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Tetramethylpyrazine Alleviates Trigeminal Neuralgia by Inhibiting HIF-1α-Mediated Neuroinflammation and Oxidative Stress

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Abstract: Objective This study investigates whether TMP alleviates TN by modulating HIF-1α-mediated neuroinflammation and oxidative stress pathways, as predicted by network pharmacology analyses identifying HIF-1α as a potential TMP target. **Methods** A rat model of CCI-ION was used. Post-surgery, rats were randomly assigned to receive TMP at 20, 40, or 80 mg/kg or CBZ at 50 mg/kg. Mechanical pain thresholds were assessed behaviorally. In the trigeminal ganglion, expression levels of HIF-1α, pro-inflammatory cytokines (IL-1β, TNF-α), and antioxidant enzymes (MnSOD, CAT) were quantified by qPCR and Western blot. Microglial activation, myelin integrity, and oxidative stress (MDA content) were evaluated by IBA-1 immunohistochemistry, Luxol Fast Blue staining, and standard biochemical assays, respectively. **Result** TMP at 80 mg/kg significantly alleviated mechanical hyperalgesia, with efficacy comparable to CBZ. It suppressed HIF-1α expression and reduced pro-inflammatory cytokines (IL-1β, TNF-α), enhanced antioxidant capacity by upregulating MnSOD and CAT and decreasing MDA, and inhibited microglial activation and demyelination. **Conclusion** TMP likely alleviates trigeminal neuralgia by inhibiting HIF-1α, leading to coordinated downregulation of neuroinflammation and oxidative stress. These results provide experimental evidence for TMP's multi-target analgesic mechanism and identify HIF-1α as a potential target for treating neuropathic pain.
Keywords: Tetramethylpyrazine, Trigeminal Neuralgia, HIF-1α, Neuroinflammation, Oxidative Stress

1. Introduction

TN presents with intense, episodic facial pain and markedly reduces patients'quality of life[1]. Although carbamazepine remains the standard first-line treatment, its efficacy is incomplete and tolerability issues reduce adherence[2]. Therefore, safer analgesics with novel mechanisms are urgently needed[3].

TMP, an active compound derived from Ligusticum chuanxiong, exhibits anti-inflammatory, antioxidant, and neuroprotective properties. Although TMP has shown preliminary efficacy in neuropathic pain models, its precise role and mechanism in TN remain unclear[4,5].

Neuroinflammation and oxidative stress are central drivers of TN pathogenesis, forming a self-sustaining cycle that sustains chronic pain[6,7,8]. Emerging evidence identifies HIF-1α as a key upstream regulator that coordinates inflammatory and oxidative responses in neuropathic conditions[9,10]. Network pharmacology screening identified HIF-1α as the sole common target for both TMP and TN, suggesting a novel mechanistic link not reported previously.

Based on this finding, we hypothesize that TMP alleviates TN by modulating HIF-1α signaling, thereby reducing neuroinflammation and oxidative stress. The study aims to experimentally validate this pathway, addressing a key gap in TMP's analgesic mechanism and supporting HIF-1α as a potential therapeutic target for TN.

2. Materials and Methods

2.1. Animals and Ethics

Adult male Sprague-Dawley rats (200–220 g) were housed under standard conditions. All procedures were approved by the Institutional Animal Care and Use Committee and conducted in accordance with ethical guidelines.

2.2. CCI-ION Model and Experimental Groups

CCI-ION was used to model trigeminal neuropathic pain. Under pentobarbital anesthesia (40 mg/kg, i.p.), the right infraorbital nerve was exposed and loosely ligated with two chromic gut sutures (4-0). Sham-operated rats underwent nerve exposure without ligation.

Two independent experiments were conducted. Experiment 1 (Dose–response): CCI-ION rats (n = 6 per group) received daily intraperitoneal injections for 14 days of vehicle (Model), TMP at 20, 40, or 80 mg/kg, or carbamazepine (CBZ) 50 mg/kg. A Sham+Vehicle group served as control. Experiment 2 (Mechanism): Rats were divided (n = 6 per group) into Sham+Vehicle, CCI-ION+Vehicle, and CCI-ION+TMP (80 mg/kg), administered as in Experiment 1.

2.3. Behavioral Assessment

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Mechanical hyperalgesia was assessed with von Frey filaments applied to the ipsilateral vibrissal pad. The 50% withdrawal threshold was determined pre-surgery (baseline) and on postoperative days 1, 3, 5, 7, 9, 11, and 13 by an experimenter blinded to group allocation.

2.4. Network Pharmacology

Potential TMP targets were retrieved from TCMSP and SwissTargetPrediction, while disease-related targets for trigeminal neuralgia were obtained from GeneCards and OMIM. A Venn analysis identified HIF-1α as the only overlapping target.(Due to heterogeneity in data sources and uncertainties in the predictive tools, network pharmacology analysis has limitations, and the obtained set of targets represents preliminary hypotheses that require validation with experimental data).

