

A molybdenum nanorod-based nutritional strategy for cardiovascular and neurobehavioral health

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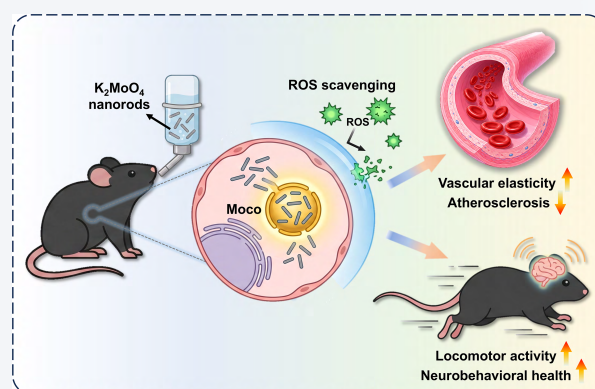
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ABSTRACT: Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, highlighting the critical need for effective and accessible nutritional interventions. In this study, our findings suggest that dietary supplementation with food-grade potassium molybdate (K_2MoO_4) nanorod confers significant cardiovascular benefits in murine models, potentially mediated through enhanced antioxidant capacity, improved vascular remodeling, and prevention of atherosclerosis. The synthesized K_2MoO_4 nanorod displayed high purity, physicochemical stability, and bioavailability, providing a reliable strategy for cardiovascular modulation. Crucially, *in vitro* evaluations demonstrated that K_2MoO_4 nanorod exerts robust endothelial cytoprotection and profound intracellular reactive oxygen species (ROS) scavenging capabilities. *In vivo*, supplementation with K_2MoO_4 nanorod increased superoxide dismutase (SOD) activity and xanthine oxidase (XOD) levels, reduced malondialdehyde (MDA) concentrations, and improved glucose metabolism, indicating reduced systemic oxidative stress and enhanced metabolic regulation. K_2MoO_4 nanorod also improved vascular elasticity, as evidenced by decreased aortic stiffness and collagen deposition. In mouse models of atherosclerosis, it significantly reduced atherosclerotic plaque formation and lipid accumulation, showing its protective role against atherogenesis. Furthermore, K_2MoO_4 nanorod enhanced locomotor activity and alleviated anxiety- and depression-like behaviors. Together, these findings identify K_2MoO_4 nanorod as a bioavailable, multifunctional molybdenum-based nutrient that supports redox homeostasis and vascular function, accompanied by favorable changes in metabolic and behavioral phenotypes.



KEYWORDS: molybdenum nanorod-based nutrient, cardiovascular disease, behavioral outcomes, oxidative stress, atherosclerosis, vascular elasticity

1 Introduction

Cardiovascular disease (CVD) remains the leading cause of mortality globally, accounting for over 17 million deaths annually,

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with a particularly high burden in low- and middle-income countries [1–3]. Despite substantial advances in clinical management, therapeutic interventions often occur at advanced stages of disease, by which point irreversible vascular damage has already been established [4–6]. Therefore, the development of safe, effective, and accessible strategies for early-stage prevention of CVD is of critical importance. Among various nutritional interventions, daily supplementation with essential trace elements (e.g., selenium, magnesium, calcium and chromium), has demonstrated efficacy in the risk of reducing CVD [7, 8]. Notably, molybdenum (Mo), an essential trace element, plays a crucial role as a cofactor for several redox-active enzymes, including xanthine

oxidase, aldehyde oxidase, and sulfite oxidase [9, 10]. These enzymes are involved in redox regulation, suggesting that Mo supplementation may offer cardiovascular protection through oxidative stress modulation [11, 12].

Potassium molybdate (K_2MoO_4) is a water-soluble, highly bioavailable molybdenum salt with established applications in agriculture and biomedicine [13, 14]. The molybdate ion (MoO_4^{2-}) participates in biosynthesis of molybdenum cofactors through conjugation with molybdopterin, thereby enabling enzymatic activity essential for oxidative homeostasis [13]. Simultaneously, the potassium ion (K^+) has been associated with cardiovascular benefits, including modulation of sodium balance and blood pressure regulation [15]. These dual functional properties position K_2MoO_4 as a promising candidate for dietary intervention in CVD. Despite these favorable characteristics, the *in vivo* effects of K_2MoO_4 remain largely unaddressed, particularly with respect to its cardiovascular safety, bioavailability, and therapeutic potential.

Hence, we synthesized a food-grade K_2MoO_4 nanorod of high purity and systematically evaluated its physiological impacts in mice. Specifically, K_2MoO_4 nanorod was administered via drinking water, and its effects on oxidative stress, vascular elasticity, atherosclerosis progression, glucose metabolism, and emotional behavior were comprehensively assessed. In this context, we explicitly hypothesize that K_2MoO_4 supplementation may support redox homeostasis through molybdenum-dependent biochemical processes, thereby contributing to the maintenance of metabolic and vascular function. We further examined whether these systemic changes were accompanied by alterations in behavioral phenotypes. The results indicate that K_2MoO_4 nanorod supplementation significantly reduces oxidative stress, enhances metabolic efficiency, improves vascular elasticity, and markedly reduces aortic plaque formation in apolipoprotein E-deficient ($\text{ApoE}^{-/-}$) mice. Furthermore, it alleviates anxiety- and depression-like behaviors of mice, suggesting potential neurobehavioral benefits. These results support the application of K_2MoO_4 nanorod as a promising

nutritional agent for the prevention and modulation of cardiovascular disease.

2 Results

2.1 Characterization of food-grade K_2MoO_4 nanorod

The synthesized K_2MoO_4 nanorod was comprehensively characterized using various analytical techniques. X-ray diffraction (XRD) patterns of K_2MoO_4 (Fig. 1(a)) matched well with the standard reference (K_2MoO_4 , JCPDS#29-1021), with only two weak peaks at 21.0° and 41.7° attributed to trace amounts of $\text{K}_2\text{Mo}_3\text{O}_{10}$ (JCPDS#37-1467), indicating its high phase purity. Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) images showed that K_2MoO_4 exhibited a short-rod morphology, with diameters around 80 nm and lengths ranging from approximately 200 to 500 nm (Fig. 1(b) and Fig. S1 in the Electronic Supplementary Material (ESM)). Energy dispersive X-ray spectroscopy (EDX) confirmed uniform distribution of K, Mo and O without detectable impurities (Fig. 1(c)). Inductively coupled plasma optical emission spectroscopy (ICP-OES) further validated the elemental stoichiometry, with a K:Mo ratio of 1.96:1.00 (Table S1 in the ESM), matching the theoretical composition of K_2MoO_4 nanorod. Based on the above analysis, the calculated phase purity of K_2MoO_4 reached 99.0%, meeting the standards for food-grade materials.

X-ray photoelectron spectroscopy (XPS) was performed to characterize the surface elemental composition and valence states of K_2MoO_4 nanorod. Survey spectra (Fig. S2 in the ESM) confirmed the exclusive presence of O, Mo and K, further confirming its elemental purity. The K 2p spectrum displayed characteristic peaks at 294.9 and 292.2 eV, corresponding to K $2p_{1/2}$ and K $2p_{3/2}$, respectively (Fig. 1(d)) [16]. In the O 1s region, three peaks of 532.5, 531.3 and 529.9 eV were observed, which were attributed to hydroxyl oxygen (O_{OH}), adsorbed oxygen (O_{ads}), and lattice oxygen

