Pulmonary Injury from Combined Exposure to Microcystin-LR and Sodium Nitrite in Mice

Pengle Pang, Kangfeng Ge, Xiaozhen Li, Shuo Zhao, Xiaoyu Chang, Chunyang Wang, Yuhuan Liu, Ke Mei, Jia He, Yijing Xie, Fang Wang, Huizhen Zhang *

College of Public Health, Zhengzhou University, Zhengzhou, China

*Corresponding author: huizhen18@126.com

Abstract: Background: Microcystin-LR (MC-LR) and sodium nitrite ($NaNO_2$) are common environmental contaminants that may co-occur in drinking water. While MC-LR has been implicated in extrahepatic toxicity including pulmonary damage, the combined effects of MC-LR and $NaNO_2$ on lung pathology are not well characterized. **Objective:** To evaluate pulmonary effects of MC-LR and $NaNO_2$ single and combined exposures in mice and to explore associated inflammatory and fibrotic responses. **Methods:** Male Balb/c mice were randomly assigned to nine groups (n = 10). Exposure lasted 6 months. Lung coefficient was calculated; histopathology and collagen deposition were assessed by H&E and Masson's trichrome staining. mRNA levels of inflammatory cytokines (IL-4, IL-10, IFN-γ) and fibrosis marker α-SMA were quantified by qPCR. **Results:** MC-LR single exposure significantly increased lung coefficient and collagen deposition, but did not upregulate α-SMA. $NaNO_2$ alone induced similar histopathological changes, with low-dose (30 mg/L) increasing α-SMA ($p<0.05$) while high-dose (300 mg/L) showed no fibrotic marker elevation. Notably, co-exposure exhibited complex dose-dependent patterns: although some combinations increased lung coefficient, collagen deposition and α-SMA mRNA expression demonstrated declining trends in the high-dose MC-LR + high-dose $NaNO_2$ (100 μg/L + 300 mg/L) group. Both pollutants reduced IL-4 and IL-10 mRNA and elevated IFN-γ expression ($p < 0.05$). **Conclusions:** MC-LR and $NaNO_2$ co-exposure produces complex, dose-dependent interactions, where collagen deposition and α-SMA expression may be reduced even when inflammatory signaling is intensified. These findings highlight that pollutant co-exposures can lead to non-additive effects and emphasize the need for mechanistic studies across various dose combinations to inform environmental health risk assessments.

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Keywords: Microcystin-LR; sodium nitrite; co-exposure; pulmonary fibrosis; inflammation

1. Introduction

Microcystins (MCs) are cyclic heptapeptide toxins produced by cyanobacteria. Microcystin-LR (MC-LR) is the most prevalent and toxic variant [1]. Although hepatotoxicity is the most recognized effect, MC-LR can accumulate in extrahepatic tissues and provoke oxidative stress, inflammation, and fibrotic responses in organs, including the lung [2, 3]. For instance, Li et al. (2016) demonstrated that chronic MC-LR exposure disrupts mitochondrial DNA maintenance in mouse lung tissue, resulting in pathological changes such as alveolar structure damage and inflammatory cell infiltration [3]. These findings highlight the lung as a vulnerable site for MC-LR toxicity.

Sodium nitrite ($NaNO_2$) is a ubiquitous contaminant present in drinking water, some foods, and agricultural runoff. $NaNO_2$ participates critically in complex physiological and pathological redox chemistry [4]. Its biological effects are notoriously dose-dependent and context-specific: at elevated concentrations, it can contribute to methemoglobinemia and the formation of potentially carcinogenic N-nitroso compounds; conversely, under controlled conditions, it serves as a nitric oxide (NO) donor, influencing vasodilation, mitochondrial function, and cellular signaling pathways [5, 6].

