

## ORIGINAL ARTICLE

# Lycopene attenuates chronic prostatitis/chronic pelvic pain syndrome by inhibiting oxidative stress and inflammation via the interaction of NF- $\kappa$ B, MAPKs, and Nrf2 signaling pathways in rats

Qinxin Zhao<sup>1,2</sup>  | Feiya Yang<sup>1</sup> | Lingquan Meng<sup>2,3</sup> | Dong Chen<sup>1</sup> | Mingshuai Wang<sup>2</sup> | Xinxing Lu<sup>2</sup> | Dexi Chen<sup>4,5</sup> | Yongguang Jiang<sup>6</sup> | Nianzeng Xing<sup>1,2</sup> 

<sup>1</sup>Department of Urology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

<sup>2</sup>Department of Urology, Beijing Chao-yang Hospital, Capital Medical University, Beijing, China

<sup>3</sup>Department of Urology, Shandong Provincial Qianfoshan Hospital, Shandong University, Jinan, China

<sup>4</sup>Beijing You'an Hospital, Capital Medical University, Beijing, China

<sup>5</sup>Beijing Institute of Hepatology, Beijing, China

<sup>6</sup>Department of Urology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China

## Correspondence

Nianzeng Xing, Department of Urology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17, Panjiayuan South Li, Chaoyang, 100021, Beijing, China.  
Email: xingnianzeng@126.com

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## Abstract

**Background:** Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is identified as a urinary andrological diseases that afflict men due to various discomforts. It is urgent and meaningful to develop the novel and effective treatments as a result of the unclear etiology and dismal therapeutic effect of CP/CPPS. Lycopene exerts a crucial role in numerous chronic inflammatory diseases owing to its potent antioxidant capacity.

**Objective:** This study aimed to observe the effect of lycopene on CP/CPPS and to explore the underlying mechanisms.

**Materials and Methods:** A CP/CPPS model with complete Freund's adjuvant was established in this study. Afterward, intragastric lycopene or corn oil was administered daily for 4 consecutive weeks. Finally, the cardiac blood and prostate tissue samples were collected from rats to carry out related evaluation and testing.

**Results:** It was found in this study that lycopene alleviated changes in prostate histopathology compared with those in the complete Freund's adjuvant-induced CP/CPPS model rats without lycopene treatment. Furthermore, lycopene was suggested to reduce the levels of chemokines MCP1 and MIP-1 $\alpha$ , down-regulate the expression levels of cytokines (such as TNF $\alpha$ , IL-1 $\beta$ , IL-2, and IL-6), and up-regulate those of CAT, GSH-PX, and T-SOD, decrease that of malondialdehyde. Moreover, it also inhibited the phosphorylation of MAPKs, NF- $\kappa$ B, and enhanced phosphorylation of the Nrf2 in the CP/CPPS rat model.

**Discussion and Conclusions:** The findings in this study suggest that lycopene exerts potent anti- CP/CPPS effects through alleviating inflammatory response and oxidative stress, which is probably attributed to the interaction of NF- $\kappa$ B, MAPKs, and Nrf2 signaling pathways in rats. As a natural antioxidant, lycopene may serve as a promising pharmaceutical preparation for treating CP/CPPS.

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## KEYWORDS

anti-inflammation, antioxidant, chronic pelvic pain syndrome, chronic prostatitis, lycopene, signaling pathways

## 1 | INTRODUCTION

Chronic prostatitis (CP), also known as the chronic pelvic pain syndrome (CPPS), is mainly characterized by long-term recurrent pain in perineum and the lower abdomen.<sup>1</sup> In addition, abnormal urination, sexual dysfunction to various degrees, and decreased fertility also threaten the physical and mental health of men.<sup>2</sup> CP/CPPS may be induced by numerous factors, such as oxidative stress (OS), pathogenic bacterial infection, as well as dysfunctions in neurological, immune, and endocrine systems.<sup>3</sup> Nonetheless, it remains unclear about the specific cause and mechanism of CP/CPPS so far, and no satisfactory efficacy is attained from traditional treatment for CP/CPPS.<sup>4</sup> What's worse, existing treatments only relieve the symptoms rather than cure the disease. Therefore, it is still meaningful and necessary to search for the effective drugs to treat CP/CPPS.

Lycopene (LYC) is a carotenoid widely distributed in tomato, pink grapefruit, pomegranate, and watermelon. LYC possesses a potent antioxidant capacity, which is ascribed to its special conjugated double bonds.<sup>5</sup> Furthermore, LYC exerts an important role in a variety of inflammatory diseases as a result of its strong antioxidant properties, as verified in tremendous experiments.<sup>6,7</sup> To our knowledge, inflammation and stress injury critically affect the development of CP/CPPS.<sup>8,9</sup> Hence, this study was carried out aiming to observe the therapeutic effect of LYC on the CP/CPPS rats and to explore the underlying therapeutic mechanism through detecting the OS- and inflammation-related indicators.