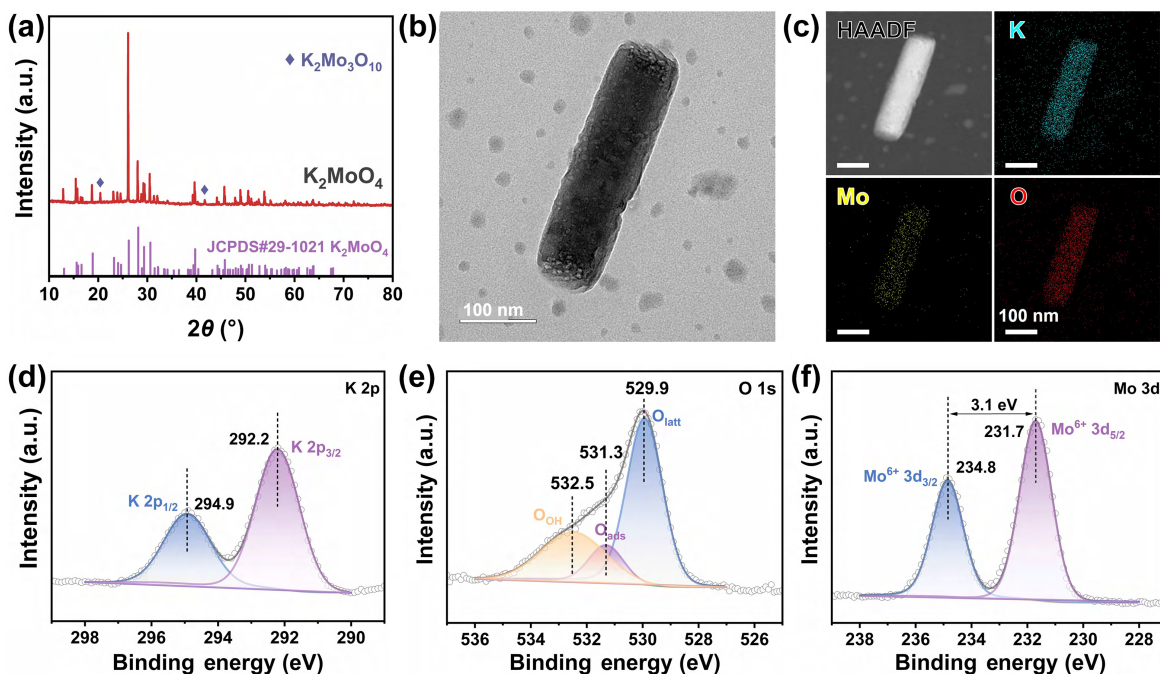


Figure 1 Structural and compositional characterization of food-grade K_2MoO_4 nanorod. (a) XRD pattern, (b) TEM image, (c) high-angle annular dark-field (HAADF) and EDX mapping images of the K_2MoO_4 . High-resolution XPS spectra of (d) K 2p, (e) O 1s, and (f) Mo 3d.

(O_{int}), respectively (Fig. 1(e)) [17, 18]. Notably, O_{OH} accounted for 29.0% of the total oxygen species, suggesting strong surface affinity for water molecules and thus excellent water solubility. The high proportion of O_{int} (59.2%) further verified the high structural stability of the K_2MoO_4 nanorod. Moreover, the Mo 3d spectrum (Fig. 1(f)) displayed two prominent peaks at 234.8 and 231.7 eV, with a binding energy separation of 3.1 eV, corresponding to $Mo^{6+} 3d_{3/2}$ and $Mo^{6+} 3d_{5/2}$ respectively [19, 20]. The stable Mo^{6+} valence state of K_2MoO_4 nanorod is consistent with the valence state of molybdenum in molybdenum cofactor (Moco), ensuring its rapid bioconversion *in vivo* [21, 22], which further confirms the excellent bioavailability of the K_2MoO_4 nanorod.

2.2 Metabolic enhancement and oxidative stress attenuation by K_2MoO_4 nanorod

To evaluate the physiological effects of K_2MoO_4 nanorod, we supplemented it into the drinking water of healthy mice, and systematically monitored multiple physiological indexes. The optimal supplementation dose was identified as 0.05 mg Mo/kg body weight (Fig. S3(a) in the ESM), and mice receiving this dose were designated as the Mo group. As indicated in Fig. 2(a), body weights were comparable between groups (Mo: 19.98 ± 0.85 g; control: 19.83 ± 1.23 g; $P = 0.795$) at baseline. After 18 days of supplementation, Mo-treated mice exhibited a significantly higher body weight (23.98 ± 1.36 g vs. 22.23 ± 1.28 g in controls; $P = 0.026$), a difference that persisted through day 28 (25.81 ± 1.32 g vs. 24.29 ± 1.29 g; $P = 0.046$), before plateauing as growth stabilized. Complete blood counts showed no significant differences between groups (Table S2 in the ESM), indicating no hematological toxicity. Organ weights, including those of the heart, liver, spleen, lung, and kidneys, were also unaffected (Fig. 2(b)), and histological examination revealed no signs of necrosis, congestion, inflammation, or tissue damage (Fig. 2(c)). These results indicated that K_2MoO_4 was well tolerated at the effective supplementation dose (0.05 mg/kg), with no observable adverse effects. Further safety assessments across a broader dose range revealed that concentrations up to 20 mg/kg remained non-toxic, while a high dose 50 mg/kg caused marked metabolic disturbances, including a 24.9% reduction in average body weight and clinical symptoms such as alopecia and emesis by day 75 (Fig. S3(b) in the ESM). These data establish both the effective and upper safety thresholds of K_2MoO_4 *in vivo*.

Having identified 0.05 mg Mo/kg body weight as a safe and biologically active dose, we evaluated the physiological effects of K_2MoO_4 supplementation at the biochemical level. Serum analysis demonstrated that K_2MoO_4 supplementation significantly increased SOD activity by 68.7%, with the Mo group reaching 82.50 ± 7.77 U/mL compared with 48.89 ± 9.03 U/mL for the control group ($P = 0.0005$, Fig. 2(d)), while MDA levels, a marker of lipid peroxidation, decreased by 26.5% from 4.95 ± 0.80 nmol/mL in controls to 3.64 ± 0.47 nmol/mL in the Mo group ($P = 0.0232$, Fig. 2(e)). The data reflects a lower level of lipid peroxidation and a corresponding alleviation of oxidative stress. Moreover, as shown in Fig. 2(f), blood glucose (GLU) levels for Mo-treated mice were 6.16 ± 1.35 mmol/L, representing a 36.1% decrease compared with the control group (9.64 ± 2.17 mmol/L, $P = 0.0262$), indicating improved glucose metabolism. No significant differences were observed in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (CREA), urea, or triglyceride (TG) levels (Figs. 2(g)–2(k)).

To determine whether K_2MoO_4 supplementation was associated with changes in a representative molybdenum cofactor-dependent enzyme, we measured hepatic XOD levels. As shown in Fig. 2(l), enzyme-linked immunosorbent assay (ELISA) analysis revealed a modest but statistically significant elevation in hepatic XOD levels in the Mo group (8.081 ± 0.045 ng/mL) compared to controls (8.013 ± 0.031 ng/mL, $P = 0.0385$). This upregulation suggests that K_2MoO_4 , as a molybdenum source, may support the biosynthesis of Moco-dependent enzymes, and enhance related enzymatic activity. These results indicate that dietary K_2MoO_4 nanorod was associated with changes in hepatic XOD levels, and systemic metabolic and antioxidant indices under the tested conditions. To isolate the direct cellular mechanisms driving these systemic antioxidant benefits, we first evaluated the cytoprotective and reactive oxygen species (ROS)-scavenging effects of K_2MoO_4 nanorods *in vitro*.

2.3 Cytocompatibility and attenuation of oxidative stress

To determine whether nanorods directly influence endothelial cell responses under oxidative-stress conditions, we performed *in vitro* experiments using human umbilical vein endothelial cells (HUVECs). A schematic representation of the experimental design is shown in Fig. 3(a). Based on an estimated exposure range derived from the *in vivo* dose, HUVECs were treated with K_2MoO_4 nanorods across a concentration gradient of 0–10 $\mu\text{g/mL}$. As shown in Fig. 3(b), cell counting kit-8 (CCK-8) analysis indicated no apparent reduction in HUVEC metabolic activity or viability within the tested concentration range after 48 h of treatment. At 0.5 and 1.0 $\mu\text{g/mL}$, the relative CCK-8 signals were 124.6% and 122.2% of the untreated control, respectively ($P = 0.014$ and $P = 0.007$), suggesting enhanced HUVEC viability and indicating increased cell proliferation.

We next examined whether K_2MoO_4 nanorods attenuated intracellular oxidative stress in an H_2O_2 -challenged HUVEC model. 2',7'-dichlorofluorescein diacetate (DCFH-DA) fluorescence markedly increased after H_2O_2 exposure, indicating elevated intracellular oxidative stress (Fig. 3(c)). Pretreatment with 0.5 or 1.0 $\mu\text{g/mL}$ K_2MoO_4 nanorods significantly reduced the fluorescence signal compared with the H_2O_2 -treated model group. Quantitative analysis showed that treatment with 0.5 and 1.0 $\mu\text{g/mL}$ K_2MoO_4 reduced the H_2O_2 -induced increase in 2',7'-dichlorofluorescein (DCF) fluorescence by approximately 81.6% and 93.0% ($P < 0.0001$, Fig. 3(d)), respectively. These results demonstrate that K_2MoO_4 nanorods attenuate H_2O_2 -induced intracellular oxidative stress in endothelial cells at the tested concentrations, supporting further investigation of endothelial redox regulation as a potential contributor to the vascular effects of K_2MoO_4 nanorods.

