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Original Article

The role of transient receptor potential vanilloid 1 (TRPV1) in *Candida albicans* infection-induced oral burning sensation: Evidenced from mouse and zebrafish models

Hyeon Mi Sung [a], Eun Young Choi [a], Ji-Young Joo [b,c], Hae Ryoun Park [d], Soo-Min Ok [b,e*], Chang-Kyu Oh [a**]

[a] *Department of Biochemistry, School of Medicine, Pusan National University, Yangsan-si, Gyeongsangnam-do, Republic of Korea*
[b] *Department of Oral Medicine, Dental Research Institute, Pusan National University Dental Hospital, Yangsan-si, Gyeongsangnam-do, Republic of Korea*
[c] *Department of Periodontology, School of Dentistry, Pusan National University, Yangsan-si, Gyeongsangnam-do, Republic of Korea*
[d] *Department of Oral, Pathology, School of Dentistry, Pusan National University, Yangsan, Republic of Korea*
[e] *Department of Oral Medicine, Dental and Life Science Institute, School of Dentistry, Pusan National University, Yangsan-si, Gyeongsangnam-do, Republic of Korea*

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Zebrafish

Abstract *Background/Purpose:* Burning sensation in the oral cavity impairs quality of life, with *Candida albicans* infection identified as a potential cause due to its inflammatory effects. This study examines the role of the transient receptor potential vanilloid 1 (TRPV1) ion channel in mediating *C. albicans*-induced burning sensations using clinical data, mouse models, and zebrafish embryos.
Materials and methods: Tongue pain intensity in 173 patients was assessed using the Numerical rating scale (NRS, 0–10) before and after nystatin treatment. Mice were infected with *C. albicans* under immunosuppression, and TRPV1 expression in trigeminal ganglia was analyzed via immunohistochemistry and Quantitative real-time PCR. Zebrafish embryos were microinjected with *C. albicans* to evaluate *trpv1(Zebrafish ortholog)* expression using in situ hybridization.

* Corresponding author. Department of Oral Medicine, School of Dentistry, Pusan National University, 49 Busandaehak-ro, Yangsan 50612, Republic of Korea.
** Corresponding author. Department of Biochemistry, School of Medicine, Pusan National University, 49 Busandaehak-ro, Yangsan 50612, Republic of Korea.
E-mail addresses: oksoomin@pusan.ac.kr (S.-M. Ok), ck1988@pusan.ac.kr (C.-K. Oh).

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Results: Patients with elevated *C. albicans* CFU levels showed higher NRS scores, which improved following nystatin treatment. Infected mice displayed nerve damage and increased TRPV1 expression in trigeminal ganglia. Zebrafish embryos also showed *trpv1* upregulation, confirming infection-induced neuroinflammation.
Conclusion: *C. albicans* infection induces oral burning sensations by increasing TRPV1 expression. Targeting TRPV1 may offer a new therapeutic approach for managing infection-related oral pain.

Introduction

Burning sensation refers to an uncomfortable or painful feeling of warmth or tingling that can occur in various parts of the body.[1–3] It often manifests as a continuous or intermittent sensation of heat or burning, ranging from mild discomfort to severe pain.[1] The causes of burning sensations are diverse, including neuropathic conditions, inflammatory responses, infections, and chemical irritants.[4–7] For example, neuropathic disorders such as diabetic neuropathy often produce burning pain due to nerve damage, while inflammatory conditions like eczema or allergic reactions can provoke a similar sensation in affected areas.[8] Psychological factors, such as anxiety or stress, are also known to exacerbate burning sensations by influencing pain perception pathways.[9–11] These sensations, triggered by various factors, can occur in many parts of the body, including the oral cavity.[2,9]

Candida albicans, a frequent fungal colonizer in the oral cavity,[12] is known to cause infections that may lead to inflammation and peripheral nerve damage, particularly in immunocompromised individuals.[13,14] Several studies report that Candida-related neuropathy occurs due to fungal toxins or inflammatory mediators that disrupt nerve function, though this has primarily been observed in systemic infections.[15,16] Daan R. M. G. Ophelders et al. suggested that intra-amniotic *C. albicans* infection triggers systemic and neuroinflammatory responses, leading to white matter injury in fetal brains. While fluconazole reduced systemic inflammation and fetal mortality, it did not prevent brain inflammation or white matter injury.[14] Cody L. Nathan et al. summarized that various fungal infections, including *C. albicans*, can affect the central nervous system.[17]