## 2 | MATERIALS AND METHODS

### 2.1 | Materials

LYC, complete Freund's adjuvant (CFA), and corn oil were obtained from Solarbio. The MILLIPIX MAP Kit (Cat. RECYTMAG-65K) was provided by Merck Millipore. The catalase (CAT), glutathione peroxidase (GSH-PX), total superoxide dismutase (T-SOD), and malondialdehyde (MDA) detection kits were supplied by Nanjing Jiancheng Institute of Biotechnology. The anti-Erk1/2 (#9101) and anti-phospho-Erk1/2 (#9911) antibodies, anti-P38 MAPK (#8690) and anti-phospho-P38 MAPK (#4511) antibodies, anti-SAPK/JNK (#9252) and anti-phospho-SAPK/JNK (#4668) antibodies, and anti-NF- $\kappa$ B P65 (#8242) and anti-phospho-NF- $\kappa$ B P65 (#3033) antibodies were obtained from Cell Signaling Technology. In addition, the anti-Nrf2 antibody (ab76026) was derived from Abcam, and the anti-phospho-Nrf2 antibody (PA5-102838) was provided by eBioscience (Affymetrix, Delaware).

### 2.2 | Animals and treatments

This study was carried out in accordance with the relevant guidelines and regulations for the care and use of laboratory animals. The study protocol was approved by the Committee of Animal Experimentation and the Ethics Committee of Capital Medical University.

A total of twenty-one six-week-old male Sprague Dawley (SD) rats (weighing 220-240 g) were purchased from Beijing Vital River Laboratory Animal Technology Co, Ltd. and raised under the specific pathogen-free (SPF) environmental conditions at  $23 \pm 2^\circ\text{C}$  and  $58 \pm 8\%$  humidity. In addition, the animals had free access to food and water, and were allowed for 1-week adaptation to the new surroundings prior to the experiment.

Thereafter, the twenty-one male SD rats were randomly assigned as four groups, including normal group ( $n = 3$ ), model group ( $n = 6$ ), low-dose lycopene group ( $n = 6$ ), and high-dose group ( $n = 6$ ) for non-treatment, intragastric corn oil, intragastric lycopene at 10 mg/(kg/d), and intragastric lycopene at 20 mg/(kg/d) treatments, respectively. Specifically, LYC was dissolved in corn oil in each group.<sup>10,11</sup>

The CP/CPPS rat models of the model group, low-dose lycopene group, and high-dose group were established through injecting CFA into the prostate with reference to our previous experience, while the normal group did not do anything.<sup>12</sup> Briefly, the SD rats were anesthetized and disinfected first of all; then, the abdominal cavity was opened, and the prostate was exposed completely. Subsequently, 100  $\mu\text{L}$  CFA was injected gently into the prostate using the 1-ml syringe, and later, the abdominal cavity was sutured with absorbable lines. LYC and corn oil were utilized on the day following successful modeling, which were then administrated intragastrically on daily for 4 consecutive weeks.

On day 30, the SD rats were anesthetized and weighed, and the blood samples were collected from the heart, while the prostate was dissected rapidly, weighed, and mostly preserved in the freezer at  $-80^\circ\text{C}$  for subsequent detection. A small portion of prostate tissues were fixed in 4% formaldehyde for histological examination.

### 2.3 | Histological evaluation

The paraffin sections from prostatitis rats were observed by H&E staining to evaluate the severity of inflammation. Typically, the severity of inflammation was assessed by the inflammatory score of 0-4,<sup>12</sup> among which 0 point denoted normal; 1 suggested mild inflammation with well-defined nested aggregation of perivascular monocytes; 2 indicated mild infiltration of perivascular monocytes; 3 was indicative of significant infiltration of perivascular

monocytes and hemorrhages, as well as more infiltration of inflammatory cells in the mesenchyme; and 4 represented significant infiltration of perivascular monocytes and hemorrhages, as well as infiltration of large amounts of monocytes and macrophages in the intercellular matrix. According to inflammatory score of 0-4, we graded several random sections of each prostate gland using a double-blind method in each unknown group. Then, the final score was obtained by dividing the total score by the number of sections. Here, we randomly selected three layers of each prostate gland.

## 2.4 | Detection of inflammatory factors in prostate tissues

The levels of IL-1 $\beta$ , MCP1, MIP-1 $\alpha$ , TNF $\alpha$ , IL-2, and IL-6 in prostate tissues were detected using the MILLIPLEX MAP Kit according to the standardized method. Each sample was assayed in triplicate, and the results were expressed as pg/mL.

## 2.5 | Measurement of the OS-related enzyme levels

The levels of CAT, GSH-PX, T-SOD, and MDA in serum and prostate tissues were measured with the detection kit in strict accordance with the manufacturer's protocols.

## 2.6 | Western blotting

In brief, the prostate tissues were lysed using the RIPA lysis buffer, and then, the proteins were quantified using the BCA kit. Thereafter, the protein samples were loaded and separated through SDS-polyacrylamide gel electrophoresis (SDS-PAGE), and transferred onto the polyvinylidene fluoride (PVDF) membranes (Bio-Rad). Afterward, the membranes were blocked with 5% dry milk in Tris-hydrochloride buffer and incubated with monoclonal anti-Erk1/2, anti-phospho-Erk1/2, anti-SAPK/JNK, anti-phospho-SAPK/JNK, anti-P38, anti-phospho-P38, anti-NF- $\kappa$ B P65, anti-phospho-NF- $\kappa$ B P65, anti-Nrf2, and anti-phospho-Nrf2, as well as anti- $\beta$ -actin antibodies (at 1:1000 dilution, respectively) at 4°C overnight. On the following day, these membranes were washed with TBST for three times and further incubated with goat anti-rabbit or mouse IgG antibody for 1 hour at room temperature. Then, ECL chemiluminescence was adopted to visualize the protein expression, and the IMAGEJ software was utilized for densitometric analysis of the protein bands.