2.4 Enhancement of vascular elasticity by Mo supplementation

We evaluated the effects of K_2MoO_4 supplementation on vascular elasticity and other longitudinal mechanical properties by conducting uniaxial tensile tests on freshly excised thoracic aortas to assess. As shown in Fig. 4(a), the representative stress-strain curves typically exhibited three distinct regions [23–25]: (1) an initial low-strain region dominated by elastin fibers stretching; (2) a medium-to-high strain region by progressive engagement and load-bearing by collagen fibers (highlighted in yellow); and (3) a failure region representing plastic deformation and rupture. The slope of the second linear stress-strain zone was used to calculate Young's modulus of the aortas, as this portion of the curve reflected the

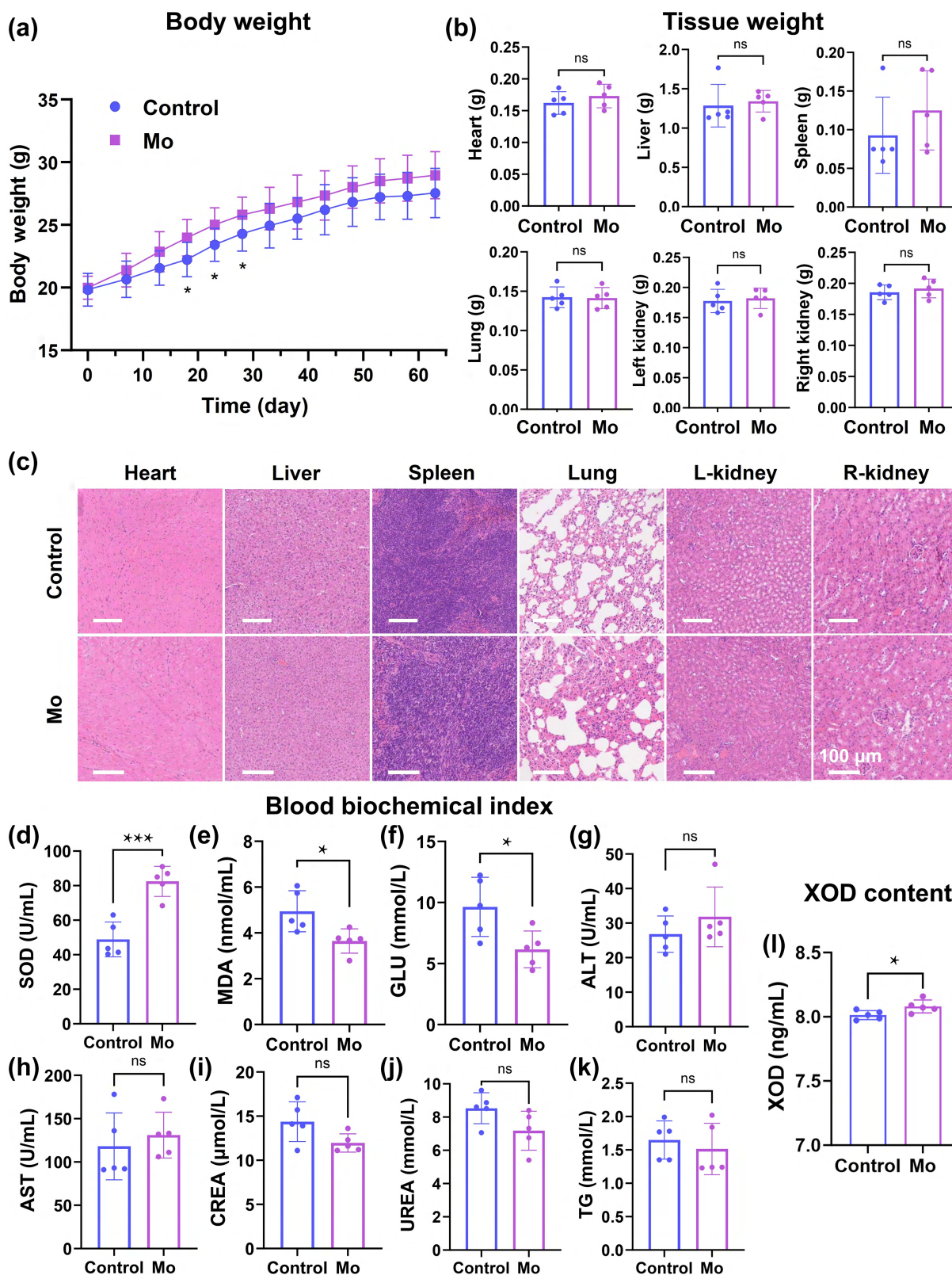


Figure 2 K_2MoO_4 nanorod promotes growth, improves metabolic regulation, and reduces oxidative stress in mice. (a) Body weight progression over time in control ($n = 8$) and K_2MoO_4 -treated (Mo, $n = 8$) groups. (b) Organ weights of heart, liver, spleen, lung, left kidney, and right kidney in control ($n = 5$) and Mo ($n = 5$) groups. (c) Representative H&E staining of mice tissues in control and Mo groups. Scale bars: 100 μ m. (d) Serum SOD activity and (e) MDA content of mice in control ($n = 5$) and Mo ($n = 5$) groups. (f) GLU levels of mice in control ($n = 5$) and Mo ($n = 5$) groups. Serum biochemical markers of mice in control ($n = 5$) and Mo ($n = 5$) groups, including (g) ALT, (h) AST, (i) CREA, and (j) UREA. (k) Serum TG levels of mice in control ($n = 5$) and Mo ($n = 5$) groups. (l) Hepatic XOD levels measured by ELISA. Data are presented as the mean $\pm$ SD. Statistical significance was determined using unpaired two-tailed Student's t-test. *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$, ns: not significant.