Neuropathic pain and conditions such as Burning Mouth Syndrome are increasingly linked to the involvement of transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1) ion channels.[18–20] TRPV1, also known as the capsaicin receptor, is an ion channel on sensory neurons that plays a crucial role in pain modulation, especially under neuroinflammatory conditions.[19,21,22] TRPV1 is typically activated by heat, acidic pH, and certain chemicals, including capsaicin, leading to depolarization and action potential firing in nociceptive neurons.[23–26] Research has shown that TRPV1 expression can increase significantly in response to chronic inflammation and neuropathic conditions, contributing to heightened pain sensitivity. Although TRPV1 is of considerable interest in studying neuropathic pain mechanisms, the lack of ideal in vivo models for neural experiments on TRPV1 limits further direct experimentation in neuropathic contexts.

The transparency of zebrafish embryos makes them an excellent model for observing neural damage and peripheral nerve changes through methods such as whole-mount in situ hybridization (WISH) and immunohistochemistry.[27–30] These features have made zebrafish embryos popular in neuroscience research, as they allow researchers to visually confirm cellular responses to various treatments or conditions, providing a valuable system for studying neural responses. Previously, we demonstrated alterations in peripheral nerves following genetic manipulation of zebrafish embryos to investigate the function of npy in diabetic neuropathy.[27]

In this paper, we investigated the potential link between *C. albicans* infection and burning sensation in the oral cavity using the patient data, mouse models, and zebrafish embryos. By examining TRPV1 expression and applying nystatin treatment in the patients, we aimed to clarify the role of Candida infection in oral burning sensations and assess the viability of TRPV1 as a target for therapeutic intervention in the infection-related neuropathic pain.

Material and methods

Patients experiments

This study included 173 consecutive patients with tongue pain (June 2018–November 2019), approved by the Ethics Review Committee of Pusan National University Dental Hospital (PNUDH-2017-026). At the initial examination, *C. albicans* detection was performed using Sabouraud agar.[31] Tongue surface samples were collected with sterilized cotton swabs and cultured at 37 °C for 48 h. Participants with $\leq 10^3$ CFU/mL were considered *C. albicans* -negative (Group A), while those with $>10^3$ CFU/mL were *C. albicans* -positive (Group B). Borderline results (10^3 CFU/mL) were included in Group B due to candidiasis risk.[32] All Group B patients received antifungal treatment with nystatin suspension. Diagnostic assessments included oral examination, panoramic radiography, *C. albicans* culture testing, salivary flow rate measurements (unstimulated and stimulated saliva), and interviews. Tongue pain intensity was evaluated using the NRS. All Group B patients received antifungal treatment with nystatin suspension (10, 000, 000 U/100 mL, 5 mL, 4 times daily). Patients were instructed to spread the

gel throughout the mouth, hold it as long as possible, and swallow. Treatment continued for at least two weeks. Pain improvement was assessed based on the NRS after treatment completion, when *C. albicans* was no longer detectable.[33]

Maintenance of *C. albicans* strains and growth conditions

A single *C. albicans* colony from YPD agar (1 % yeast extract, 2 % peptone, 2 % dextrose, 1.5 % agar) was inoculated into YPD broth and incubated at 30 °C for 24 h (180 rpm). Cells were centrifuged, washed, and resuspended in PBS. The optical density (OD_{570}) was measured to determine concentration.

Inoculation procedure using mouse model

Animal protocols adhered to IACUC guidelines (2022-060-A1C1). Male BALB/c mice (6—8 weeks, 20—22 g) were immunosuppressed with cortisone acetate (4 mg, subcutaneously) and tetracycline (0.5 mg/mL in water) from one day before inoculation. Mice were anesthetized with Zoletil and Rompun before oral inoculation of *C. albicans* suspension (2.5×10^7 viable cells/mL) via swabs held in the oral cavity for 90 min.[34] The process was repeated on day six to maintain fungal burden.