## 2.7 | Statistical analysis

All data were collected and analyzed by SPSS (22.0) and expressed as mean  $\pm$  standard deviation (SD). Statistical comparisons among

different groups were calculated through one-way analysis of variance (ANOVA) and Fisher's least significant differences (LSD) test. A difference of  $P < .05$  was considered as statistically significant.

## 3 | RESULTS

### 3.1 | Prostatic histopathology

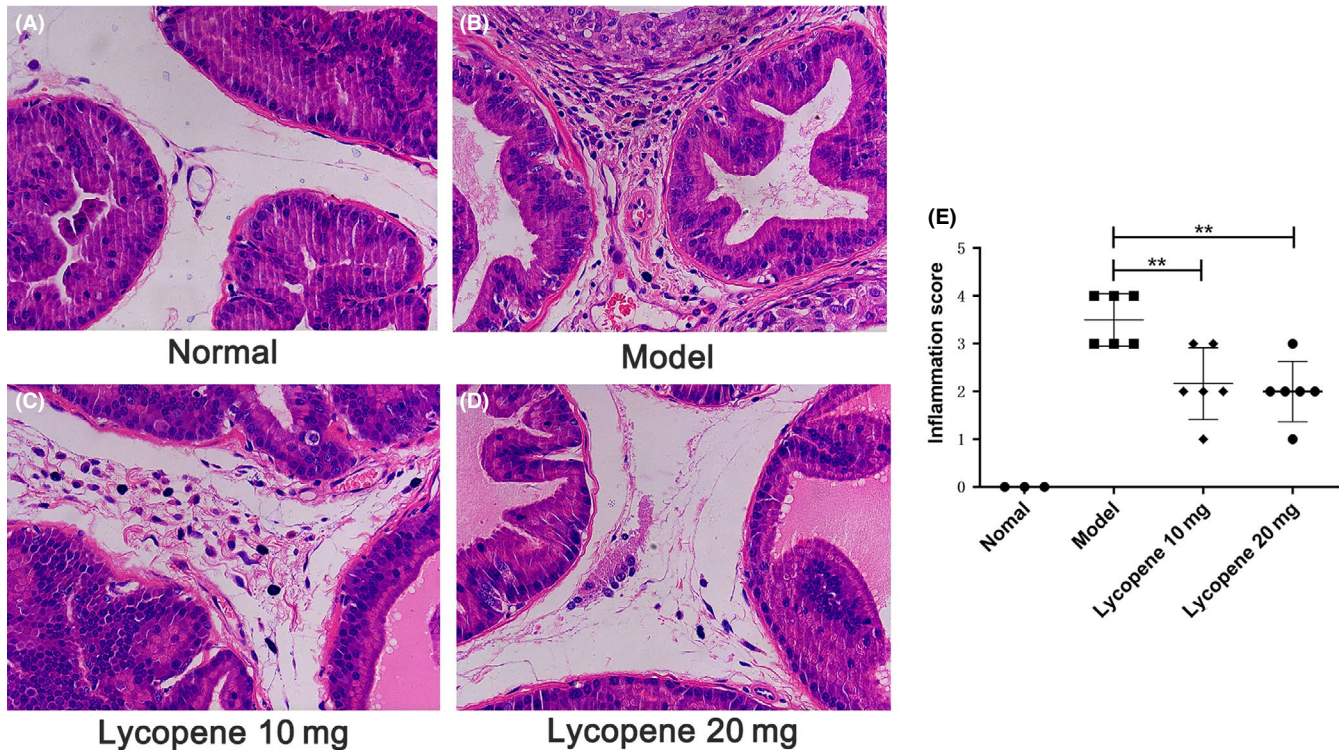
H&E staining was carried out to observe the morphological structures of prostate tissues in the normal group, model group, and LYC-treated groups. In the model group, marked inflammatory cell infiltration, interstitial fibrosis, massive interstitial edema with remarkable inflammatory vacuoles and severe vascular congestion were observed in the prostate tissues. By contrast, relatively normal acini and mild hyperplasia of glandular epithelial cells without destruction or atrophy were observed in the prostate tissues of the LYC treatment group. Furthermore, decreased infiltration of inflammatory cells was observed in the LYC treatment groups in a dose-dependent manner. Moreover, the inflammation score regarding the prostatic histopathological alterations in each group was analyzed, so as to evaluate the inflammation degree. Compared with the model group, the inflammation scores in the LYC treatment groups were markedly reduced (Figure 1).

### 3.2 | Effects of LYC on inflammatory factors in prostate tissues

Inflammatory factors have been recognized as the most direct indicators of the severity of inflammation. As seen from Figure 2, the levels of TNF $\alpha$ , IL-1 $\beta$ , MCP1, MIP-1 $\alpha$ , IL-2, and IL-6 were remarkably elevated in model rats compared with those in normal rats. However, LYC evidently reduced the up-regulation of these specific inflammatory factors (Figure 2).

### 3.3 | Effects of LYC on the activities of OS-related enzymes

The activities of antioxidant enzymes (including CAT, T-SOD, and GSH-PX) were analyzed to evaluate the antioxidant capacities. MDA, an end product of lipid peroxidation in biochemical assays, plays a critical role in monitoring and indicating the degree of oxidative damage. As demonstrated in Figure 3, whether in prostate tissues or serum, the activities of CAT, GSH-PX, and T-SOD decreased in the model group (Figure 3A-C, E-G), while the activities of MDA increased (Figure 3D, H). However, in the LYC treatment groups, the activities of CAT, T-SOD, and GSH-PX were dramatically strengthened in a dose-dependent manner compared with the model group in both prostate tissues and serum (Figure 3A-C, E-G). On the contrary, the MDA levels were markedly down-regulated (Figure 3D, H).