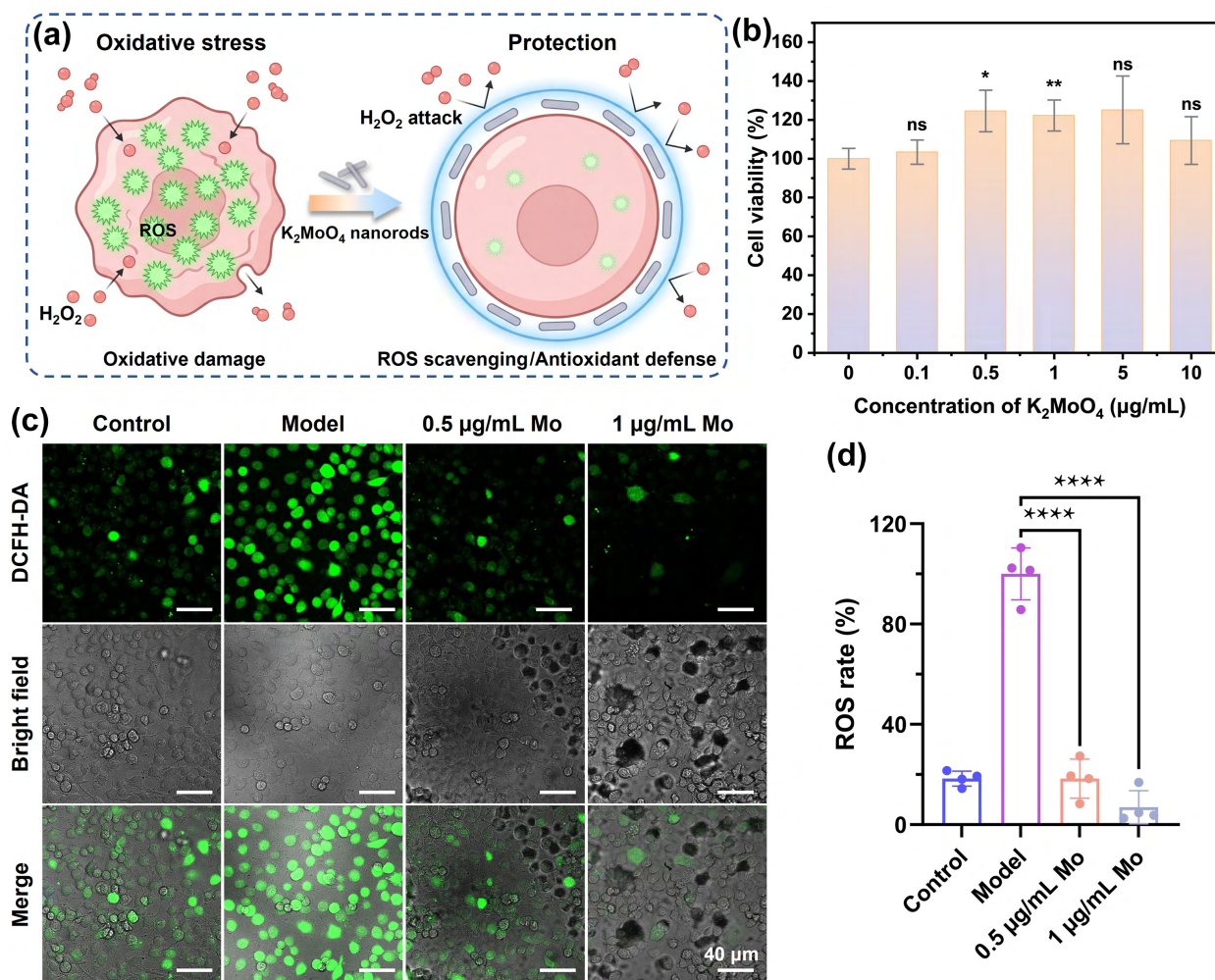


Figure 3 *In vitro* cytocompatibility and attenuation of intracellular oxidative stress by K₂MoO₄ nanorods on HUVECs. (a) Schematic illustration of K₂MoO₄ nanorods protecting HUVECs against H₂O₂-induced oxidative stress by scavenging intracellular ROS and promoting cell viability. (b) Relative cell viability of HUVECs treated with varying concentrations of K₂MoO₄ nanorod (0–10 μg/mL) for 48 h, measured by CCK-8 assay. (c) Representative fluorescence microscopy images of intracellular ROS levels in HUVECs stained with DCFH-DA probe. Cells were pre-treated with 0.5 or 1.0 μg/mL K₂MoO₄ prior to H₂O₂-induced oxidative stress challenge. Scale bars: 40 μm. (d) Quantitative analysis of relative ROS fluorescence intensity across different treatment groups. Data are presented as mean ± SD (*n* = 4 per group). Statistical significance was determined using unpaired two-tailed Student's *t*-test. *****P* < 0.0001, ***P* < 0.01, **P* < 0.05, ns: not significant.

progressive uncrimping and tension alignment of collagen fibers, which gradually transitioned from a wavy relaxed state to a load-bearing configuration, ultimately determining arterial stiffness at higher strain levels [23, 24]. Compared with controls, the Mo-treated group exhibited a 31.1% reduction in Young's modulus (Fig. 4(b)), indicating a significantly improvement in aortic wall elasticity following K₂MoO₄ supplementation.

To investigate whether histological changes underlay the enhanced aortic elasticity, Masson staining was performed to evaluate extracellular matrix composition. As shown in Fig. 4(c), the Mo groups exhibited a visibly reduced collagen fibers (stained blue) in the aortic media compared to controls, while the cross-sectional area of the intima-media layer remained similar between two groups (0.100 ± 0.007 mm² for controls vs. 0.106 ± 0.009 mm² for Mo groups, Fig. S4 in the ESM). These findings suggested that K₂MoO₄ supplementation had minimal impact on overall vessel wall thickness and morphology, but reduced collagen fiber content, thereby improving the vascular elasticity.

To further assess vascular biomechanics at the microscale, atomic force microscopy (AFM) was performed on the inner surface of

aortic segments (Fig. 4(d)). In detail, the blood vessel was longitudinally incised, trimmed into small segments, and flattened onto silicon substrates for nanomechanical analysis after 12 h. Topographic AFM imaging revealed irregular surface morphology in both groups (Fig. 4(e)), with comparable roughness values between the control group (−0.146 ± 0.353 μm) and the Mo group (0.0396 ± 0.156 μm). Although surface morphology did not differ substantially, mechanical property mapping provided additional insight. The Mo group showed a slight, non-significant reduction in adhesion force (8.582 ± 5.782 nN) compared to controls (14.762 ± 3.111 nN, Fig. 4(f)), suggesting compositional changes within the aortic matrix. In particular, the average indentation depth of the Mo group (38.017 ± 3.227 nm) was 1.35-fold higher than in controls (28.383 ± 7.521 nm, Fig. 4(g)), indicating a softer tissue structure. Correspondingly, the average Derjaguin–Muller–Toporov (DMT) modulus of the aorta in the Mo group was 15.7% lower than that in the control group (Fig. 4(h)), consistent with a reduction in collagen content and enhanced transverse elasticity of the aortic wall. These results indicate that K₂MoO₄ supplementation improves both longitudinal and transverse vascular elasticity, likely through modulation of extracellular matrix composition,

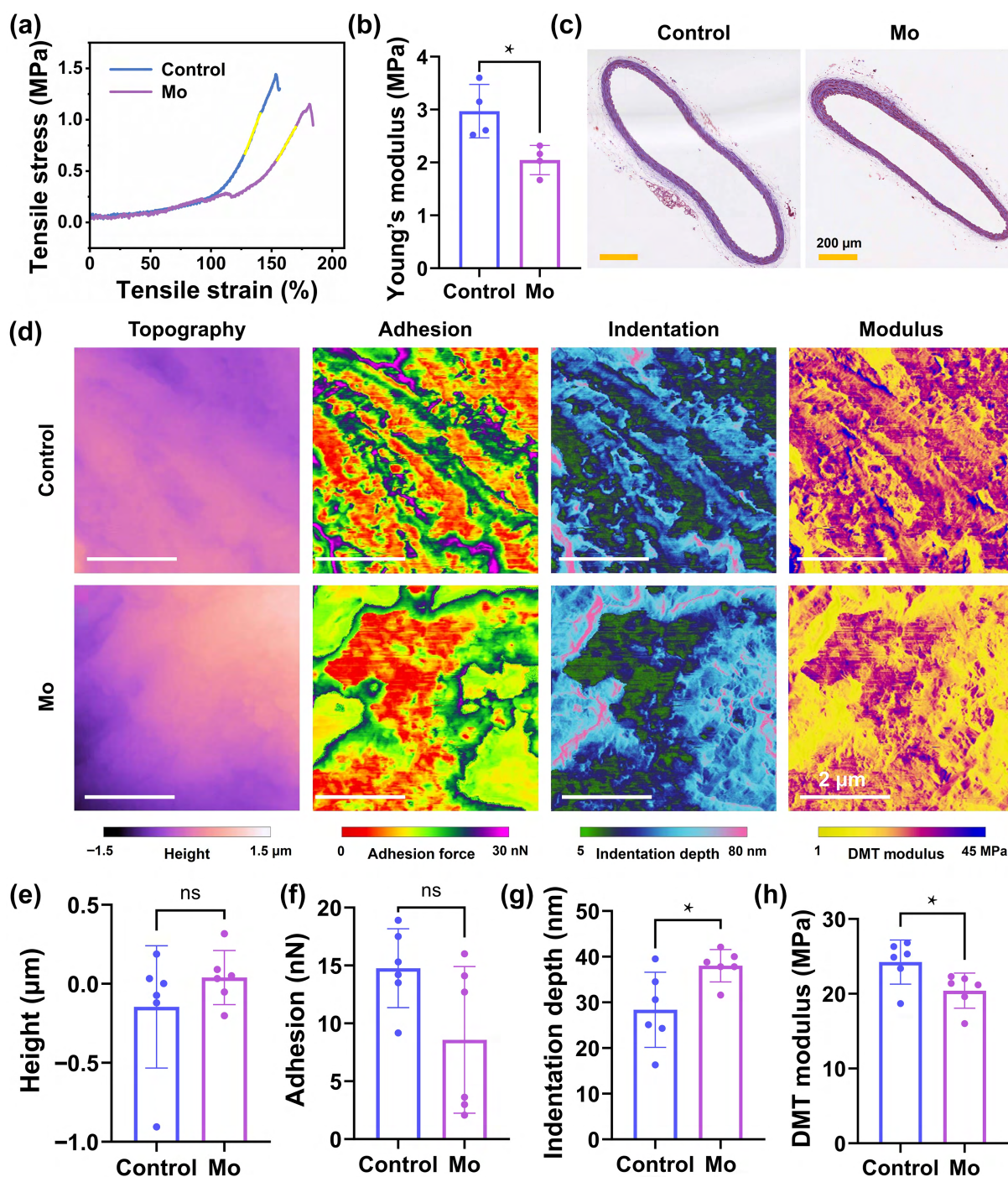


Figure 4 K_2MoO_4 improves vascular elasticity. (a) Representative uniaxial tensile stress-strain curves of intact aortas from control and Mo-treated groups. (b) Averaged Young's modulus of aortas, calculated from the medium-to-high strain region using Fung's Law, in control ($n = 4$) and Mo ($n = 4$) groups. (c) Representative Masson-stained sections of aortic roots from control and Mo-treated mice. Collagen fibers are stained blue. Scale bars: 200 μm . (d) Representative AFM maps of the aortic inner surface, showing topography, adhesion force, indentation depth, and elastic modulus. Scale bars: 2 μm . (e) Averaged height, (f) adhesion, (g) indentation depth, and (h) DMT modulus mappings of aortic samples from control ($n = 6$) and Mo ($n = 6$) groups. Data are presented as mean $\pm$ SD. Statistical significance was assessed using an unpaired Student's two-sided t-test compared with the control group. * $P < 0.05$, ns: not significant.

particularly by reducing collagen fiber deposition, without inducing structural damage or altering overall vascular morphology.