Hematoxylin and eosin staining

Tongue tissues were collected, fixed in 4 % formaldehyde for 24 h at room temperature, embedded in paraffin, and sectioned at 5 μm thickness. Sections were mounted on slides, deparaffinized in xylene (5 min, twice), and rehydrated through a graded ethanol series (100 %, 95 %, 70 %, 50 %). Rehydrated sections were stained with Mayer's hematoxylin for 8 min, rinsed in tap water for 10 min, and optionally differentiated in 0.3 % acid alcohol for 1 min. Slides were "blued" in Scott's tap water substitute or 0.1 % ammonium hydroxide for 2 min, rinsed, and counterstained with 1 % alcoholic eosin Y for 2 min. Sections were rinsed, dehydrated, cleared in xylene (3 min, twice), and mounted with DPX medium.

Periodic acid-Schiff staining

Tissues fixed in 10 % formalin were paraffin-embedded, sectioned (5 μm), deparaffinized, and rehydrated. Slides were oxidized in 0.5 % periodic acid for 10 min, treated with Schiff reagent for 15 min, rinsed in tap water, and counterstained with Mayer's hematoxylin. Sections were dehydrated, cleared in xylene, and mounted.

Immunohistochemistry

Sections were deparaffinized, rehydrated, and subjected to antigen retrieval in citrate buffer (pH 6.0) at 95 °C for 20 min. Endogenous peroxidase was blocked using 3 % hydrogen peroxide in methanol for 10 min, followed by blocking in 5 % BSA/PBS for 30 min. Primary antibody (p—NF—H, Thermo Fisher) was applied overnight at 4 °C, followed by incubation with a biotinylated secondary antibody for 30 min. Visualization was achieved using 3,3′-diaminobenzidine (DAB), and slides were counterstained, dehydrated, and mounted.

Quantitative real-time polymerase chain reaction

Total RNA from zebrafish embryos was extracted with TRIzol reagent (Invitrogen, Waltham, MA, USA), reverse-transcribed using SuperScript IV (Thermo Fisher Scientific, Waltham, MA, USA), and analyzed via quantitative real-time polymerase chain reaction using PowerUp SYBR Green Master Mix (Thermo Fisher Scientific, Waltham, MA, USA). Expression levels were normalized to β-actin as the control.

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) reagent (5 mg/mL in PBS) was added to treated cells and incubated at 37 °C for 1 h. After removing the reagent, 100 μL of DMSO was added to dissolve formazan crystals, and absorbance was measured at 540 nm.

Maintenance of adult zebrafish and embryos and infection

Wild-type adult zebrafish (provided by IBS, CGI, South Korea) were maintained in an automated aquarium system (Techniplast, Maggio, Italy) at 28.5 °C with a 14-h light/10-h dark cycle (pH 7.0, electrical conductivity: 1000 μS), following the IACUC guidelines from Pusan National University (PNU-2023-0359). Embryos collected at 0.5 hpf were microinjected with *C. albicans* (10^5—10^7 CFU/mL) in the yolk using a Femtojet 4i microinjector (Eppendorf, Hamburg, Germany).

Whole-mount in situ hybridization

Embryos were fixed in 4 % paraformaldehyde (PFA), dehydrated in methanol, and treated with acetone at −20 °C. After washing, embryos were incubated in hybridization buffer (50 % formamide, 5 × SSC, 500 μg/mL torula RNA, 50 μg/mL heparin, 0.1 % Tween-20, 9 mM citric acid) at 65 °C for 2 h. They were then incubated with an anti-DIG trpv1 (Zebrafish ortholog) probe in hybridization buffer at 65 °C for 2 days. Post-hybridization, embryos were washed and incubated in blocking solution (2 % heat-inactivated goat serum, 2 mg/mL BSA in PBT) for 2 h at room temperature. DIG-AP antibody (1:4000, Roche) was applied overnight at 4 °C. The signal was visualized using BCIP/NBT in AP buffer at room temperature, stopped with 1 mM EDTA/PBS, and cleared with methanol. Embryos were imaged in 3 % methylcellulose.