MC-LR and $NaNO_2$ may co-occur in real-world exposure scenarios, particularly in regions where surface waters are affected by both cyanobacterial blooms and agricultural runoff [7]. For example, eutrophic lakes and reservoirs contaminated with cyanobacteria can release MC-LR into drinking water sources, while intensive farming and the use of nitrogen-based fertilizers contribute to elevated nitrite levels through leaching and runoff. In rural and peri-urban areas, untreated or insufficiently treated water from such sources may contain both contaminants simultaneously [8]. Furthermore, in certain aquaculture

and food processing practices, fish and seafood from affected waters may accumulate MC-LR, while nitrite is used as a preservative or can form during storage, leading to combined dietary exposure [9, 10]. These overlapping pathways highlight the plausibility of simultaneous MC-LR and $NaNO_2$ intake in human populations and justify the need to study their joint toxicological effects. Human populations are commonly exposed to mixtures of contaminants rather than single agents, and mixture toxicity often yields non-additive outcomes (synergism, antagonism, or complex dose-dependent interactions) that cannot be predicted from single-agent data [11, 12]. The pulmonary outcomes of combined MC-LR and $NaNO_2$ exposure are poorly understood.

In this study, we used a Balb/c mouse model to examine how MC-LR and $NaNO_2$, alone or together, influence lung mass (lung coefficient), histological architecture and collagen deposition, inflammatory cytokine expression (IL-4, IL-10, IFN-γ), and the fibrotic marker α-SMA.

2. Methods

2.1 Chemicals and reagents

MC-LR (purity > 95%) was purchased from Beijing Express Technology Co., Ltd. $NaNO_2$ (analytical grade) came from Macklin Biochemical Co., Ltd. Antibodies and molecular biology reagents (Masson kit, TRIzol, reverse transcription and SYBR Green qPCR kits) were obtained from Abcam (UK) and TaKaRa (Dalian, China), respectively.

2.2 Animal Treatment

Six-week-old specific pathogen-free (SPF) male Balb/c mice were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. (License No.: SCXK (Beijing) 2021-0006). After 1 week of adaptive feeding, mice were randomly divided into 9 groups (n=10 per group): control group, M1 group (10 μg/L MC-LR), M2 group (100 μg/L MC-LR), N1 group (30 mg/L $NaNO_2$), N2 group (300 mg/L $NaNO_2$), M1N1 group (10 μg/L MC-LR + 30 mg/L $NaNO_2$), M1N2 group (10 μg/L MC-LR + 300 mg/L $NaNO_2$), M2N1 group (100 μg/L MC-LR + 30 mg/L $NaNO_2$), and M2N2 group (100 μg/L MC-LR + 300 mg/L $NaNO_2$). Mice were exposed via free access to contaminated drinking water. The exposure duration was 6 months. The breeding environment was maintained at a temperature of 23 ± 1℃, humidity of 50 ± 5%, with a 12 h light/dark cycle. All experimental protocols were approved by the Animal Ethics Committee of Zhengzhou University (ethical approval number: ZZUIRB2022-09).

2.3 Sample collection and lung coefficient calculation

At study end, mice were anesthetized with sodium pentobarbital (40 mg/kg, i.p.), weighed, and euthanized. Lungs were excised, washed in cold saline, blotted dry and weighed. Lung coefficient was calculated as: (lung wet weight / body weight) × 100%. Six randomly selected mice per group were used for lung coefficient analysis.

2.4 Histopathology and collagen assessment

Portions of lung tissue were fixed in 4% paraformaldehyde, paraffin-embedded, sectioned (4 μm) and stained with hematoxylin–eosin (H&E) for general histology and Masson's trichrome for collagen deposition. Five random fields per section were imaged by light microscopy and collagen area fraction was quantified using Image-Pro Plus 6.0.

2.5 Quantitative real-time PCR (qPCR)

Total RNA was extracted from lung tissue using TRIzol and reverse transcribed to cDNA. qPCR was performed using SYBR Green chemistry. Target genes included IL-4, IL-10, IFN-γ and α-SMA; β-actin served as the internal control. Relative expression was calculated by the $2^{-\Delta\Delta Ct}$ method. Primer sequences are listed in Table 1.

2.6 Statistical analysis

Data are presented as mean ± SD. One-way ANOVA with LSD post hoc tests was used for group comparisons. Two-way ANOVA was used when assessing potential interactions between MC-LR and $NaNO_2$. Statistical significance was considered at $p < 0.05$. Analyses were performed in SPSS 21.0.