**FIGURE 1** Representative micrographs of prostatic tissue sections. A, Normal group showed the glandular cavity of prostatic tissue was intact, and hardly any infiltrating inflammatory cells were observed in the mesenchyme. B, The prostatic tissue of model group had a large number of inflammatory cell infiltration intercellular substance. In addition, interstitial edema, interstitial fibrosis, and congestion in blood vessels were observed. C-D, In lycopene-treated groups, decreased infiltrating inflammatory cells were observed in lycopene-treated groups in a dose-dependent way. E, The inflammation score for each group was analyzed. Magnification is 400 $\times$ . \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$

### 3.4 | Effects of LYC on the CP/CPPS-related signaling pathways

To further investigate the underlying mechanism of LYC in treating CP/CPPS, the activities of NF- $\kappa$ B, Nrf2, and MAPKs were detected by Western blotting. As demonstrated in Figure 4A, CFA-induced CP/CPPS enhanced the activities of the p-P65 subunit of NF- $\kappa$ B, p-Nrf2, p-P38 MAPK, p-Erk1/2, and p-JNK. However, the increased activities of the activities of p-P65, p-P38 MAPK, p-Erk1/2, and p-JNK were suppressed, while p-Nrf2 was enhanced by LYC p-Nrf2 in a dose-dependent manner. In other words, LYC inhibited the phosphorylation of p65 subunit, up-regulated the protein expression of phosphorylated-Nrf2 rather than Nrf2, and restrained the phosphorylation level instead of the total protein amounts of p38 MAPK, Erk1/2, and JNK. According to Figure 4B-D the above results were further verified by the quantitative analysis of the density of each band relative to the corresponding  $\beta$ -actin band. Furthermore, we speculated the possible mechanism of LYC in the treatment of CP/CPPS in Figure 5.

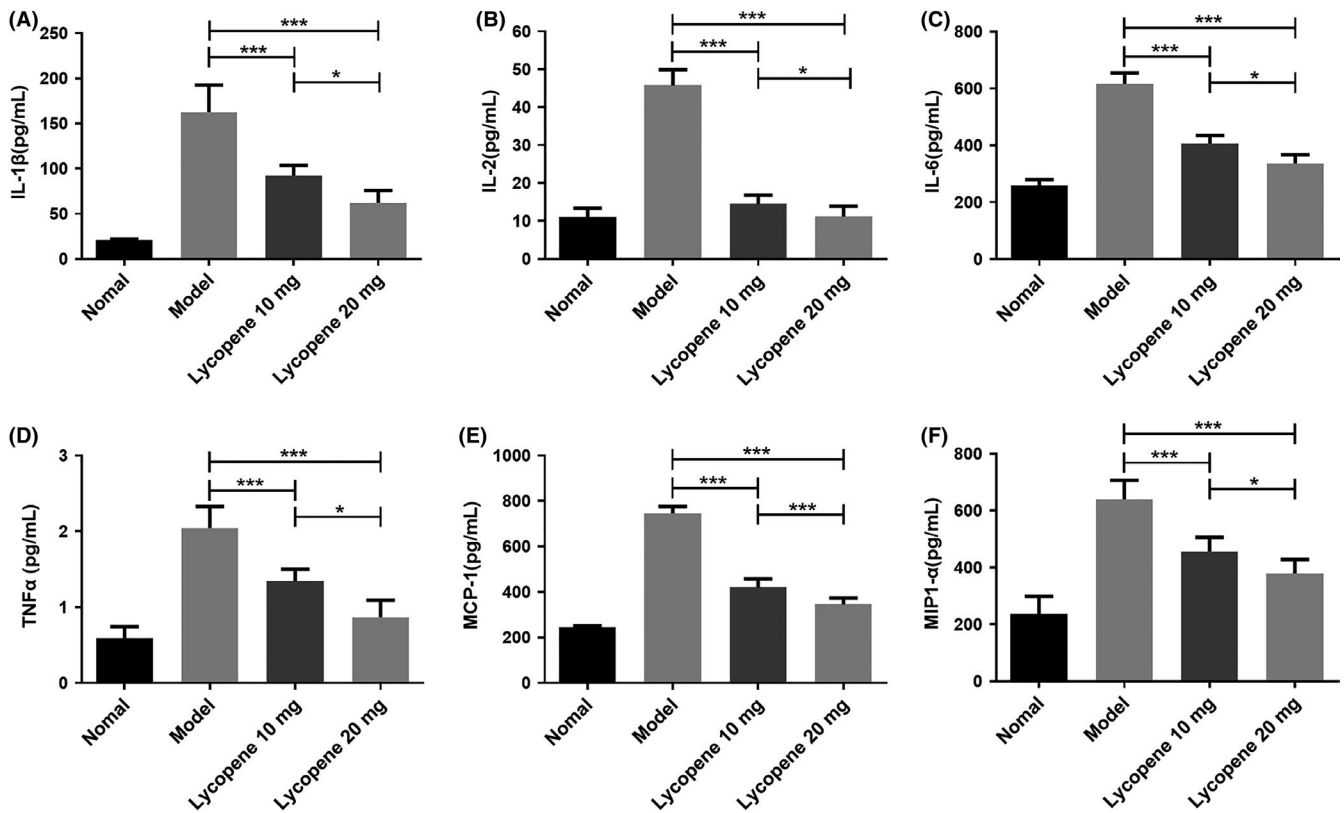
## 4 | DISCUSSION

The findings in this study demonstrated that the intra-prostatic injection of CFA successfully induced CP/CPPS in the rat model. It