Statistical analysis of data

All experiments were conducted in triplicate. Results were analyzed using Student's t-test, with a P-value <0.05 considered statistically significant. Data are presented as

mean ± standard error of the mean (SEM), unless otherwise specified.

Results

A high titer of *C. albicans* is associated with a burning sensation in oral burning sensation patients

One hundred seventy-three patients who visited Pusan National University Dental Hospital were divided into Group A ($\leq 10^2$ CFU) and Group B ($\geq 10^3$ CFU) based on colony-forming units (CFU) (Fig. 1A, Table 1). Aside from the *C. albicans* count, both groups exhibited a similar distribution of systemic diseases, including cardiovascular, gastrointestinal, immune, and psychiatric conditions (Table 1). However, when evaluating oral burning sensations using the NRS, Group B displayed a significantly higher mean NRS compared to Group A. These results suggest that patients with higher *C. albicans* counts experience more intense oral burning sensations (Fig. 1B).

C. albicans infection severity and treatment response

Following treatment with nystatin, we assessed the reduction in burning sensations among Group B patients, who had initially shown high *C. albicans* CFU levels (Fig. 2A). Approximately 75 % of these patients reported a recovery of more than 50 % in oral burning sensation after nystatin administration (Fig. 2B). However, treatment responses varied, indicating differences in individual effectiveness. The proportion of patients reporting an 80 % or greater reduction in burning sensation was higher in those with elevated *C. albicans* titers ($\geq 10^5$ CFU) (Fig. 2C).

Infection of *C. albicans* is confirmed through histological experiments

To establish an immunocompromised mouse model, mice were provided water supplemented with ampicillin throughout the experiment. Additionally, 24 h prior to *C. albicans* strain inoculation on the tongue, the mice received a subcutaneous injection of cortisone acetate (Fig. 3A). The infection period lasted for 12 days, after which the mice were sacrificed for evaluation. Compared to control mice, *C. albicans* -infected mice exhibited visible white spots on their tongues (Fig. 3B). Histological validation was performed using H&E and **periodic acid-Schiff** (PAS) staining. Infected mice showed *C. albicans* colonies on their tongues through H&E staining (Fig. 3C). PAS staining corroborated these findings, highlighting fungal colonies consistent with H&E results (Fig. 3D).

A

	Dental fungal culture and identification test			
Group A	negative	10^1	10^2	
Group B	10^3	10^4	10^5	10^7

B

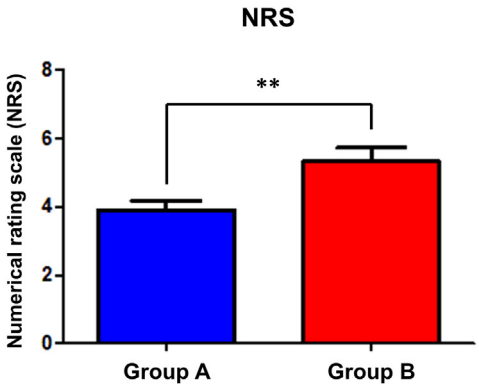

Figure 1 Association of elevated *C. albicans* titer with burning sensation in burning sensation in oral cavity patients (A) Table showing *C. albicans* CFU levels in group A and group B. (B) Graph illustrating the difference in NRS scores between group A and group B. *C. albicans*, *Candida albicans*, CFU, Colony-forming unit, NRS, Numerical rating scale.

Table 1 Patient characterization. Fisher's exact test and Mann—Whitney U test were used to analyze the data.