2.5 Suppression of atherosclerotic progression by Mo supplementation

Given that atherosclerosis constitutes a primary pathological basis

of CVD [6, 26], we employed ApoE^{-/-} mice fed with a high-fat diet to evaluate the cardiovascular protective effects of Mo supplementation. Following the same Mo supplementation protocol as in previous experiments, K_2MoO_4 was administered via drinking water throughout the intervention period. Body weight measurements showed no significant difference between control and Mo-treated ApoE^{-/-} mice during the initial 65 days (Fig. 5(a)).

However, beyond day 65, control mice exhibited continued weight gain, while the Mo-treated group showed a slower rate of weight increase, resulting in a progressively significant divergence. This trend suggests that K_2MoO_4 intake may modulate lipid metabolism, thereby mitigating excessive weight gain.

To assess plaque lesion development, optical images of the aortic surface stained with Oil Red O were acquired after 12 weeks of feeding (Fig. 5(b)). Quantitative analysis revealed a 32.4% reduction in plaque burden in the Mo group, based on lesion area relative to the total aortic surface (Fig. 5(c)). Further histological evaluation of aortic root cross-sections included hematoxylin and eosin (H&E) staining for overall morphology, Masson's trichrome staining for collagen deposition, and Oil Red O for lipid accumulation (Fig. 5(d)). In the $ApoE^{-/-}$ control group, H&E staining revealed substantial thickened intima and prominent plaque formation. In

contrast, K_2MoO_4 -treated mice maintained more preserved vascular architecture, with smaller plaques, thinner intimal layers, and less luminal narrowing (Fig. 5(e)). Masson staining demonstrated extensive collagen accumulation in control mice, while collagen content was markedly reduced in the Mo group. Similarly, Oil Red O staining showed a notable decrease in lipid deposition within the aortic wall following K_2MoO_4 treatment. These results indicate that dietary K_2MoO_4 supplementation effectively suppresses atherosclerotic progression in $ApoE^{-/-}$ mice, likely by promoting lipid metabolic regulation and limiting collagen deposition. Because oxidative stress and vascular dysfunction may also influence neurovascular homeostasis and behavioral outcomes [27–29], we investigated whether K_2MoO_4 supplementation was accompanied by changes in behavioral phenotypes.

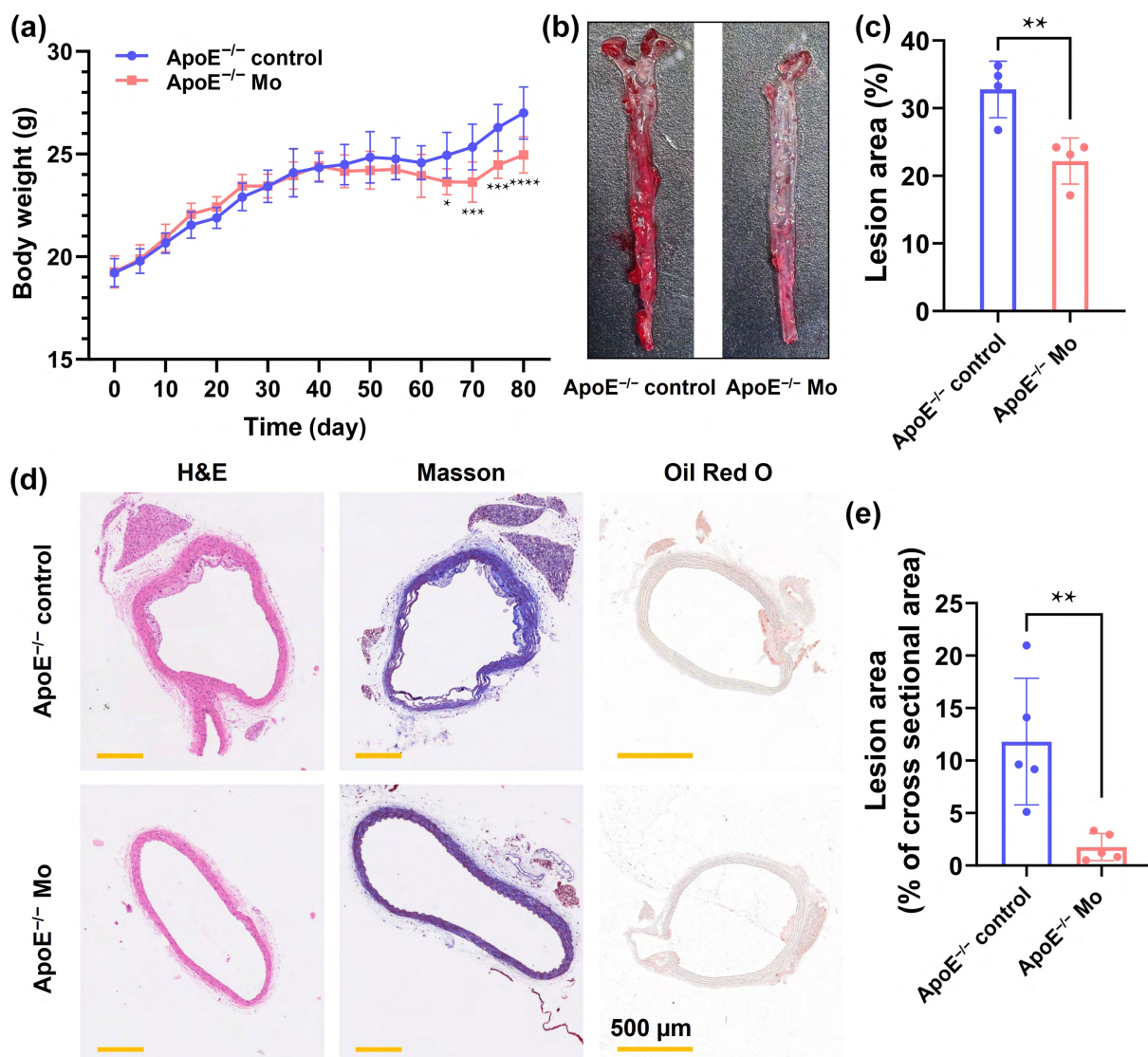


Figure 5 K_2MoO_4 supplementation attenuates atherosclerotic development in $ApoE^{-/-}$ mice. (a) Body weight changes of $ApoE^{-/-}$ mice in control ($n = 9$) and Mo-treated ($n = 9$) groups. (b) Representative en-face images of whole aortas stained with Oil Red O, visualizing atherosclerotic lesions in $ApoE^{-/-}$ control ($n = 4$) and Mo ($n = 4$) groups. (c) Quantification of Oil Red O-positive lesion area expressed as a percentage of total aortic surface area ($n = 4$ per group). (d) Representative cross-sectional images of aortic roots stained with H&E, Masson, and Oil Red O, illustrating differences in plaque morphology, collagen deposition, and lipid accumulation between control and Mo-treated $ApoE^{-/-}$ mice. Scale bars: 500 μ m. (e) Quantification of plaque area in aortic root sections shown in panel (d) ($n = 5$ per group). Data are presented as mean $\pm$ SD. Statistical significance was assessed using an unpaired Student's two-sided t-test compared with the control group. **** $P < 0.0001$, *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$.