was found in this rat model that LYC exerted an anti-inflammatory effect through down-regulating the levels of inflammatory factors IL-1 $\beta$ , TNF $\alpha$ , MCP1, MIP-1 $\alpha$ , IL-6, and IL-2; in addition, it also possessed an antioxidant effect through up-regulating the levels of CAT, GSH-PX, and T-SOD, while reducing that of MDA. Further, the effects of LYC on CP/CPPS in the anti-inflammatory and antioxidant signaling pathways were also examined according to the above results. The findings discovered that LYC up-regulated the protein expression of phosphorylated-Nrf2, while restraining the phosphorylation of p38 MAPK, Erk1/2, JNK, and NF- $\kappa$ B.

In our study, the CP/CPPS rat model induced by CFA was associated with histopathological changes in the prostate, which manifested as significant prostatic damage with marked infiltration of inflammatory cells, edema, and fibrosis of intercellular substance. These observations were in line with the previous study<sup>13</sup>; besides, the CP/CPPS method of model induction was easily operable. What's more, these models were found to be corresponded with the characteristics of non-bacterial CP/CPPS in human, which contributed to investigating the pathogenesis of CP/CPPS. Moreover, qualitative observation and quantitative analysis of the prostatic histopathology suggested that LYC notably reduced the infiltration of inflammatory cells, interstitial edema, and fibrosis in the CP/CPPS rats.

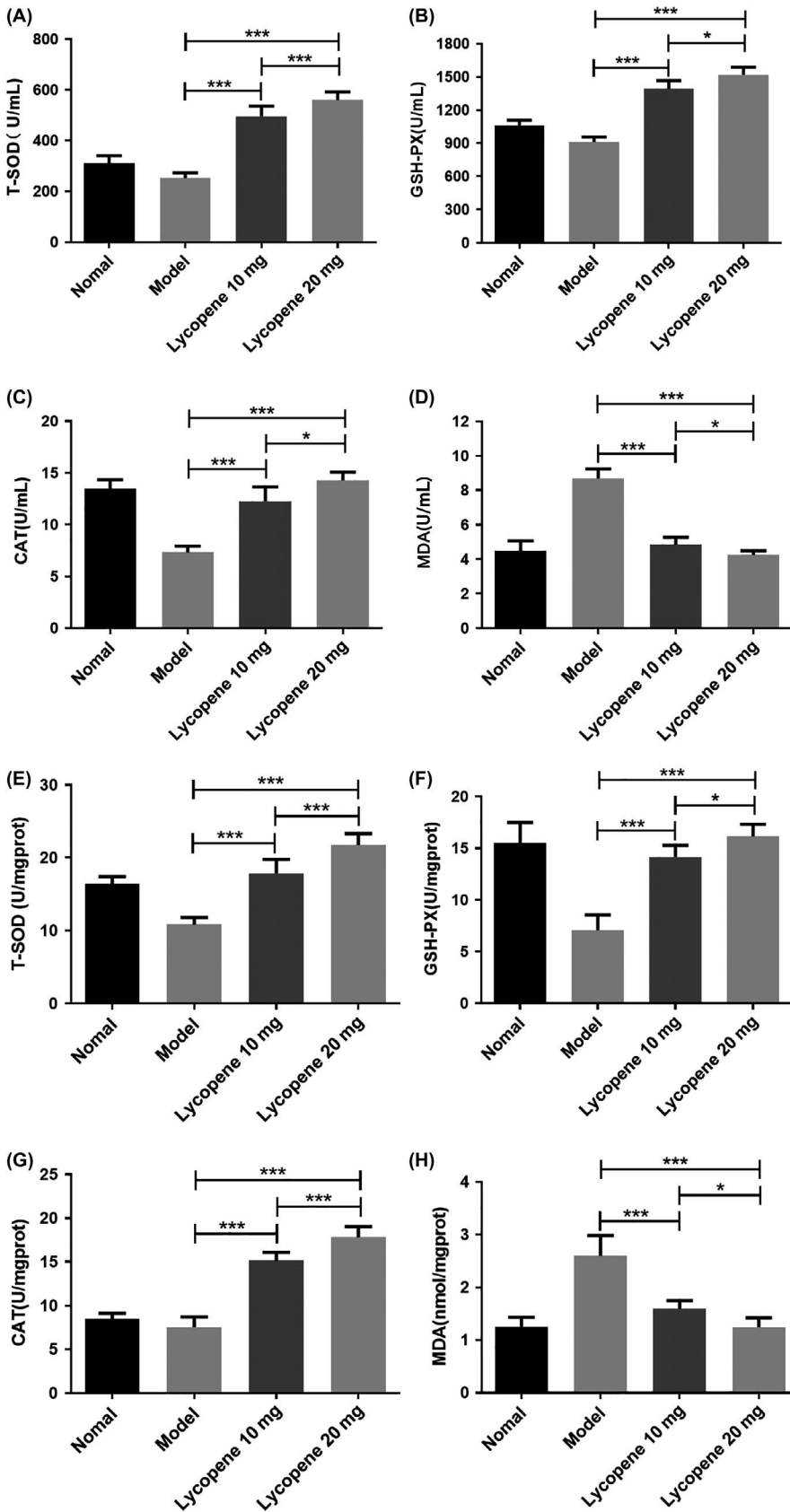
In recent years, most scholars have paid special attention to the effects of chemokines and cytokines on the development of CP/