Variable	Group A Patients overall registered (N = 91)	Group B Patients overall registered (N = 82)	P value
Sex			
Female	62 (68)	66 (80)	0.0644
Male	29 (32)	16 (20)	
Age(years)			
Mean ± SD	58.1 ± 14.6	65 ± 11.5	
Age group (y), n (%)			
1—10	1 (1.1)	0 (0.0)	0.3173
11—20	0 (0.0)	1 (1.2)	0.3173
21—30	3 (3.3)	0 (0.0)	0.0833
31—40	6 (6.6)	2 (2.4)	0.1573
41—50	14 (15.4)	6 (7.3)	0.0736
51—60	22 (24.2)	19 (23.2)	0.6394
61—70	25 (27.5)	25 (30.5)	1
71—80	18 (19.8)	24 (29.3)	0.3545
>81	2 (2.2)	5 (6.1)	0.2568
Diagnosed with, *n(%)			
Negative	43 (47.3)		
101	41 (45.1)		
102	7 (6.4)		
103		37 (45.1))	
104		31 (37.8)	
105		13 (15.9)	
107		1 (1.2)	
Salivation rate			
Resting saliva	42.68	20.77	0.0059
Stimulated saliva	99.21	46.36	1.18E-05
Denture	10	19	0.0947
Comorbidities, n(%)			
Cardiovascular disease	41	38	0.7357
Gastrointestinal disease	4	10	0.1088
Immune disease	9	6	0.4386
Kidney disease	0	0	
Liver disease	5	1	0.1025
Musculoskeletal disorders	10	9	0.8185
Ocular disease	1	1	1
Psychiatric disease	5	8	0.4054
Respiratory diseases	0	3	0.0833
Urologic diseases	1	1	1
Alcoholism	4	3	0.7055

Infection of *C. albicans* induce TRPV1 signal in trigeminal ganglion

To investigate whether *C. albicans* infection induces nerve damage, immunohistochemical staining for phosphorylated neurofilament heavy chain (p—NF—H) was performed on tongue samples from both control and infected groups. A significant increase in p—NF—H signal intensity was observed in the tongues of the *C. albicans* -infected group (Fig. 4A). To assess additional markers of nerve injury, trigeminal ganglion cells were isolated and cultured ex vivo. While *C. albicans* infection did not alter nerve growth factor (NGF) mRNA levels, it significantly increased TRPV1 mRNA expression (Fig, 4).

To confirm whether *C. albicans* directly induces cellular damage in trigeminal ganglion cells, an MTT assay was performed, revealing reduced cell viability in the *C. albicans* -infected group compared to controls (Fig. 4C). In a zebrafish larvae model, *C. albicans* inoculation further validated these findings. WISH results demonstrated that higher *C. albicans* colony numbers corresponded with increased *trpv1* signals in the trigeminal ganglion of zebrafish larvae (Fig. 4). These findings collectively suggest that *C. albicans* infection may promote nerve