2.6 Improvement of emotional and behavioral performance by Mo supplementation

In addition to its cardiovascular benefits, Mo supplementation significantly improved behavioral performance and emotional regulation, as demonstrated by a series of standardized behavioral tests. In the open field test (OFT), as visually evidenced by the denser trajectory tracking and more intense heat map signals in both the central and peripheral zones (Fig. 6(a)), mice in the Mo group exhibited significantly enhanced spontaneous locomotor activity. They traveled a total distance of 2145.32 ± 327.16 cm, representing a 40.9% increase over the control group (1522.64 ± 571.79 cm, Fig. 6(b)). Correspondingly, immobility time was reduced by 45.3%, from 85.51 ± 29.02 s in groups to 46.81 ± 12.48 s in the Mo group (Fig. 6(c)). Central zone exploration, a commonly used indicator of anxiety, was markedly elevated in Mo-treated mice: total distance traveled in the center rose by 90.5% (269.57 ± 64.19 vs. 141.52 ± 77.26 cm, Fig. 6(d)), and the number of central entries nearly doubled (22.29 ± 4.20 vs. 11.14 ± 5.33 , Fig. 6(e)), suggesting reduced anxiety behavior.

In the tail suspension test (TST), heat map visualizations indicated a broader range of intense struggling movements in the Mo-treated mice (Fig. 6(f)), translating to a clear antidepressant-like behavior. Specifically, total global activity was elevated by 57.2% (9911.16 ± 2295.22 vs. 6304.82 ± 1721.11 cm², Fig. 6(g)). The duration of high-activity bouts (Fig. 6(h)) increased by over twofold

from 27.89 ± 15.77 s in controls to 68.44 ± 18.49 s in the Mo group, and the frequency rose from 36.00 ± 16.34 to 61.17 ± 12.39 times (Fig. 6(i)), accompanied by a 29.2% decrease in immobility time (96.22 ± 25.51 s vs. 135.84 ± 27.70 s, Fig. 6(j)).

Similarly, in the elevated plus maze (EPM), trajectory and heat maps revealed that Mo-treated mice ventured more frequently and actively into the unprotected areas (Fig. 6(k)). These mice demonstrated significantly reduced anxiety responses, spending 135.3% more time in the open arms (Fig. 6(l)) and exhibiting a 50.9% increase in open arm entries (Fig. 6(m)). These findings suggest that K₂MoO₄ supplementation enhances motor activity and alleviates anxiety- and depression-like behaviors in mice, potentially through enhanced antioxidant defenses and molybdenum-dependent enzymatic regulation of neural metabolism.

3 Discussion

This study suggests that dietary supplementation with high-purity K₂MoO₄ nanorod yields significant cardiovascular health improvements in mouse model by improving vascular elasticity and delaying progression of atherosclerosis. These observed therapeutic outcomes are attributable to the dual biochemical functions of molybdenum as a redox-active trace element involved in both maintaining redox homeostasis and serving as an essential cofactor in molybdenum-dependent enzymatic processes. The physiological efficacy of K₂MoO₄ nanorod depends critically on its

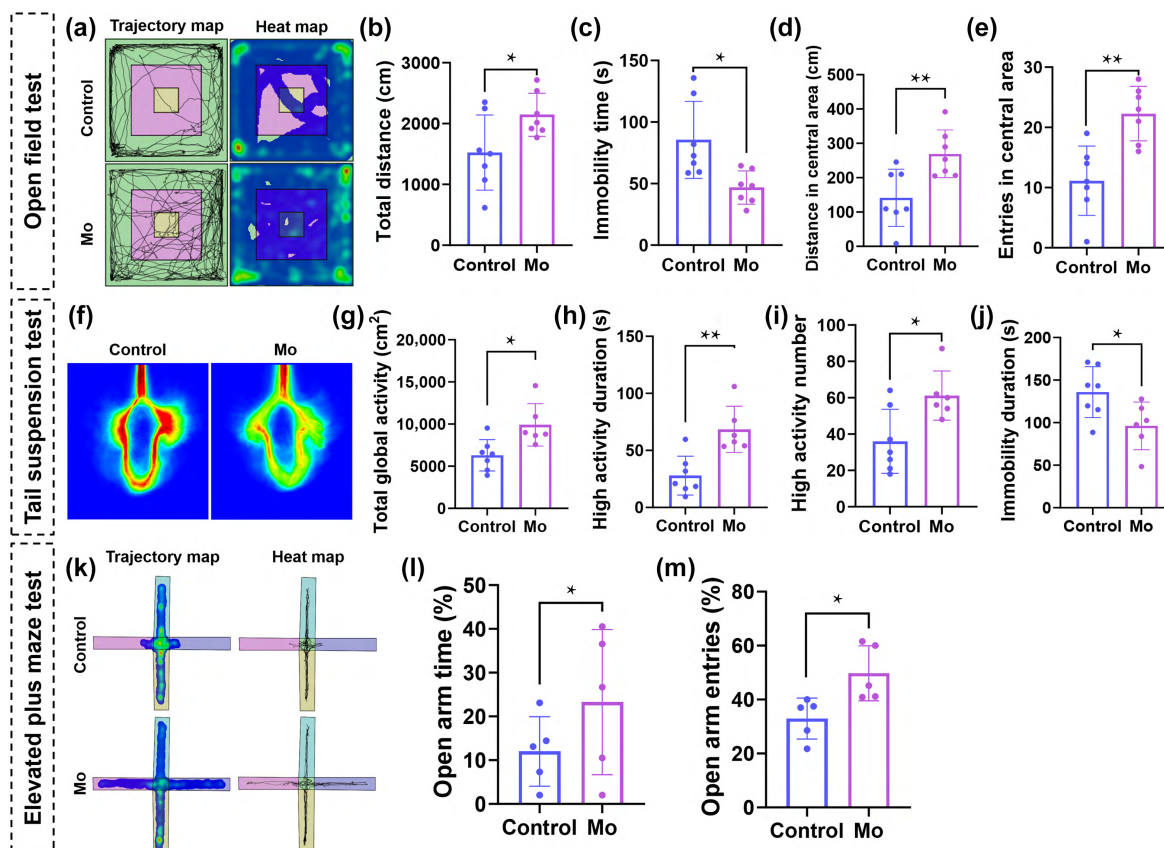


Figure 6 K₂MoO₄ enhances behavioral performance and alleviates anxiety- and depression-like behaviors in mice. OFT: (a) representative trajectory maps and heat maps, (b) alongside quantitative analysis of total distance traveled, (c) immobility time, (d) distance traveled in central area, and (e) number of central area entries in control ($n = 7$) and Mo-treated ($n = 7$) mice. TST: (f) representative heat maps, (g) alongside total global activity, (h) duration, and (i) frequency of high-activity bouts, and (j) total immobility time in control ($n = 7$) and Mo-treated ($n = 6$) mice. EPM: (k) representative trajectory and heat maps, (l) alongside proportion of time spent in the open arms and (m) frequency of open arm entries in control ($n = 5$) and Mo-treated ($n = 5$) mice. Data are presented as mean $\pm$ SD. Statistical significance was assessed using an unpaired Student's two-sided t-test compared with the control group. ** $P < 0.01$, * $P < 0.05$.

physicochemical properties. The synthesized compound exhibited high purity, phase homogeneity, and a chemically stable Mo^{6+} oxidation state, consistent with the molybdenum valence in Moco. These characteristics collectively ensure superior bioavailability and biological activity. Upon ingestion, molybdate ions (MoO_4^{2-}) act as precursors for Moco biosynthesis, facilitating the activation of Moco-dependent enzymes such as XOD, which plays a central role in purine metabolism and ROS regulation. The increase in hepatic XOD levels observed after K_2MoO_4 supplementation indicates that a representative molybdenum cofactor-dependent biochemical component was altered, while markedly reducing MDA and GLU concentrations. These changes reflect an overall enhancement in systemic antioxidant capacity and metabolic homeostasis, both of which are critical for protecting vascular tissues from oxidative damage, a key driver of endothelial dysfunction and vascular stiffening. The HUVEC experiments provide complementary cell-level evidence for the vascular findings observed *in vivo*. K_2MoO_4 nanorods attenuated H_2O_2 -induced intracellular DCF fluorescence without reducing cell viability at the tested concentrations, suggesting that modulation of endothelial oxidative stress may contribute to the preservation of vascular function. These results support a beneficial role of K_2MoO_4 nanorods in maintaining endothelial redox homeostasis and are consistent with the vascular protection observed *in vivo*. While the precise molecular mechanisms remain to be further elucidated, the current findings highlight endothelial redox regulation as a likely contributor to the observed biological effects.