2.5. Molecular Analyses

On day 15, ipsilateral TG were collected for analysis.

RT-qPCR: Total RNA was extracted, reverse-transcribed, and amplified with SYBR Green. Gene expression (HIF-1α, IL-1β, TNF-α, MnSOD, and CAT) was normalized to GAPDH and quantified by the 2^−ΔΔCt method.

Western blot: Protein lysates were subjected to SDS-PAGE, transferred to PVDF membranes, and probed with antibodies against HIF-1α, IL-1β, TNF-α, MnSOD, CAT, and β-actin (loading control). Band intensities were quantified with ImageJ.

MDA assay: Lipid peroxidation in TG homogenates was measured using a commercial TBARS (thiobarbituric acid reactive substances) assay kit.

2.6. Histopathological Assessment

Immunohistochemistry: Paraffin-embedded TG sections were stained with an anti-IBA-1 antibody to visualize activated microglia. Positive cells were counted in three randomly selected high-power fields (HPFs) per sample.

LFB staining: Myelin integrity in the infraorbital nerve was assessed on paraffin sections using Luxol Fast Blue staining.

2.7. Statistical Analysis

Data are presented as mean ± SEM. Mechanical pain thresholds were analyzed using a two-way repeated-measures ANOVA. Intergroup comparisons were conducted with a one-way ANOVA followed by Tukey's post hoc test. $P < 0.05$ was considered statistically significant. All analyses were performed with GraphPad Prism 8.0.

3. Results

3.1 Network Pharmacology Identifies HIF-1α as a Key Target

Potential targets of TMP were screened using network pharmacology. We retrieved three TMP targets and 886 TN-related targets from public databases. Venn diagram analysis showed that HIF-1α was the only overlapping target between the two sets (Fig. 1A). The high specificity of this overlap suggests that HIF-1α may mediate TMP's effects and was designated as the core target for subsequent mechanistic studies.

A

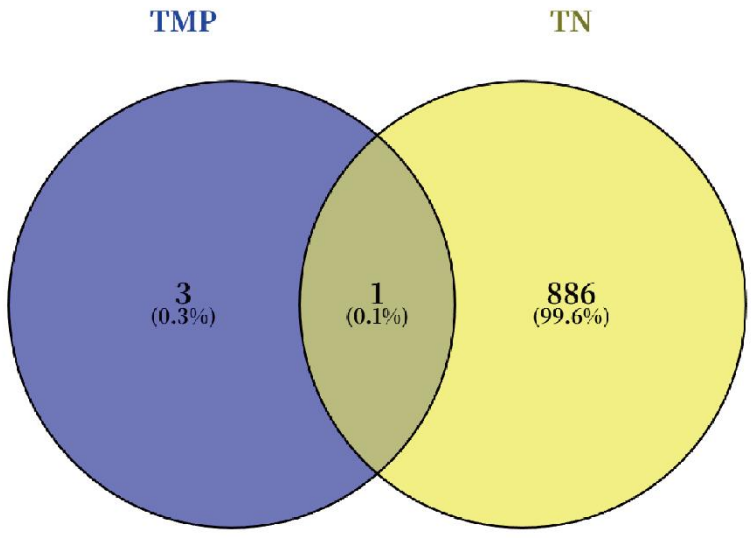

Figure 1. Venn diagram of the targets of TMP and TN. There are 3 targets for TMP and 886 targets for TN, with one overlapping target—HIF-1α.

3.2 TMP Attenuates Pain Behavior in a Dose-Dependent Manner

CCI-ION surgery produced a sustained decrease in mechanical pain threshold relative to the sham group, confirming successful model establishment. TMP elicited dose-dependent analgesia. The 20 mg/kg dose yielded minimal, transient effects, whereas the medium (40 mg/kg) and high (80 mg/kg) doses, as well as CBZ (50 mg/kg), significantly elevated pain thresholds from day 5 post-surgery onward. The 80 mg/kg TMP dose produced the strongest effect, with analgesic potency similar to CBZ ($p < 0.001$; Fig. 2A). Based on this profile, the 80 mg/kg dose was selected for subsequent mechanistic investigation.