Table 1. qPCR primers

Gene	Forward primer	Reverse primer
IFN-γ	TTGTTGCTGATGGGTTGTTG	TGGACCTGTGGGTTGTTGTT
IL-4	GGTCTCAACCCCCAGCTAGT	GCCGATGATCTCTCTCAAGTGA
IL-10	GCTCTTACTGACTGGCATGAG	CGCAGCTCTAGGAGCATGTG

α-SMA	AGGACATCAAGGAGAAGCTG	TTGGTGATGATGCTGTTGTTG
β-actin	GTGCTATGTTGCTCTAGACTTCG	ATGCCACAGGATTCCATACC

Results

3.1 Effects of MC-LR and $NaNO_2$ co-exposure on lung coefficient in mice

MC-LR and $NaNO_2$ co-exposure had significant effects on the lung coefficient in mice, as shown in Figure 1. Compared with the control group, the lung coefficient in the group exposed to 100 μg/L MC-LR alone significantly increased ($p < 0.01$), while there was no significant change in the group exposed to 10 μg/L MC-LR alone. The single exposure to $NaNO_2$ showed similar changes. Among the co-exposure groups, there was no significant change in the lung coefficient in the groups co-exposed to 10 μg/L MC-LR with 30 mg/L or 300 mg/L $NaNO_2$; however, the lung coefficient significantly increased in the group co-exposed to 100 μg/L MC-LR and 30 mg/L $NaNO_2$ ($p < 0.05$), and the increase was more significant in the group co-exposed to 100 μg/L MC-LR and 300 mg/L $NaNO_2$ ($p < 0.01$). These results indicate that the combined exposure to MC-LR and $NaNO_2$ leads to an increase in the lung coefficient in mice, suggesting lung injury.

3.2 Collagen fiber deposition in lung tissues of mice exposed to MC-LR and $NaNO_2$ co-exposure

As shown in Figure 2, Masson's trichrome staining revealed pronounced collagen deposition in lungs of mice exposed to MC-LR alone (blue staining) compared with control. In contrast, lungs from co-exposed animals exhibited less extensive collagen deposition than MC-LR single-exposed mice, suggesting an attenuation of fibrotic matrix accumulation with combined exposure under our experimental conditions.

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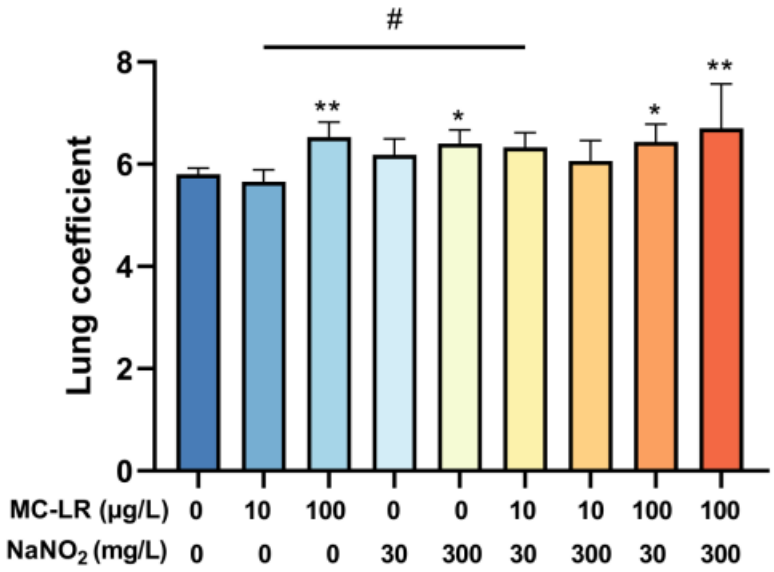

Figure 1. Effects of co-exposure to MC-LR and $NaNO_2$ on lung coefficient in mice. Note: *$p < 0.05$ vs. control group; **$p < 0.01$ vs. control group; #$p < 0.05$ vs. corresponding single-exposure group.