At the tissue level, improved vascular elasticity following K_2MoO_4 supplementation was accompanied by both macro- and microscale structural remodeling of the aortic extracellular matrix. Reduced collagen deposition, together with decreased aortic stiffness, suggests a shift toward a more elastin-rich compliant matrix. As mentioned above, by suppressing excess ROS, K_2MoO_4 can preserve elastin integrity and suppress collagen overaccumulation, thereby improving arterial compliance and mechanical resilience [30]. These results highlight the potential of redox-targeted nutritional interventions in reversing early biomechanical deterioration of the vasculature. Beyond structural improvements, K_2MoO_4 also exerted protective effects in mouse models of atherosclerosis. Treated mice displayed significantly reduced plaque burden and lipid accumulation, through dual mechanisms: enhanced ROS scavenging, which inhibits low-density lipoprotein (LDL) oxidation and subsequent foam cell formation [31, 32], and improved lipid metabolism via molybdenum-dependent enzymes (e.g., sulfite oxidase). Additionally, the attenuated weight gain observed in the Mo group further supports improved systemic metabolic regulation. Notably, the 32.4% reduction in plaque burden of the observed anti-atherosclerotic effect is comparable to literatures reported benchmarks for standard pharmacological interventions. For instance, statin therapies (e.g., atorvastatin or rosuvastatin) typically achieve a 30% to 40% reduction in plaque area in high-fat diet fed ApoE^{-/-} murine models [33, 34]. Despite this promising efficacy, the absence of an internal parallel positive control group (such as a statin-treated group) in the current *in vivo* experimental design remains a limitation.

Beyond cardiovascular protection, K_2MoO_4 supplementation also improved behavioral and emotional parameters. Treated mice exhibited increased locomotor activity, reduced anxiety-like behavior, and antidepressant-like responses across multiple behavioral assays. These effects stem from the systemic

improvements in antioxidant defenses and energy metabolism. Enhanced SOD activity and reduced glucose levels suggest improved mitochondrial function, which can facilitate better neuronal signaling and behavioral performance. Although the direct neurological actions of molybdenum remain underexplored, its involvement in sulfur-containing amino acid metabolism could influence neurotransmitter biosynthesis (e.g., serotonin) [35, 36], warranting further investigation into its neuromodulatory potential. The behavioral changes observed after K_2MoO_4 nanorod supplementation may be associated with alterations in systemic redox, metabolic, and vascular status. Because cerebral blood flow, cerebrovascular endothelial function, and blood–brain barrier integrity were not directly assessed in the present study, however, these findings should not be interpreted as evidence of a direct neurovascular or neuromodulatory effect. Further studies incorporating direct measurements of cerebrovascular function and morphology will be required to determine whether the behavioral phenotypes are mechanistically related to changes in neurovascular homeostasis.

While this study establishes the broad *in vivo* physiological efficacy and baseline safety of K_2MoO_4 nanorods, several limitations must be acknowledged to guide future research. First, although K_2MoO_4 nanorod supplementation was associated with changes in redox status, metabolism, vascular mechanics, atherosclerosis-related pathology, and behavioral phenotypes, the present study does not establish a common molecular mechanism linking these observations. The proposed involvement of Moco-dependent processes therefore remains a working hypothesis rather than a demonstrated causal pathway. Although XOD expression was altered following supplementation, XOD activity, Moco abundance, and the activities of other Moco-dependent enzymes were not directly measured. In addition, the newly added HUVEC experiments showed reduced H_2O_2 -induced intracellular oxidative stress but could not distinguish among direct ROS scavenging, reduced ROS production, or activation of endogenous antioxidant responses. Thus, these findings support a role for endothelial redox regulation but do not identify the underlying molecular pathways. Future studies should combine transcriptomic and proteomic profiling with direct measurements of Moco abundance and Moco-dependent enzyme activities to clarify the molecular processes associated with K_2MoO_4 supplementation. Evaluation of antioxidant signaling pathways, including nuclear factor erythroid 2-related factor 2 (Nrf2) activation and downstream target expression, together with pharmacological or genetic interventions, will be needed to establish causality. Detailed histological and immunohistochemical analyses of vascular elastin integrity, collagen subtypes, endothelial markers, and local inflammatory responses would further help connect the observed macroscopic biomechanical findings with tissue-level alterations and clarify whether and how molybdenum-dependent processes contribute to the observed physiological changes.

Second, the present mouse data cannot be directly extrapolated to the prevention or treatment of cardiovascular or neurovascular diseases in humans. The tissue distribution, pharmacokinetics, bioavailability, and long-term fate of K_2MoO_4 nanorods remain to be characterized, particularly in comparison with soluble molybdate and conventional molybdenum formulations. Potential risks associated with excessive molybdenum exposure also warrant careful evaluation. These include possible effects on purine and uric acid metabolism, which may be relevant to individuals with hyperuricemia or gout, as well as interactions with copper homeostasis. Accordingly, systematic toxicological,

pharmacokinetic, and nutritional-interaction studies are required before the translational relevance of this formulation can be assessed.

Third, only one supplementation dose (0.05 mg/kg) and a 75-day observation period were evaluated. Although this dose was selected based on preliminary screening and no overt adverse effects were observed, it was not optimized for individual vascular, pathological, or behavioral endpoints, and the findings therefore indicate preliminary tolerability rather than comprehensive safety. Future studies should incorporate multiple dose levels, longer observation periods, and both healthy and disease-specific models to define dose-response relationships and assess potential delayed or cumulative adverse effects. In addition, species-specific differences in absorption, metabolism, tissue distribution, clearance, and nutrient homeostasis may limit direct extrapolation from mice to humans, while potential interactions with standard cardiovascular therapies remain unknown because combination treatments were not evaluated. Finally, the absence of an equimolar potassium control prevents clear distinction between the effects of molybdate and potassium ions. Moreover, although Oil Red O staining, MDA measurements, and serum triglyceride analysis provided useful information on lipid accumulation and oxidative status, more comprehensive serum lipid profiling and inflammatory assessments were not performed. Therefore, the potential contributions of lipid metabolism and inflammatory pathways to the observed reduction in plaque burden warrant further investigation. Future studies incorporating appropriate ionic, vehicle, and positive pharmacological controls, together with comprehensive serum lipid profiling, circulating and tissue-level inflammatory assessments, and direct evaluation of cerebrovascular function, will help define the specificity, magnitude, and biological basis of the observed vascular and behavioral effects.

Overall, the present findings support an association between K_2MoO_4 nanorod supplementation and multiple physiological phenotypes in mice, with redox and vascular homeostasis providing a plausible integrative framework. Future studies integrating behavioral assessments with direct measurements of cerebral blood flow, cerebrovascular endothelial function, blood-brain barrier integrity, neuroinflammation, and oxidative-stress markers in brain tissue will help clarify potential links between behavioral phenotypes, cerebrovascular function, and brain redox status. More broadly, the underlying molecular relationships, tissue specificity, and translational significance of the observed effects remain to be established through targeted mechanistic and safety investigations.

4 Conclusions

In summary, K_2MoO_4 supplementation was associated with improved systemic redox indices, endothelial responses to oxidative stress, vascular mechanical properties, and atherosclerosis-related pathology in mice, together with changes in metabolic and behavioral phenotypes. These findings support redox and vascular homeostasis as a plausible framework for integrating the observed effects. However, the specific molecular pathways, the contribution of the nanorod morphology, the relationship between the vascular and behavioral findings, and the long-term safety and translational relevance of this formulation remain to be established. Future studies incorporating pathway-specific analyses, direct comparisons with soluble K_2MoO_4 , dose-response evaluation, and longer-term pharmacokinetic and safety assessments will be required.

5 Experimental

5.1 Synthesis of potassium molybdate nanorod

All chemicals used were of analytical grade and purchased from Shanghai Aladdin Biochemical Technology Co., Ltd. K_2MoO_4 was synthesized by mixing 37.0 g of K_2CO_3 and 35.5 g of MoO_3 , which was gradually added to 180 mL of deionized water at 100 °C under ultrasonic treatment. The reaction proceeded for 1 h until the solution became clear. Finally, the resulting solution was subsequently freeze-dried to obtain potassium molybdate powder.

5.2 Material characterization

Power XRD patterns were analyzed on Bruker D8 Advance diffractometer with Cu $K\alpha$ radiation (40 kV, 40 mA, $\lambda = 0.15418$ nm) over a 2θ range of 5°–80° at a scan speed of 8°/min. SEM was performed on a Regulus 8230 microscope. TEM and EDX were conducted using a Tecnai G2 F30 S-TWIN instrument (300 kV). XPS was conducted on a Thermo Scientific K-Alpha system. ICP-OES was performed using an Agilent ICPOES 730.