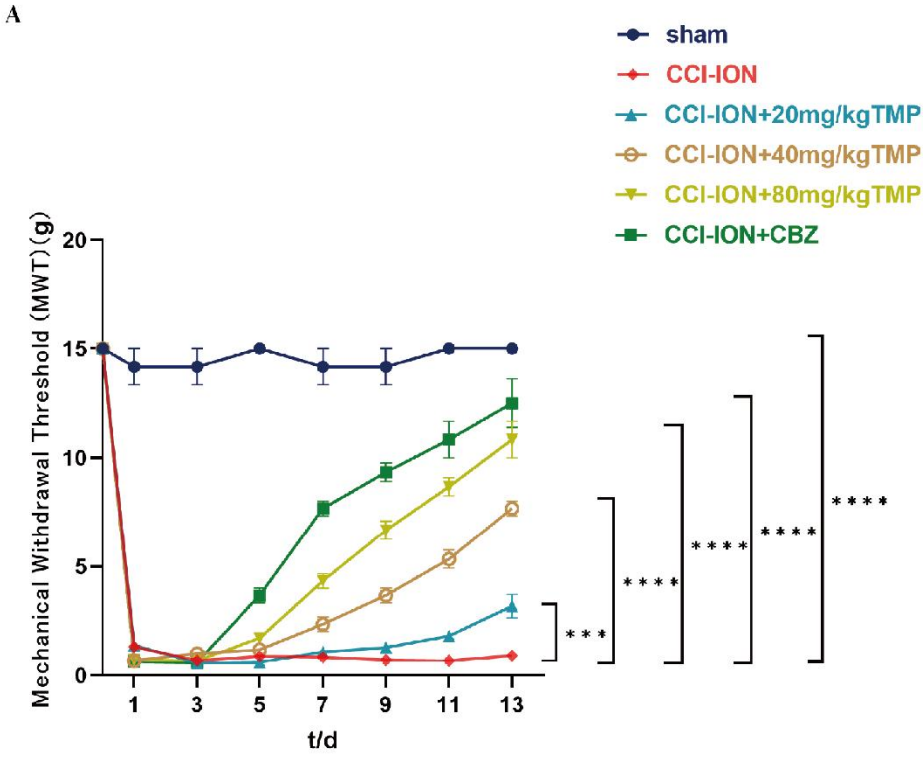

Figure 2. TMP alleviates CCI-ION-induced mechanical hyperalgesia in a dose-dependent manner. The line graph shows the changes in mechanical pain threshold in the rat infraorbital nerve area over time. Sham: sham surgery group; CCI-ION: model group; 20/40/80 TMP: model + TMP (20/40/80 mg/kg) treatment groups; CBZ: CBZ positive control group. Data are presented as mean ± SD, n = 6. ***$p < 0.001$, ****$p < 0.0001$.

3.3 TMP Suppresses the HIF-1α Pathway and Neuroinflammation

To clarify TMP's dose–response relationship with HIF-1α and its downstream inflammatory factors, we assessed related molecule expression in the TG across experimental groups. Both qPCR and Western blot showed that the CCI-ION model significantly upregulated HIF-1α, IL-1β, and TNF-α mRNA and protein levels. TMP reversed this upregulation in a dose-dependent manner. The 80 mg/kg dose produced the strongest inhibition ($P < 0.0001$), comparable to CBZ ($P > 0.05$). The 40 mg/kg dose also yielded a significant reduction ($P < 0.001$), while the 20 mg/kg dose had a weaker effect ($P < 0.01$) (Fig. 3A–F). Collectively, these results indicate that TMP inhibits HIF-1α expression and the downstream neuroinflammatory response in the TG in a dose-dependent manner, with 80 mg/kg identified as the optimal effective dose.