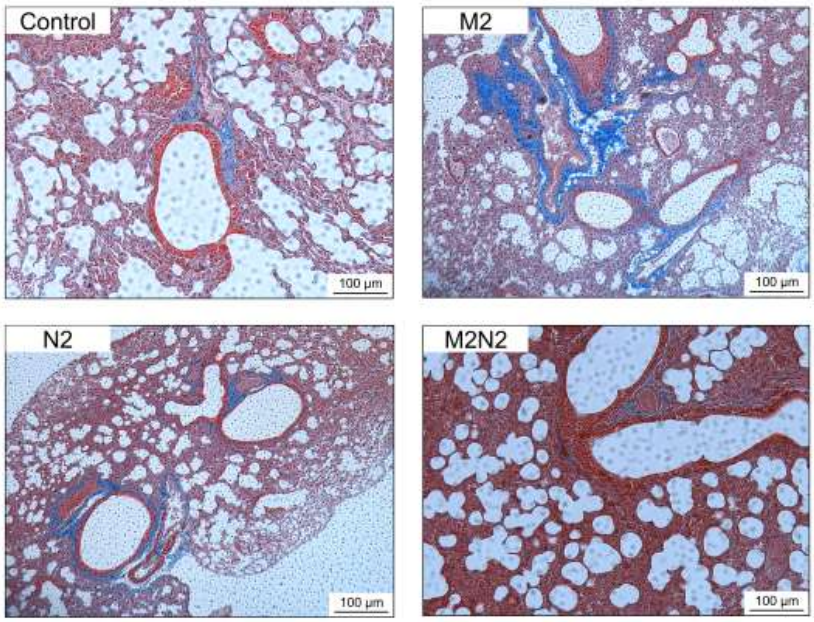

Figure 2. Masson staining to observe changes in collagen deposition in lung tissues of mice co-exposed to MC-LR and $NaNO_2$. Note: M2: 100 μg/L MC-LR; N2: 300 mg/L $NaNO_2$

3.3 Expression of inflammatory factors in lung tissues of mice exposed to MC-LR and $NaNO_2$ co-exposure

As shown in Figure 3, MC-LR and $NaNO_2$ co-exposure had significant effects on the mRNA expression levels of inflammatory factors in mouse lung tissues. Compared with the control group, exposure to MC-LR or $NaNO_2$ alone both led to significant decreases in the expression of IL-4 and IL-10 ($p < 0.05$), while the expression of IFN-γ significantly increased ($p < 0.05$). In the co-exposure groups, the expression levels of IL-4 and IL-10 further decreased compared with the single-exposure groups, with significant differences in some combinations ($p < 0.05$); the expression of IFN-γ showed a trend of further increase, and the most significant increase was observed in the co-exposure group of high-dose MC-LR (100 μg/L) and $NaNO_2$ ($p < 0.01$). These results suggest that co-exposure to MC-LR and $NaNO_2$ can synergistically promote the upregulation of the pro-inflammatory factor IFN-γ and inhibit the expression of the anti-inflammatory factors IL-4 and IL-10, which may exacerbate pulmonary inflammatory responses.

3.4 Expression of α-SMA in lung tissues of mice exposed to MC-LR and $NaNO_2$ co-exposure

As shown in Figure 4, compared with the control group, the expression of α-SMA mRNA in lung tissues of mice exposed to low-dose $NaNO_2$ (30 mg/L) significantly increased ($p < 0.05$). There was a statistically significant difference between the high-dose MC-LR and low-dose $NaNO_2$ co-exposure group (MC-LR 100 μg/L + $NaNO_2$ 30 mg/L) and the high-dose MC-LR (100 μg/L) single-exposure group ($p < 0.05$). In addition, the high-dose co-exposure group (MC-LR 100 μg/L + $NaNO_2$ 300 mg/L) showed no significant difference compared with the control group ($p > 0.05$). These results indicate that co-exposure to MC-LR and $NaNO_2$ may exert a dose-dependent effect on pulmonary fibrosis in mice.