5.3 Animal experiments

All male mice were obtained from Beijing Viewsolid Biotechnology Co., Ltd. C57BL/6 mice (7 weeks old) were used to evaluate physiological effects of trace molybdenum supplementation via K_2MoO_4 , including behavioral performance, arterial elasticity, and biochemical parameters. The diet was AIN-76A (M100001, Beijing Bai Ao Biotechnology Co., Ltd.). The ApoE^{−/−} mice on a C57BL/6 background (6 weeks old) were used in the atherosclerosis prevention experiment. The mice were fed a high-fat purified Western Diet (model D12079B, SPF Biotechnology Co., Ltd.) containing 41% of energy from fat and 0.15% additional cholesterol.

All mice were maintained in an airconditioned room (19–26 °C) under a 12-h/12-h light/dark cycle (8 AM–8 PM light, 8 PM–8 AM dark) and were given free access to food and water. After one week of acclimation, mice were randomly assigned to the experimental groups ($n = 8$ per group). The prepared K_2MoO_4 was added to the drinking water at doses calculated by body weight: 0 (control), 0.05, 0.25, and 1.25 mg/kg per day. The actual concentrations of K_2MoO_4 in the drinking water of each group of mice were 0, 0.62, 3.1, and 15.5 µg/mL, respectively, based on the average body weight of 25 g per mouse and the average daily water intake of about 5 mL. The 0.05 mg/kg body weight dosage corresponds to an estimated daily intake of approximately 1.25 µg of elemental Mo and 1 µg of elemental K per mouse. For the dietary safety evaluation, the dose of each group was set as 0 (control), 20, 50, and 80 mg/kg per day, respectively. Similarly, the groups used in the atherosclerosis prevention experiment were given doses of 0 (control) and 8 mg/kg.

5.4 Blood tests and XOD quantification

Blood was collected from the orbital venous plexus of mice. Complete blood counts were performed using 100 µL of whole blood on a Mindray BC-5130 Vet blood cell analyzer. Serum biochemistry tests were conducted using 100 µL of serum with a Hitachi automatic biochemical analyzer. Fresh liver supernatant samples were collected using a commercial ELISA kit following the manufacturer's protocol, and the absorbance at 450 nm was measured using an AMR-100 fully automated enzyme marker for the quantification of XOD content.

5.5 *In vitro* cell experiments

HUVECs were cultured in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% Penicillin-Streptomycin at 37 °C in a humidified atmosphere containing 5% CO₂.

To evaluate cytocompatibility, HUVECs were seeded into 96-well plates at a density of 1×10^4 cells per well and cultured overnight. The medium was then replaced with fresh medium containing varying concentrations of K₂MoO₄ nanorods (0, 0.1, 0.5, 1, 5, and 10 µg/mL). After 48 h of incubation, 10 µL of CCK-8 solution was added to each well, and the plates were incubated for an additional 30 min in the dark. The absorbance at 450 nm was measured using a microplate reader. Cell viability was calculated as a percentage relative to the untreated control group.

To assess the intracellular ROS scavenging capability, HUVECs were seeded in multi-well plates and pre-treated with K₂MoO₄ nanorods at selected serum-relevant concentrations (0.5 and 1.0 µg/mL) for 24 h. The cells were then challenged with H₂O₂ (100 µM) for 2 h to induce oxidative stress. Following the H₂O₂ challenge, the cells were washed gently with phosphate-buffered saline (PBS) and incubated with 10 µM of DCFH-DA fluorescent probe in serum-free medium for 20 min at 37 °C in the dark. After washing three times with PBS to completely remove the unbound probe, the intracellular ROS levels were immediately observed and captured using confocal laser scanning microscope (Nikon, A1R (N-SIM), Japan). The relative ROS fluorescence intensity was quantitatively analyzed using ImageJ software.

5.6 Aortic mechanical testing

Thoracic aortas were excised and subjected to tensile testing using a QX-W100 biomechanical testing system (Shanghai Qixiang). Aortas were mounted between clamps and stretched at 100 mm/min with a force limit of 20 N. The tensile stress (σ) and strain (ε) were calculated by the following equations (Eqs. (1) and (2)):

$$\sigma \text{ (MPa)} = F/A \quad (1)$$

$$\varepsilon \text{ (%) } = \Delta L/L_0 \quad (2)$$

where F is the applied force (N), A is the aortic intima-media area (mm²) measured from aortic cross-sectional sections photographed under Zeiss confocal microscope, ΔL is the elongation (mm), and L_0 is the initial length of the aortas (mm). Young's modulus was calculated from the slope of the medium-high strain region of the aortic stress-strain curve.

The micro-scale mechanical properties of aorta were measured using an AFM (Bruker Dimension XR). Sections of mice thoracic aortas (3 mm × 5 mm) were taken, rinsed clean with saline and then glued to silicon wafers (inner surface facing up). After 12 h equilibration, AFM measurements were performed using a ScanAsyst-Air probe (tip radius: 650 nm, resonance frequency: 70 kHz, spring constant: 0.40 N/m; deflection sensitivity: 55.0 nm/V). A Sapphire-12M substrate was applied for calibration. Each sample was scanned at six independent sites (25 µm² per site), and mean values were calculated. The DMT model was used to fit force-indentation data.

5.7 Aorta en-face staining and plaque analysis

Aortas were dissected, stripped of superficial fat, opened longitudinally, and stained with Oil Red O to visualize lipid

deposition. After excess dye removal, the tissue was fixed on a petri dish coated with black silicon for imaging. Lesion area was quantified using ImageJ as the percentage of total aortic area occupied by plaques.

5.8 Histological staining and quantification

Aortas were paraffin-embedded, sectioned, and then stained with H&E and Masson. At the same time, aortas were embedded and sectioned with a LEICA CM1900 frozen sectioning machine, and the sections were stained using Oil Red O. The stained sections were digitized to obtain images using 3DHISTECH Panoramic ScanII software with an Olympus BX51 microscope. Plaque area was then quantified using ImageJ.

5.9 Behavioral testing

Behavioral tests were conducted between 9 AM and 5 PM following 1-day acclimation. Equipment was cleaned with 75% ethanol before each session. Mice in the control and Mo-treated groups were tested using Smart v3.0 or Labmaze software in the following assays:

Open field test: Each mouse was placed at the midpoint of a square Plexiglass cage (40 cm × 40 cm) and immediately left. The animal behavior analysis software Smart v3.0 or Labmaze was opened to automatically record the mouse's activities in the box within 5 min.

Tail suspension test: The tail suspension device is an operating box with a width of 18 cm and a height of 20 cm. A small clip to the top of the operating box was attached and the tape wrapped around the tail of the mouse was secured. The distance between the head of the mouse and the bottom of the box is 4–5 cm. The tail suspension process lasted for 6 min, and the activity data of mice within 4 min were recorded.

Elevated cross maze test: The specifications of the open and closed arms of the overhead cross are 30 cm × 5 cm. The mouse was placed quickly on a cross platform at the intersection of the open and closed arms of the elevated cross maze (note that the mouse faces the open arm) and left immediately. The animal behavior analysis software Smart v3.0 or Labmaze was then turned on to automatically record the activity of the mice in the elevated cross maze for 5 min.

5.10 Statistical analysis

All data are presented as mean ± standard deviation (SD). Statistical significance was assessed using an unpaired Student's two-sided t -test by GraphPad Prism. The probability value: **** $P < 0.0001$, *** $P < 0.001$, ** $P < 0.01$, * $P < 0.05$, ns: not significant.

Electronic Supplementary Material: Supplementary material (including further material characterizations (TEM, XPS, and ICP-OES) and more *in vivo* tests data) is available in the online version of this article at <https://doi.org/10.26599/NR.2026.94909007>.

Data availability

All data needed to support the conclusions in the paper are presented in the manuscript and the Electronic Supplementary Material. Additional data related to this paper may be requested from the corresponding author upon request.

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Declaration of competing interest

All the contributing authors report no conflict of interests in this work.

Author contribution statement

B. B. B.: Investigator, data curation, writing – original draft. Z. J. G., Q. C. L., Z. H. C., F. W. C.: Investigator, data curation, writing – original draft. S. J. Y., N. N. S.: Conceptualization, investigator, data curation, writing – review & editing. M. M. L.: Conceptualization, investigator, data curation, writing – review & editing.

Informed consent

Not applicable.

Ethics statement

All animal experimental protocols were approved by the Institutional Animal Care and Use Committee of Beijing View Solid Biotechnology (Ethical code: VS2126A01278) and performed according to standard guidelines.

Use of AI statement

None.

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