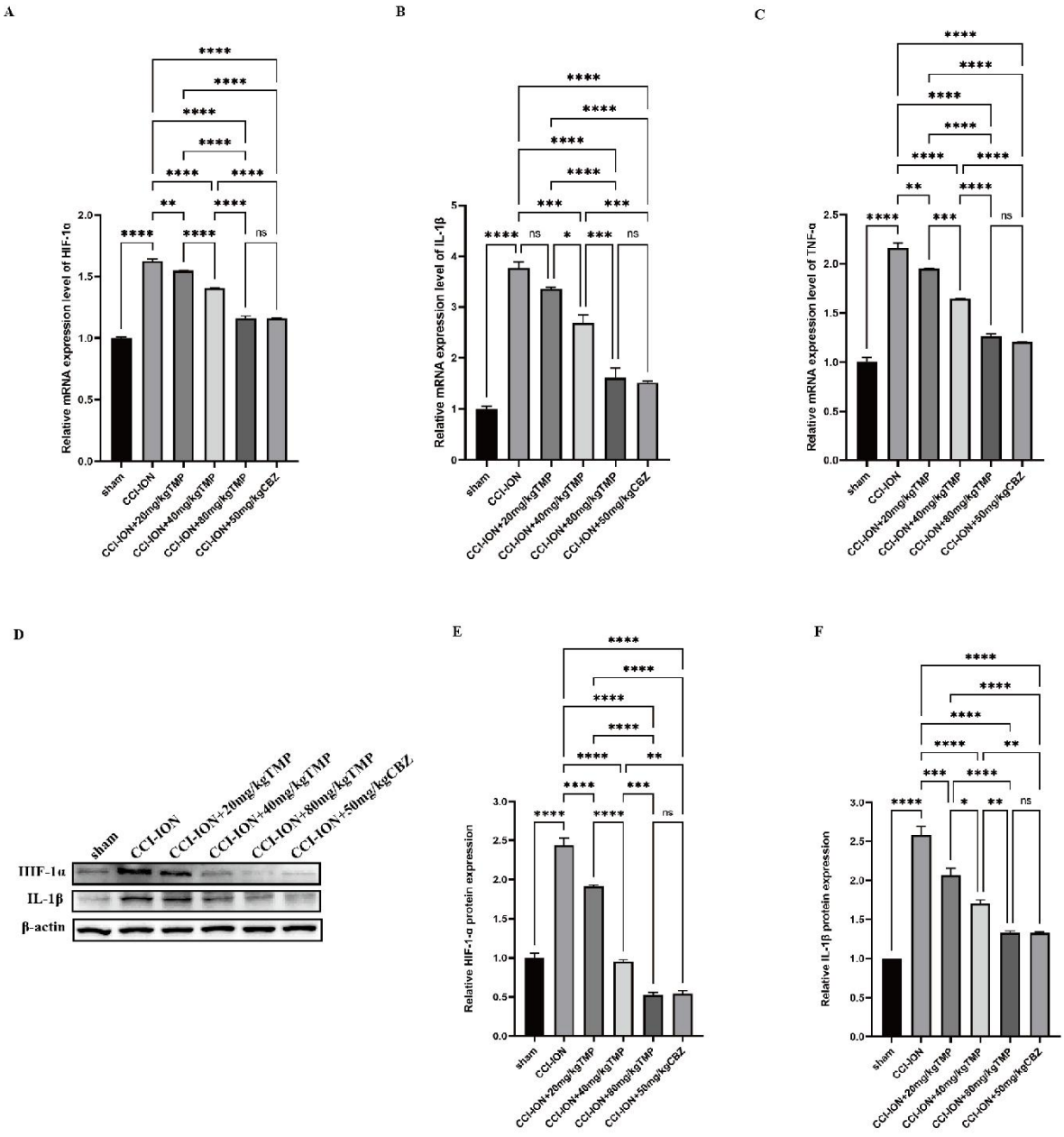

Figure 3. Effects of different concentrations of TMP on the mRNA and protein expression of HIF-1α and inflammatory factors in the TG. (A-C) Relative mRNA expression levels of HIF-1α (A), IL-1β (B), TNF-α (C) in the TG detected by qPCR. (D-F) Protein expression levels of HIF-1α and IL-1β in the TG detected by Western Blot and corresponding quantitative graphs (E, F). Data are presented as mean ± SD, *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

3.4 TMP (80 mg/kg) Effectively Reverses CCI-ION-Induced Mechanical Hyperalgesia

To validate the behavioral efficacy of the optimal TMP dose (80 mg/kg), we measured mechanical pain thresholds in sham, model, and TMP-treated groups over 14 days. The sham group maintained a stable threshold throughout. The CCI-ION model group showed a persistent reduction in pain threshold from day 1 ($p < 0.0001$), indicating sustained hyperalgesia. TMP at 80 mg/kg significantly increased the pain threshold from day 7 onward, with the effect progressively strengthening and peaking on day 14 ($p < 0.0001$; Fig. 4A). These results demonstrate that 80 mg/kg TMP effectively reverses established mechanical hyperalgesia in CCI-ION rats.

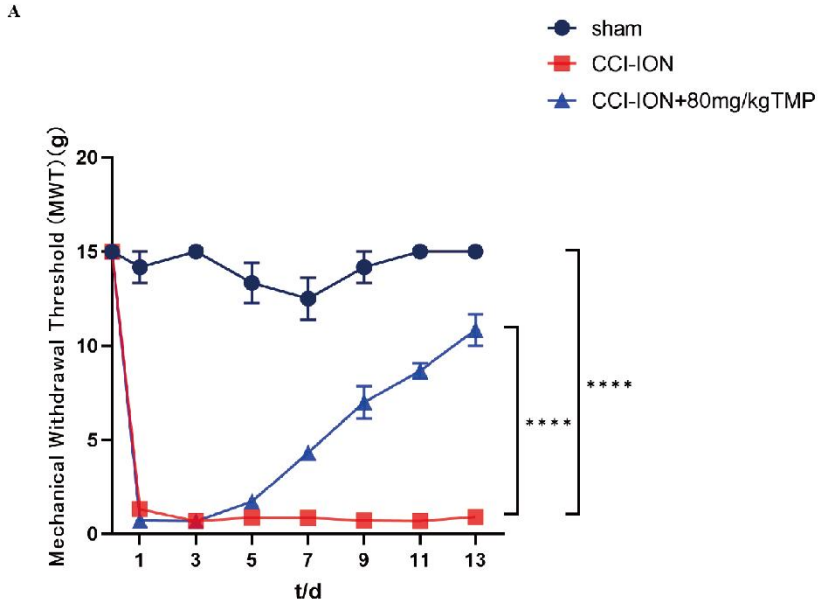

Figure 4. 80 mg/kg TMP alleviates CCI-ION-induced mechanical hyperalgesia. 1) The pain threshold in the CCI-ION group was significantly lower than that in the Sham group, indicating successful modeling. 2) The TMP-80 mg/kg group significantly alleviated mechanical hyperalgesia in rats. Data are presented as mean ± SD, n = 6. ***p < 0.001, ****p < 0.0001.