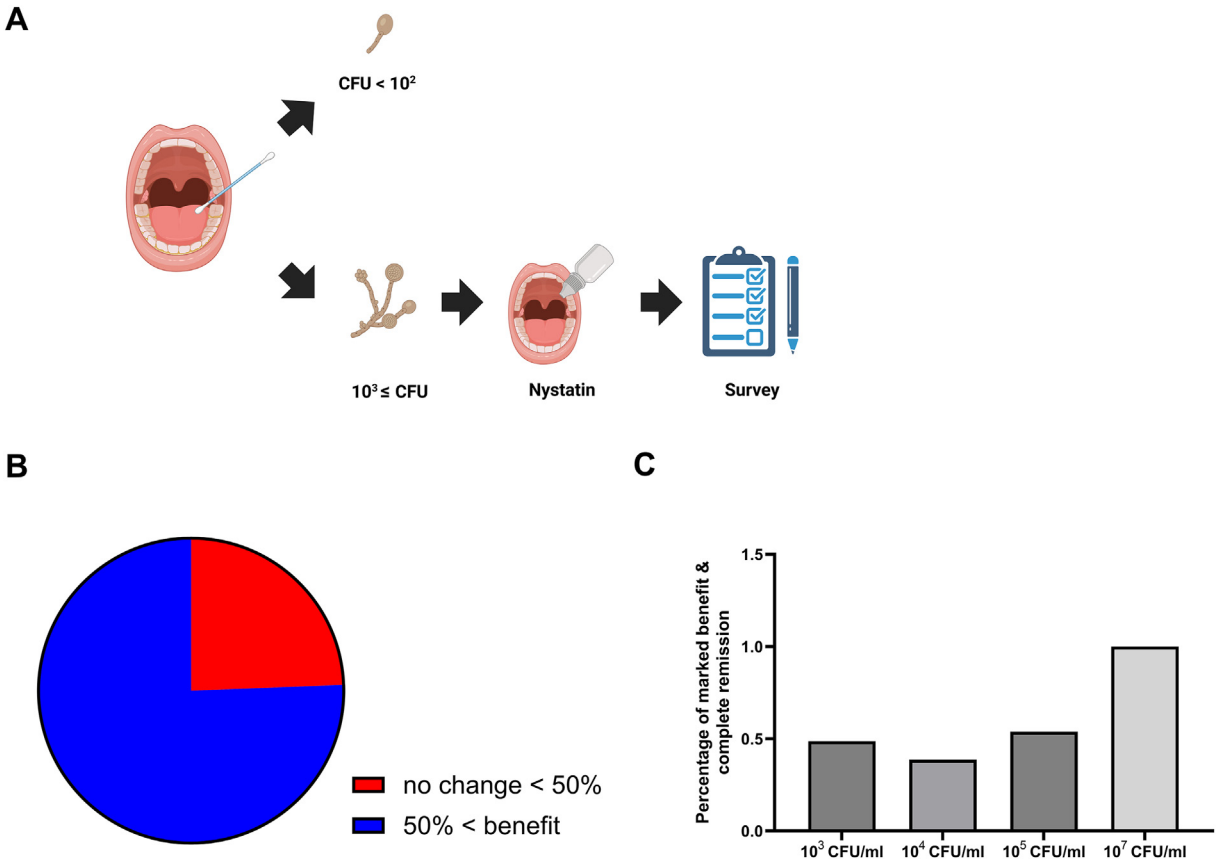

Figure 2 Nystatin reduced *C. albicans* infection-induced burning sensation in oral cavity (A) Scheme of patient's survey after nystatin treatment (B) Graph depicting the change in burning sensation in oral cavity in group B following nystatin treatment. (C) Bar graph showing the dose-dependent reduction in burning sensation following nystatin treatment across varying *C. albicans* concentrations. *C. albicans*, *Candida albicans*.

damage, as evidenced by TRPV1 upregulation across multiple models.

Discussion

Burning sensations in the oral cavity are a challenging condition for many patients, often occurring without a clear underlying cause, which underscores the importance of understanding its mechanisms for effective treatment.[2,35,36] Given the observed correlation between *C. albicans* levels and the severity of oral burning sensations, we hypothesized *C. albicans* infection contributes to this condition. Through clinical and experimental models, we found that high *C. albicans* levels were associated with increased oral burning sensations (Fig. 1), and nystatin treatment significantly alleviated symptoms in most patients (Fig. 2B). In zebrafish, *C. albicans* infection induced *trpv1* expression (Fig. 4D). These findings suggest *C. albicans* infection activate pain pathways via TRPV1.

TRPV1 is a well-known pain receptor extensively studied related to inflammatory pain and neurogenic inflammation.[18–21,23–26] It is activated by various stimuli, including heat, acidity, and chemical compounds, and is highly expressed in sensory neurons. Research has shown that TRPV1 plays a crucial role in mediating pain responses, particularly in conditions involving mucosal inflammation, such as burning sensations.[4,37,38] Inflammation and tissue damage can lead to the release of endogenous ligands that activate TRPV1, resulting in pain and burning sensations.[39,40] Studies have demonstrated that TRPV1 expression increases in inflamed tissues, suggesting that this receptor amplifies pain signals.[40] Our findings align with these studies, as we observed increased *trpv1* expression in *C. albicans* -infected zebrafish, implying that *C. albicans* infection may stimulate TRPV1 pathways (Fig. 4D), leading to enhanced oral burning sensations.

This study is the first to directly demonstrate that *C. albicans* induces burning sensations in the mouth by upregulating TRPV1 expression, as evidenced by animal models. While TRPV1 research in zebrafish embryos is limited, it provides valuable insights into conserved pain pathways across species. Unlike in mammals, where TRPV1 is activated by capsaicin, zebrafish *trpv1* responds to heat and pH changes, reflecting species-specific activation mechanisms. However, the upregulation of *trpv1* in the trigeminal ganglion of *C. albicans*-infected zebrafish parallels mammalian responses, suggesting a conserved role of TRPV1 in neuroinflammation-induced pain across species.