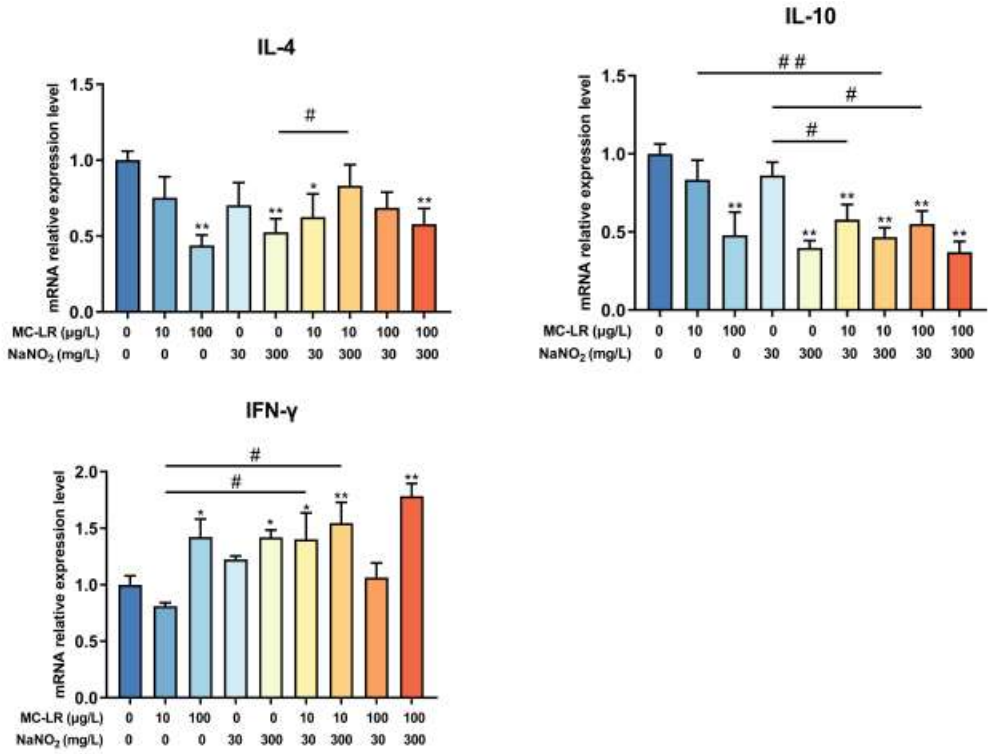

Figure 3. Effects of co-exposure to MC-LR and $NaNO_2$ on mRNA levels of inflammatory factors IL-4, IL-10 and IFN-γ. Note: *$p < 0.05$ vs. control group; **$p < 0.01$ vs. control group; #$p < 0.05$ vs. corresponding single-exposure group

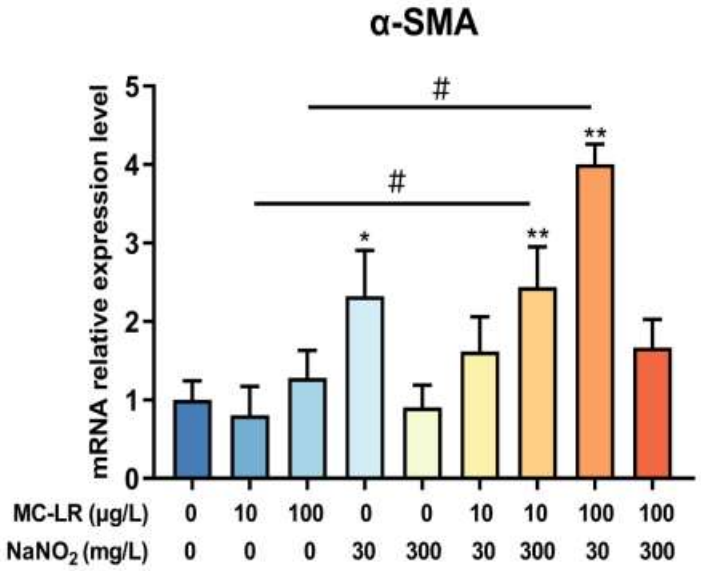

Figure 4. Effects of co-exposure to MC-LR and $NaNO_2$ on α-SMA mRNA levels in lung tissues of mice. Note: *$p < 0.05$ vs. control group; **$p < 0.01$ vs. control group; #$p < 0.05$ vs. corresponding single-exposure group.