3.5 TMP Inhibits HIF-1α Expression and Attenuates Neuroinflammation in the Trigeminal Ganglion

To validate the anti-inflammatory mechanism of the optimal TMP dose (80 mg/kg), we assessed HIF-1α and downstream cytokine expression after TMP treatment. Both qPCR and Western blot showed that CCI-ION surgery significantly upregulated HIF-1α at the mRNA and protein levels, an effect markedly reversed by TMP ($P < 0.001$; Fig. 5A–C). Consistently, the pro-inflammatory cytokines IL-1β and TNF-α were substantially increased in the model group and effectively suppressed by TMP ($P < 0.01$; Fig. 5D–H). These findings indicate that TMP's anti-inflammatory effects are linked to the inhibition of HIF-1α expression and the attenuation of downstream neuroinflammatory signaling.

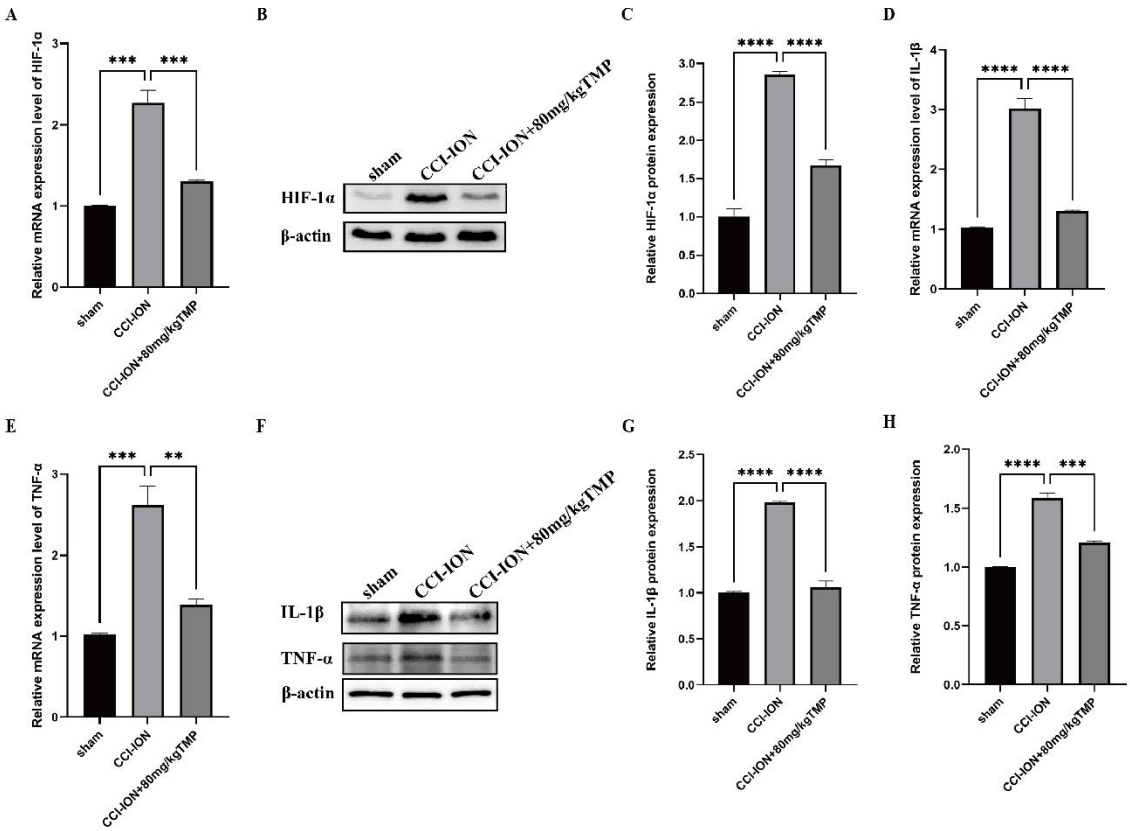

Figure 5. HIF-1α is a key target of TMP action; TMP downregulates the expression of pro-inflammatory factors in the TG . (A-C) qPCR (A) and Western Blot (B-C) detect the expression of HIF-1α at mRNA and protein levels in the TG. (D-E) qPCR results show that TMP reduces the mRNA levels of IL-1β (D) and TNF-α (E). (F-G) Western Blot and quantitative analysis synchronously show that TMP reduces the protein levels of IL-1β (G) and TNF-α (H). Data are presented as mean ± SD, **p < 0.01, ***p < 0.001, ****p < 0.0001 .