**FIGURE 2** The expression level of cytokines of each group in prostatic tissue. Lycopene showed anti-inflammatory effect through decreasing inflammatory cytokines levels in prostate tissue. A-F, We could see that a significant raising in the levels of IL-1 $\beta$ , TNF $\alpha$ , MCP1, and MIP-1 $\alpha$ , IL-2, and IL-6 was found in model rats vs normal rats. In lycopene-treated groups, lycopene reduced significantly the levels of inflammatory cytokines of prostatic tissue including IL-1 $\beta$ , IL-2, IL-6, TNF $\alpha$ , MCP1, and MIP-1 $\alpha$ . Furthermore, compared with the low-dose lycopene group, the high-dose lycopene group significantly reduced the levels of inflammatory cytokines above. Data are shown as mean  $\pm$  SD. \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$

CP/PPS.<sup>14</sup> MIP-1 $\alpha$  and MCP-1, the important members of the chemokine CC family, are closely related to chronic inflammation and immune effects and play critical roles in the activation, infiltration, and migration of monocytes, macrophages, and T and B cells.<sup>15</sup> Quick et al<sup>16</sup> had established the CP/CP/PPS rat model and found that MCP-1 and MIP-1 $\alpha$  were up-regulated in prostatic fluid, in addition, they also confirmed that these two chemokines were associated with chronic pain. On the other hand, IL-1 $\beta$  and TNF- $\alpha$  were the vital proinflammatory factors, which are confirmed in numerous studies to greatly affect the development of CP/CP/PPS.<sup>17,18</sup> IL-6 is a major immune factor in inflammatory response, which regulates IL-2 production and down-regulates the synthesis of IL-1 $\beta$  and TNF- $\alpha$ . As suggested in plenty of studies, IL-6 and IL-2 levels are elevated in serum and prostatic fluid in CP/CP/PPS patients.<sup>19,20</sup> Besides, research also suggests that TNF- $\alpha$  activates the NF- $\kappa$ B pathway through inducing the phosphorylation and degradation of I $\kappa$ B, as well as the nuclear transport of the liberated NF- $\kappa$ B (mainly in the form of p65 subunit), eventually inducing the expression of various inflammatory factors (such as TNF- $\alpha$ , MIP-1 $\alpha$ , MCP-1, IL-1 $\beta$ , and IL-6), which dramatically affects the hyperalgesic action in CP.<sup>21</sup> In addition, LYC has been shown to suppress the TNF- $\alpha$ -mediated expression of intercellular adhesion molecule-1 (ICAM-1) through affecting the NF- $\kappa$ B signaling pathway.<sup>22</sup> Furthermore, Bai<sup>23</sup> also discovered that

LYC restrained the activation of NF- $\kappa$ B. The MAPKs-mediated signaling pathway is an important inflammatory signaling pathway, and the basic model is that cells receive stimulus signals and transmit them through the cascade of phosphatase activation. Notably, p38 MAPKs, ERKs, and JNKs are the three subfamilies of MAP kinases, which can be activated by TNF- $\alpha$  and ROS, and play crucial roles in triggering the phosphorylation of numerous important signaling molecules (like NF- $\kappa$ B).<sup>24</sup> NF- $\kappa$ B, the full name of nuclear factor kappa B, is comprised of five families and usually in the form of heterodimers, among which, the dimers formed by p65 and p50 are quite common. When cells are in a resting state, NF- $\kappa$ B binds to its inhibitor I $\kappa$ B to form a trimer; however, when cells are stimulated by inflammatory factors and other signals, I $\kappa$ B is degraded by protease, and p65 is thereby transferred into the nucleus to regulate the transcription level.<sup>25</sup> In our experiment, when both phosphorylated and non-phosphorylated antibodies were used to incubate with samples from each group, LYC remarkably suppressed the expression of phosphorylated antibodies associated with MAPKs and NF- $\kappa$ B, but their total protein levels remained unchanged, which demonstrated that LYC prevented the activation rather than the biosynthesis of MAPKs and NF- $\kappa$ B. Furthermore, the production of inflammatory factors was also reduced, which was ascribed to the inhibition of MAPKs and NF- $\kappa$ B activation by LYC.