4. Discussion

This study systematically evaluated the effects of MC-LR and $NaNO_2$, under single and combined exposure conditions, on pulmonary inflammation and fibrosis in mice. A key finding is that, under our experimental conditions (6-month drinking water exposure in mice), neither MC-LR exposure alone nor high-dose $NaNO_2$ (300 mg/L) exposure alone resulted in a profile definitively indicative of established pulmonary fibrosis, based on the combined assessment of histology (collagen deposition) and the myofibroblast marker α-SMA. While high-dose MC-LR induced significant collagen deposition and lung injury (increased coefficient), it did not significantly upregulate α-SMA mRNA, a hallmark of activated myofibroblasts and progressive fibrosis. Similarly, high-dose $NaNO_2$ alone failed to significantly increase either collagen deposition or α-SMA expression compared to control. Only low-dose $NaNO_2$ (30 mg/L) alone showed a significant increase in α-SMA. However, combined exposure exhibited a complex, dose-dependent effect: although the direction of cytokine changes was consistent (increased IFN-γ, decreased IL-4 and IL-10), the magnitude of collagen deposition and α-SMA upregulation was reduced in some co-exposure groups, suggesting a certain antagonistic trend. This finding indicates that, in real environmental scenarios, the health effects of mixed pollutants may not be simply additive, but rather shaped by the interaction of multiple biological mechanisms.

Regarding pulmonary toxicity, several recent experimental studies report that microcystin-LR (MC-LR) can induce lung injury characterized by oxidative stress, mitochondrial dysfunction and pro-inflammatory signaling (e.g. NF-κB/NLRP3 activation) in vitro and in vivo [13, 14]. However, direct, conclusive evidence that MC-LR per se causes or consistently promotes pulmonary fibrosis in animal models or humans is limited. Importantly, some recent experimental reports indicate that certain microcystin congeners, including MC-RR, and even MC-LR under specific dosing or exposure regimens, may attenuate experimentally induced lung fibrosis by modulating GRP78/UPR^{ER} signaling and macrophage M2 polarization [15, 16]. Taken together, these heterogeneous findings suggest that the effects of MC-LR on lung extracellular matrix remodeling depend strongly on exposure route, dose and timing as well as on the fibrosis model used. Therefore, while our observation of increased collagen deposition under MC-LR single exposure aligns with its potential to cause injury and initiate reversible extracellular matrix remodeling, it should not be interpreted as definitive evidence for MC-LR-driven progressive fibrosis, especially in light of emerging literature suggesting potential anti-fibrotic properties under specific conditions. These results must be contextualized within the complex and sometimes contradictory landscape of MC-LR pulmonary effects.

Although MC-LR has been reported to cause lung injury and promote pro-inflammatory responses, its direct role in driving pulmonary fibrosis remains uncertain, and $NaNO_2$ is recognized primarily as an inducer of oxidative/nitrosative stress and vascular injury that can secondarily contribute to tissue remodeling [17], our high-dose $NaNO_2$ single exposure did not result in significant increases in either collagen deposition or α-SMA expression. In this context, the outcomes of their co-exposure were particularly revealing. Rather than producing a straightforward synergistic effect on fibrotic endpoints, co-exposure under specific combinations (e.g., high-dose MC-LR with $NaNO_2$) resulted in a significant attenuation of collagen deposition and α-SMA expression relative to the MC-LR single-exposure group. This pattern of non-additive outcomes, where combined exposure yields effects distinct from simple summation, is not uncommon in mixed-pollutant toxicology [18]. In real environmental contexts, drinking water, food, and air often contain multiple pollutants simultaneously, and the exposure scenarios are far more complex than single-

pollutant experiments. Johannson et al. (2014) found in a population study that combined exposure to multiple air pollutants (such as $PM_{2.5}$, NO_2, and O_3) was significantly associated with the risk of idiopathic pulmonary fibrosis, and that interactions between pollutants could influence the speed and severity of disease progression [19]. The results of the present study suggest that even in animal models, the effects of mixed exposure can vary dramatically depending on dose, ratio, and exposure duration, which is of important reference value for environmental health risk assessment.