3.6 TMP Ameliorates Oxidative Stress in the Trigeminal Ganglion

To determine whether TMP ameliorates oxidative stress, we measured malondialdehyde (MDA) levels and the expression of key antioxidant enzymes (CAT, MnSOD) in the TG. CCI-ION injury significantly increased MDA content, while TMP (80 mg/kg) reduced MDA accumulation ($p < 0.01$; Fig. 6A). Concurrently, CAT and MnSOD mRNA and protein levels were suppressed in the model group, and TMP administration effectively restored their expression ($p < 0.01$; Fig. 6B–F). These findings indicate that alleviating local oxidative stress is an additional mechanism underlying TMP's analgesic effect, possibly linked to modulation of HIF-1α and downstream antioxidant pathways.

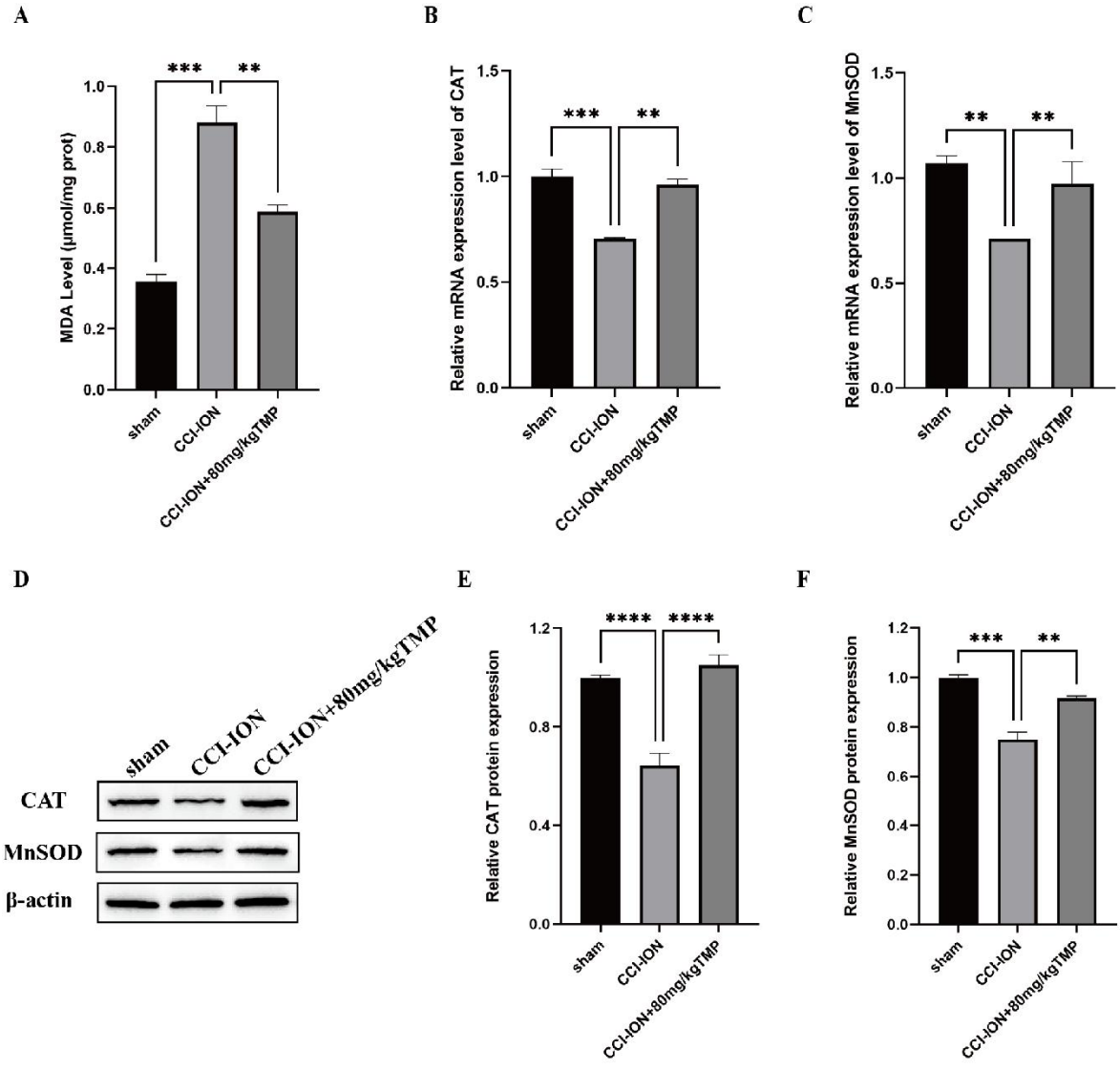

Figure 6. TMP restores antioxidant defenses and alleviates oxidative damage in the TG .(A) Biochemical assay detection of the lipid peroxidation end product MDA content in the TG. (B-C) qPCR detection of mRNA expression levels of the core antioxidant enzymes (B) CAT and (C) MnSOD in the TG. (D-F) Western Blot synchronously detects the protein expression levels of the core antioxidant enzymes CAT and MnSOD in the TG. Data are presented as mean ± SD , **p < 0.01, ***p < 0.001, ****p < 0.0001.