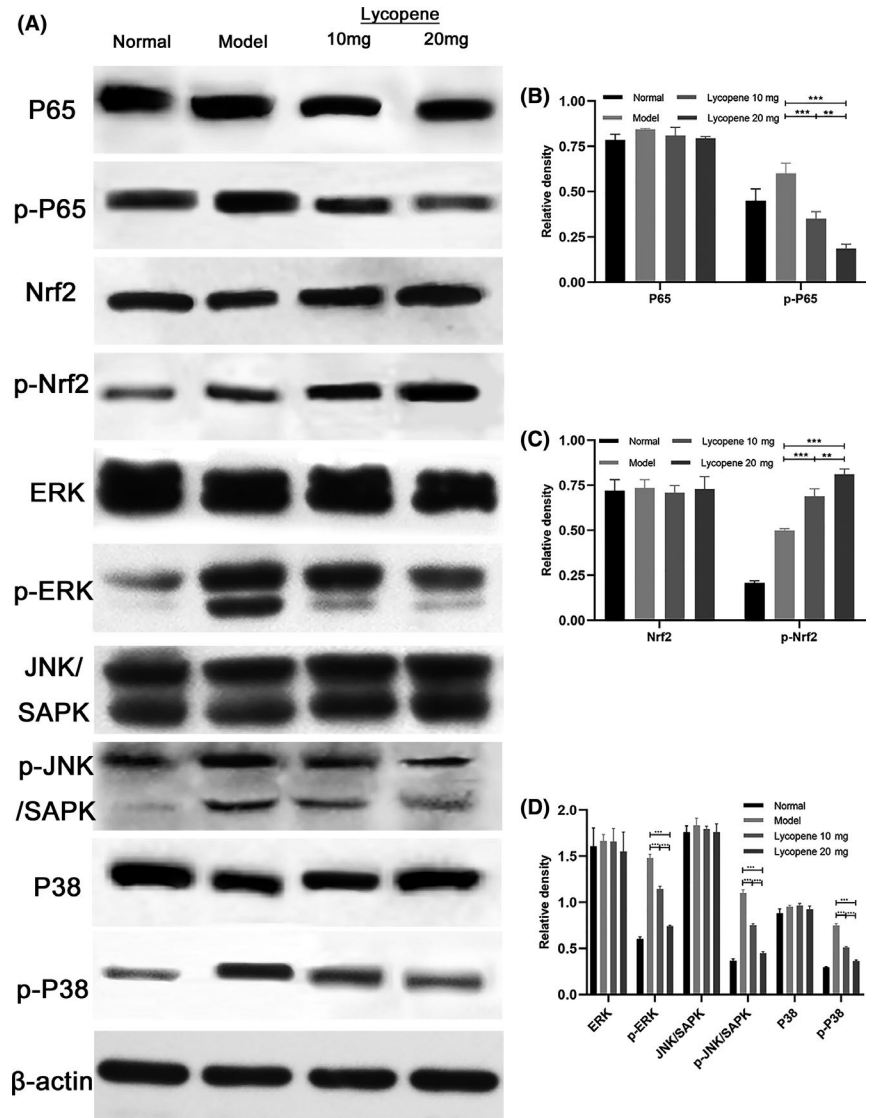


**FIGURE 3** Lycopene up-regulated antioxidant enzyme activities of CP/ CPPS rat and down-regulated biochemical assays of lipid peroxidation. A-C, In lycopene-treated groups, lycopene both increased significantly the levels of T-SOD, CAT, and GSH-PX in prostate tissue in a dose-dependent way compared to the model group. D, Lycopene-treated groups reduced significantly MDA levels in prostate tissue in a dose-dependent way compared to the model group. E-G, Lycopene-treated groups increased the levels of T-SOD, CAT, and GSH-PX in serum. H, Lycopene-treated groups decreased serous MDA levels in serum. Data are shown as mean  $\pm$  SD. \* $P$  < .05, \*\* $P$  < .01, \*\*\* $P$  < .001

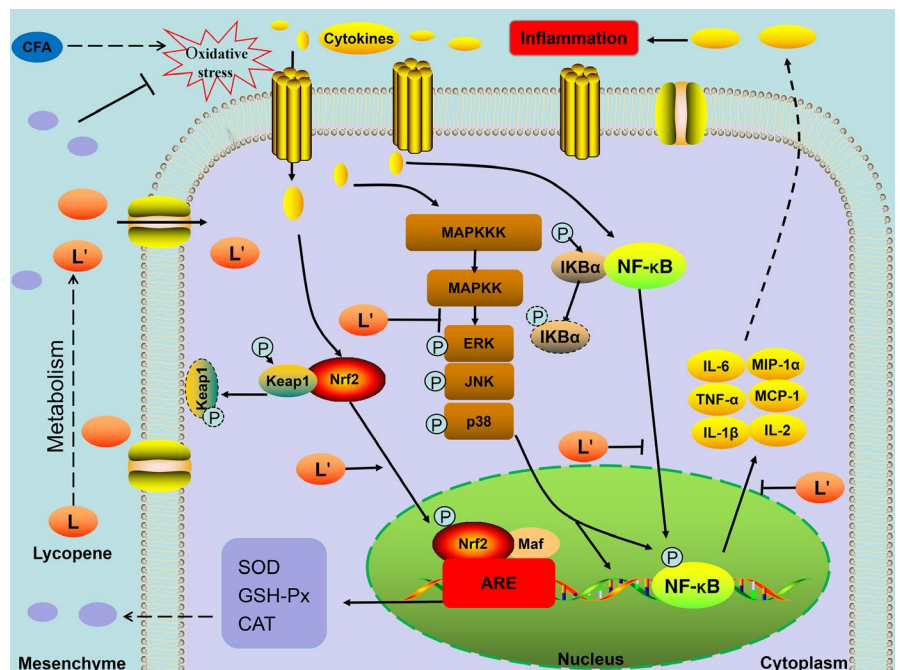
In recent years, the critical role of ROS in CP/ CPPS has been recognized. Studies have shown that the levels of oxygenase have increased, regardless of the compositions in the local (such

as prostate tissues and prostatic fluid) or systemic blood circulation of CP/ CPPS. This may be due to the damage of both basal and epithelial cells in the prostate, which leads to the aggregation of

**FIGURE 4** Lycopene suppressed NF- $\kappa$ B, MAPKs, and enhanced Nrf2 signaling pathways. A, Lycopene in different doses suppressed the phosphorylation of P65 rather than the total amount of P65 showed by Western blotting, up-regulated the activation of Nrf2 without affecting the total amount of Nrf2, restrained the phosphorylation of P38, ERK1/2, and JNK/SAPK rather than the total amount. B, C, D, Relative density analysis of each band compared with the corresponding  $\beta$ -actin band, corresponding to sequences A, respectively. Relative density is the ratio of each band/ $\beta$ -actin. Data are presented as mean  $\pm$  SD. \* $P < .05$ ; \*\* $P < .01$ ; \*\*\* $P < .001$ . These experiments were repeated at least three times