In light of our results, the marked increase in IFN-γ could be a potential reason for the reduced fibrosis. Weng et al. (2007) reported that IFN-γ can exert anti-fibrotic effects by inhibiting the TGF-β signaling pathway and reducing fibroblast proliferation and type I collagen synthesis [20]. Therefore, even in the presence of persistent inflammation in this study, high IFN-γ expression may have partially limited collagen deposition and α-SMA upregulation. Furthermore, Wang et al. found that oral administration of MC-LR significantly alleviated pulmonary fibrosis in bleomycin-induced rat models and fluorescein isothiocyanate-induced mouse models, accompanied by the inhibition of TGF-β1/Smad signaling, as well as the blockade of epithelial-mesenchymal transition and fibroblast-to-myofibroblast transition. Mechanistically, MC-LR can bind to GRP78 and inhibit the endoplasmic reticulum unfolded protein response signaling pathway, thereby reducing M2 polarization of $CD206^+$ macrophages [15]. This mechanism suggests that under co-exposure conditions, high-dose MC-LR may partially counteract the pro-fibrotic effects of $NaNO_2$ by inhibiting the activation and differentiation of pro-fibrotic cell populations, resulting in reduced collagen deposition and α-SMA levels.

This study also found that low-dose $NaNO_2$ (30 mg/L) single exposure significantly increased α-SMA levels, whereas high-dose $NaNO_2$ (300 mg/L) alone did not induce significant fibrotic marker upregulation. Notably, co-exposure with MC-LR produced divergent outcomes depending on $NaNO_2$ concentration. This suggests that MC-LR may exert bidirectional regulatory effects on $NaNO_2$-induced fibroblast activation, depending on concentration. Notably, a recent study on $NaNO_2$-induced pulmonary toxicity further supports the pro-fibrotic potential of $NaNO_2$, as it reported that $NaNO_2$ exposure elevated key fibrotic regulators including TGF-β, α-SMA, and collagen deposition in lung tissues, consistent with our findings of increased α-SMA and collagen accumulation in $NaNO_2$ single-exposure groups. That study also demonstrated that interventions targeting these fibrotic pathways (e.g., glycyrrhizic acid) could reduce α-SMA expression and collagen deposition, highlighting the plasticity of $NaNO_2$-induced fibrotic responses to regulatory factors. In our context, high-dose MC-LR co-exposure may act as a similar regulatory factor, attenuating $NaNO_2$-induced α-SMA upregulation possibly through interfering with pathways involving TGF-β or other fibrotic mediators, analogous to how glycyrrhizic acid mitigates $NaNO_2$-induced fibrosis by targeting these markers [21]. This mechanism fits well with the observed decrease in fibrotic markers under high-dose co-exposure in this study. Another possible explanation is that the metabolic products of the two pollutants may compete in the body, thereby altering each other's toxicological effects. Some studies have shown that MC-LR can interfere with cell signaling by inhibiting protein phosphatases 1 and 2A, while NO and related reactive nitrogen species, as metabolites of $NaNO_2$, can react with protein thiols, altering their conformation and function [5, 22]. Such signaling interference could reduce the activation level of fibrosis-related pathways.

This study has certain limitations. First, we focused mainly on mRNA-level markers of inflammation and fibrosis, without direct measurements at the protein level or of tissue function, which might underestimate certain biological effects. Second, oxidative stress, bioenergetic metabolism, and apoptosis—possible key mechanistic

endpoints—were not measured, leaving mechanistic explanations of the interactions to be further validated. Future research should combine proteomics, metabolomics, and other multi-omics techniques, and incorporate animal models with different genetic backgrounds, to reveal the full picture of MC-LR and $NaNO_2$ co-exposure.

Conclusions

MC-LR and $NaNO_2$ co-exposure produces complex, dose-dependent interactions, where collagen deposition and α-SMA expression may be reduced even when inflammatory signaling is intensified. These findings highlight that pollutant co-exposures can yield non-additive effects and underscore the need for mechanistic and dose-matrix studies to inform environmental health risk assessments.

Conflicts of interest

The authors declare no conflict of interest.

Authors' contributions

Kangfeng Ge: Writing–review & editing, Writing–original draft, Software, Methodology, Data curation, Conceptualization. Huizhen Zhang: Supervision, Project administration, Funding acquisition. All authors contributed to interpreting the results and critically revising the draft.

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