3.7 TMP Suppresses Immune Cell Activation in the Trigeminal Ganglion and Improves Myelin Integrity

To further assess the neuroinflammatory and structural consequences of CCI-ION, we evaluated microglial activation in the TG and myelin integrity in the infraorbital nerve. Immunohistochemistry showed a marked increase in IBA-1–positive microglia in the model group, which TMP (80 mg/kg) significantly reduced ($p < 0.01$; Fig. 7A, C). LFB staining revealed

severe demyelination in the infraorbital nerve of model rats, with disrupted structure and reduced staining. TMP markedly preserved myelin integrity and attenuated demyelination ($p < 0.01$; Fig. 7B, D). Collectively, these findings indicate that TMP mitigates neuroinflammation and protects nerve structure after CCI-ION.

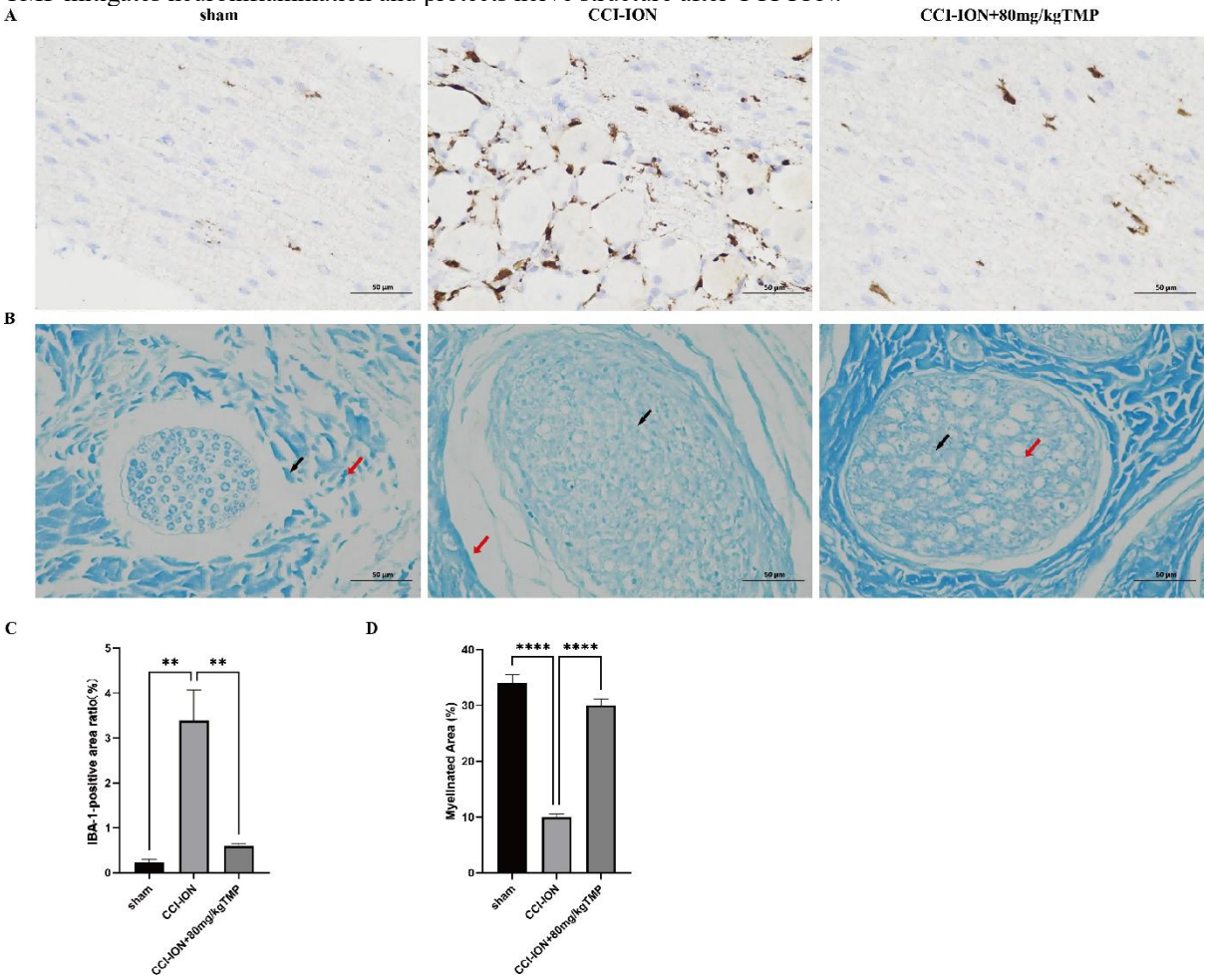

Figure 7. TMP suppresses immune cell activation in the TG and alleviates infraorbital nerve demyelination. (A) Representative immunohistochemical images showing IBA-1$^+$ microglia (brown) in the TG (scale bar, 50 μm). (B) Representative LFB staining of the infraorbital nerve; dark blue indicates intact myelin (red arrows), while pale areas indicate demyelination or tissue gaps (black arrows) (scale bar, 50 μm). (C) Quantification of IBA-1 positive area ratio.(D) Quantification of myelinated area percentage.Data are presented as mean ± SD , **$p < 0.01$, ****$p < 0.0001$.

4. Discussion

This study shows that TMP alleviates TN in a CCI-ION rat model. It primarily achieves this by targeting HIF-1α and by modulating interconnected neuroinflammatory and oxidative stress pathways. Although TMP's anti-inflammatory and antioxidant properties are well documented in other diseases [3,4,5], our results provide new evidence that HIF-1α acts as a pivotal upstream regulator through which TMP coordinates these effects in TN.

Network pharmacology predicted HIF-1α as the sole shared target for TMP and TN, guiding our experimental focus. We observed a dose-dependent analgesic effect of TMP, with 80 mg/kg achieving efficacy comparable to carbamazepine. Importantly, TMP inhibited HIF-1α expression and its downstream pro-inflammatory cytokines IL-1β and TNF-α in a clear dose-dependent manner. The parallel of behavioral improvement and molecular changes suggests that HIF-1α inhibition is a central mechanism of TMP's analgesic action in TN. Additionally, TMP reduced microglial activation and demyelination—key features of TN—likely by mitigating the neuroinflammatory and oxidative stress milieu.

