MSG inhibits renal function decline and damage in both IMN patients with and CBSA-induced MN rats. MSG attenuates podocyte injury by regulating AHR/NF-κB/Nrf2 signaling axis in CBSA-induced rats.

the CBSA-induced rats (Fig. 6). Our previous finding demonstrated intrarenal nuclear translocation of AHR in patients with IMN, DKD and immunoglobulin A nephropathy [26]. In addition, the latest publication indicates markedly increased mRNA expressions of *AHR* and its target genes, including *CYP1A1*, *CYP1A2* and *CYP1B1*, in the renal tissues of the patients with CKD at five stages [23]. This is accompanied by upregulated AHR nuclear translocation [23]. Similar findings are also found in rats treated with 5/6 nephrectomy and adenine as well as mice treated with unilateral ureteral obstruction at the different time [23,34]. These findings indicate that AHR signaling is extensive activated in various pathological types of patients with CKD. Several recent publications demonstrated that Chinese traditional patent medicines, such as Jian-Pi-Yi-Shen formula, Dahuang Fuzi decoction and Bupi Yishen formula ameliorated CKD partly by inhibiting AHR signaling [43–45].

Oxidative stress and inflammation are associated with various pathogenesis in a wide range of chronic diseases. Both oxidative stress and inflammation alter the expression of several genes such as NF-κB and Nrf2. An earlier study indicated NF-κB activation in the podocytes of the autologous phase of PHN rats [46]. Mezzano et al. reported a marked increase in MCP-1 expression at both mRNA and protein levels in the progressive IMN patients [47]. In addition, Yoshimoto et al. demonstrated an interstitial infiltration of CD68-positive cells accompanied by increased MCP-1 expression is the most significant indicator of end-stage renal disease in IMN [48]. Moreover, Takano et al. uncovered that selective inhibition of COX-2 decreased proteinuria in the PHN rats while inhibition of both cyclooxygenase-1 and COX-2 exhibited a maximum antiproteinuric effect [49]. By contrast, an earlier study demonstrated that Cobalt protoporphyrin, a potent HO-1 inducer, markedly blunted proteinuria, immune complex deposition and immunoglobulin G production in CBSA-induced mice [50]. These studies suggest dysregulation of NF-κB/Nrf2 pathways in MN. Our current another finding is that MSG improves dysregulation of NF-κB/Nrf2 pathways in the CBSA-induced rats. Several TCM prescriptions such as Sanqi oral solution and Zhen-wu-tang attenuated CBSA-induced MN by improving NF-κB and/or Nrf2 pathways in rats [16,17,51]. The current study and that of others indicates that TCM improve MN partly by regulating NF-κB/Nrf2 pathways.

Mechanistically, this study further reveals that MSG mitigates podocyte lesion by improving NF-κB/Nrf2 pathways via inhibiting AHR signaling (Fig. 6). A previous study has shown that AHR protein level was positively related to NF-κB protein level in the peripheral blood mononuclear cells of CKD patients [28]. Addi et al. reported that indole-3 acetic acid, an AHR ligand, induced activation of tissue factor through AHR/NF-κB pathway in human umbilical vein endothelial cells [29]. However, this research group further uncovered that COX-2 protein level was markedly inhibited in the indole-3 acetic acid-stimulated human umbilical vein endothelial cells treated with CH223191 and BAY 11–7082 [52]. The latest study suggests that modified Dahuang Fuzi decoction improved CKD by

inhibiting AHR/NF-ƙB pathway [44]. In addition, Zhao et al. reported that inhibitory effect of Tangshen formula on NF-ƙB p-p65 was associated with inhibition of AHR in the kidney tissues of uninephrectomized-induced DKD rats treated with streptozotocin injection [53]. Similarly, AHR deficiency ameliorated oxidative stress-mediated mesangial cell activation, macrophage infiltration and renal fibrosis in DKD mice [54]. In addition, our previous study has also suggested that a number of poricoic acids simultaneously inhibited NF-ƙB/Nrf2 and AHR pathways in the obstructed kidney of unilateral ureteral obstruction mice [55]. Taken together, activation of AHR is closely associated with NF-ƙB/Nrf2 pathway and NF-ƙB/Nrf2 pathway may be the downstream targets of AHR signaling.

5. Conclusions

This study shows that treatment with MSG ameliorates proteinuria and enhances renal function in patients with IMN. Mechanistically, treatment with MSG retards renal lesion by inhibiting AHR and NF-ƙB/Nrf2 signaling pathway in the CBSA-injected rats. This finding may provide a promising therapy for treatment of IMN through oxidative stress and inflammation.

Author contribution statement

Ying-Yong Zhao: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.
Xiao-Jun Li: Performed the experiments.
Ming Pei: Performed the experiments; Contributed reagents, materials, analysis tools or data.
Shi-Xing Ma, Xiao-yong Yu: Analyzed and interpreted the data.
Ting-Ting Duan, Liang Zou: Contributed reagents, materials, analysis tools or data.

Data availability statement

Data included in article/supplementary material/referenced in article.

Availability of data and materials

All data used to support the findings of this study are available from the corresponding author upon request.

Funding statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20019.

Abbreviations

12-LOX	12-lipoxygenase
AHR	aryl hydrocarbon receptor
ALT	alanine aminotransferase
aPLA$_2$R	anti-phospholipase A$_2$ receptor
AST	aspartate aminotransferase
C3	complement 3
CKD	chronic kidney disease
COX-2	cyclooxygenase-2
CYP1A1	*cytochrome P450 family 1 subfamily A member 1*
CYP1A2	*cytochrome P450 family 1 subfamily A member 2*
CYP1B1	*cytochrome P450 family 1 subfamily B member 1*
DKD	diabetic kidney disease
eGFR	estimated glomerular filtration rate
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
GCLC	glutamate-cysteine ligase catalytic subunit

GCLM	glutamate-cysteine ligase modifier subunit
HE	hematoxylin-eosin
HO-1	heme oxygenase 1
IMN	idiopathic membranous nephropathy
iNOS	inducible nitric oxide synthase
Keap1	Kelch-like ECH-associated protein 1
MCP-1	monocyte chemotactic protein-1
MN	membranous nephropathy
MnSOD	manganese superoxide dismutase
MSG	moshen granule
NF-ƙB	nuclear factor kappa B
NQO1	nicotinamide adenine dinucleotide phosphate quinone dehydrogenase 1
Nrf2	nuclear factor erythroid 2-related factor 2
P/C	protein/creatinine
PHN	passive Heymann nephritis
p-IƙBα	phosphorylated inhibitor of kappa B alpha
PLA_2R	phospholipase A_2 receptor
RT-PCR	real-time polymerase chain reaction
TC	total cholesterol
TCM	traditional Chinese medicines

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