**FIGURE 5** Possible molecular mechanism diagram demonstrated that protective signaling pathways of lycopene in CFA-induced CP/CPSS. As illustrated, lycopene may inhibit the inflammation signaling cascades in different ways induced by CFA. Lycopene may suppress the activation of P38, Erk1/2, JNK/SAPK, and NF- $\kappa$ B, while enhance the activation of Nrf2. L is short for lycopene; L' is short for lycopene metabolites. P is short for phosphorylation. The  $\dashv$  indicates inhibition or blockade, and  $\rightarrow$  indicates activation or induction



inflammatory cells and excessive release of ROS, and eventually resulting in changes in the protein structures and functions, as well as DNA modification.<sup>26</sup>

LYC is a major carotenoid that contains a large number of conjugated double bonds, making it a strong antioxidant compared with the beta carotene. It is mainly oxidized and cracked in vivo, most of the metabolites are isomers formed after the shortening of the carbon chain. The earliest reported metabolites of lycopene in humans were 5,6-dihydroxy-5',6'-dihydrolycopene, and 2,6-cyclolycopene-1. These metabolites can be detected from plasma and tissues by high-performance liquid chromatography.<sup>27</sup> Furthermore, as a scavenger of lipid peroxidation free radicals, LYC prevents oxidative injury from crucial biological molecules, such as lipids, proteins, and DNA.<sup>28</sup> MDA is a lipid peroxidation product, which changes the biological membrane activities and impairs the normal cellular function, and it is usually used as a biomarker of oxidative damage.<sup>29</sup> On the contrary, SOD is the first killer of oxygen free radicals in the body, which converts the superoxide free radicals into hydrogen peroxide and water through carrying out the disproportionation reaction under the action of enzymes. Thereafter, GSH-PX and CAT can transform the resultant hydrogen peroxide into water, so as to protect cells from OS-induced injury. In this study, our findings suggested that LYC increased the activities of antioxidant enzymes (including CAT, SOD, and GSH-PX), which were the redox protectors and mitigated OS.<sup>30</sup> Therefore, SOD, CAT, and GSH-PX indirectly reflect the oxidation resistance.

LYC is also suggested in numerous studies to reduce the production and expression of inflammatory factors through inhibiting NF- $\kappa$ B activation.<sup>31,32</sup> Palozza<sup>33</sup> further explained that the possible mechanism of LYC in reducing the inflammatory factors might be that LYC was a lipophilic compound closely associated with cell membrane, where carotenoid regulated the activities of transcription factors and redox-sensitive kinases. Our findings were supported by these studies and interpretations.

Further, our study focused on the Nrf2/ARE signaling pathway, which was of critical importance in the antioxidant stress of cells. Nrf2 is a critical OS-related transcription factor, which is uncoupled with its inhibitor Keap1 upon stimulation by ROS or inflammatory cytokines. Thereafter, the activated Nrf2 is transported into the nucleus for gene transcription and expression. Specifically, the elevated production of free radicals enhances the nuclear translocation of Nrf2, which then enhances the transcription of antioxidant enzymes, thus mitigating OS injury.<sup>34</sup> Additionally, Cao<sup>35</sup> discovered that LYC relieved the hippocampal lesions through suppressing the OS-mediated inflammation in rats. Furthermore, the authors analyzed that the underlying causes were that LYC strengthened the nuclear translocation of Nrf2 together with the expression of its backward genes, which were in line with our results. Besides, the research conducted by Wang<sup>36</sup> demonstrated that LYC alleviated neuroinflammation and cognitive impairments by regulating the interactions between the MAPKs, the NF- $\kappa$ B, and the Nrf2 signaling pathways. Our results indicated that LYC further enhanced the activities of GSH-PX, CAT, and SOD through intensifying the

expression of transcription factor Nrf2 via the Nrf2/ARE signaling pathway, which exerted the antioxidative effects. To sum up, this is the first report about the possible mechanism of LYC in treating CP/CPSPS according to the available literature. However, the more detailed mechanism in the interactions between LYC and the NF- $\kappa$ B, the MAPKs, the Nrf2 signaling pathways should be further explored due to the financial shortage.

## 5 | CONCLUSION

The findings in this study suggest that lycopene exerts potent anti-CP/CPSPS effects through alleviating inflammatory response and oxidative stress, which is probably attributed to the interaction of NF- $\kappa$ B, MAPKs, and Nrf2 signaling pathways in rats. As a natural antioxidant, lycopene may serve as a promising pharmaceutical preparation for treating CP/CPSPS.

## ACKNOWLEDGMENTS

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## AUTHORS CONTRIBUTION

Q. Z., L. M., and N. X. conceived and designed the research. Q. Z. and L. M. performed experiments. F. Y., D. C., and M. W. collect and analyzed the data. Q. Z., D. C., X. L., and Y. J. interpreted the results of the experiments. Q. Z. drafted and edited the manuscript. All of the authors approved the final manuscript.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data can be provided upon reasonable request.

## ORCID

Qinxin Zhao  <https://orcid.org/0000-0001-5489-399X>

Nianzeng Xing  <https://orcid.org/0000-0002-2696-5279>

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