Our findings reveal a hierarchical regulatory role for HIF-1α in TMP's action. HIF-1α, a known integrator of cellular stress signals, is upregulated in the trigeminal ganglion in our model, likely reflecting pathology beyond hypoxia and potentially driven by inflammation and ROS [11]. We propose that TMP suppresses HIF-1α, thereby disrupting a positive feedback loop. HIF-1α can directly upregulate pro-inflammatory genes such as IL-1β and TNF-α [12,13] and can synergize with NF-κB signaling [14]. Our observation that TMP reduces both HIF-1α and these cytokines supports this mechanism.

Concurrently, TMP restored the expression of antioxidant enzymes CAT and MnSOD. This effect aligns with the documented crosstalk between HIF-1α and the Nrf2 pathway; chronic HIF-1α activation can suppress Nrf2-driven transcription and antioxidant defenses [15]. Accordingly, TMP may enhance cellular antioxidant capacity by inhibiting HIF-1α and relieving Nrf2 suppression. The marked reduction in MDA levels confirms an improved oxidative stress status. The interplay between neuroinflammation and oxidative stress is cyclical [16]: for example, TNF-α induces ROS

[17,18], while ROS activate inflammasomes such as NLRP3 to amplify IL-1β release [19]. TMP's effect at the HIF-1α node likely disrupts this cycle, helping to explain the observed histological improvements.

These findings should be contextualized within TMP's well-established multi-target pharmacology, which includes blocking voltage-gated calcium channels and improving microcirculation [20,21]. The HIF-1α–driven mechanism identified here may act synergistically with these effects, contributing to an integrated network that mitigates neuropathic pain.

Despite these insights, this study has several limitations. First, the small sample size and short observation period limit interpretation and underscore the need for validation in larger, long-term studies. More importantly, although this study aims to explore potential mechanisms rather than validate the network pharmacology approach itself, our pharmacological data identified only one overlapping target, a result that may stem from database biases, tool limitations, or incomplete information. Therefore, a definitive causal relationship between TMP and efficacy still needs to be directly validated by HIF-1α activators or siRNA-rescue experiments to establish the necessity of this target. Finally, the precise upstream signaling by which TMP inhibits HIF-1α (for example, PI3K/Akt/mTOR) remains an open question for future investigation.

5. Conclusion

This study shows that TMP alleviates trigeminal neuralgia in a CCI-ION rat model by dose-dependent inhibition of HIF-1α. By targeting HIF-1α, TMP concurrently reduces neuroinflammation and oxidative stress, two key drivers of TN pathology. These findings illuminate a novel mechanism underlying TMP's analgesic effect and identify HIF-1α as a promising target for neuropathic pain.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

Acknowledgments A

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