The increased *trpv1* expression in *C. albicans* -infected zebrafish embryos indicate that infection-induced neuroinflammation elevates *trpv1* expression, consistent with its

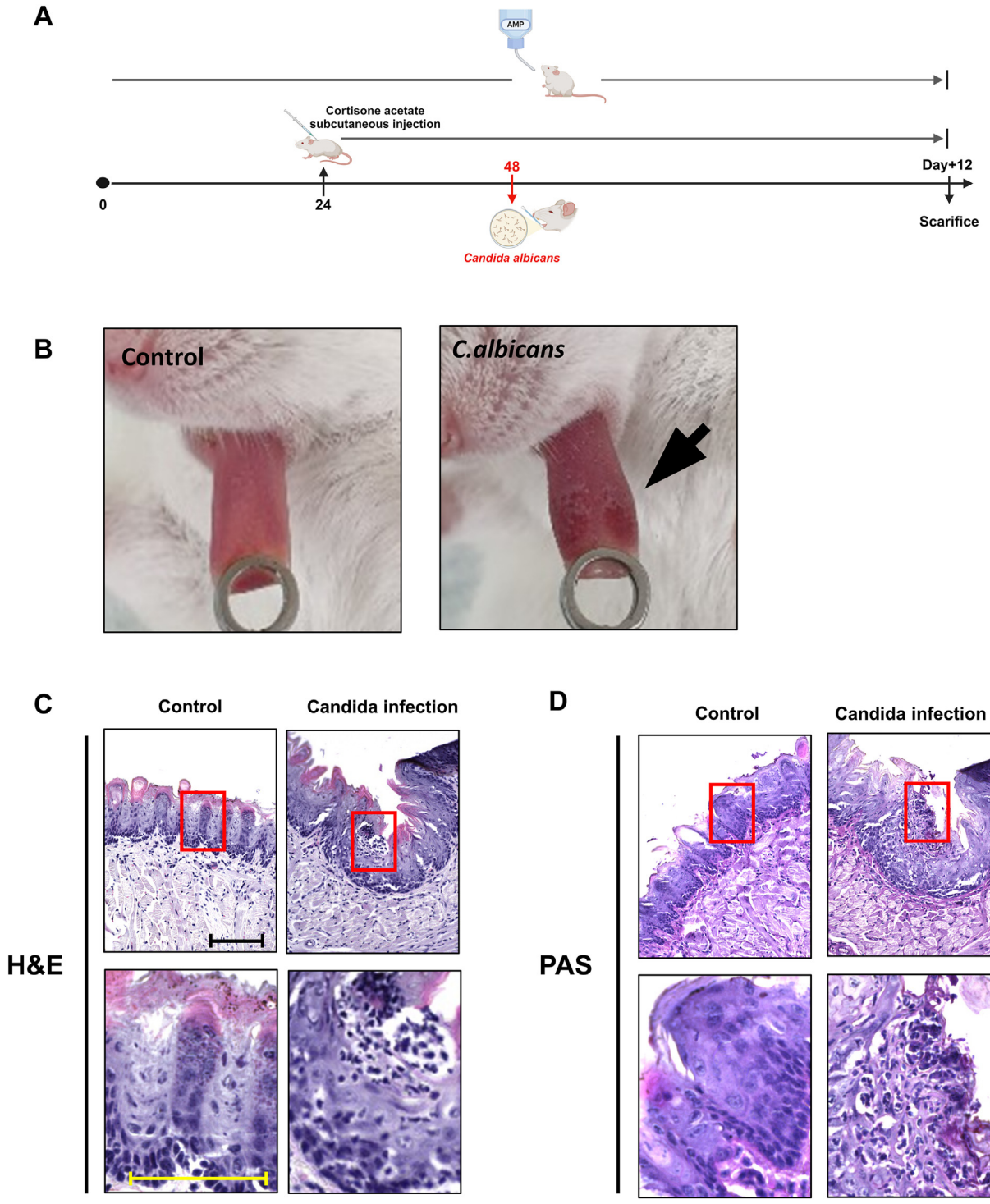

Figure 3 Confirmation of *C. albicans* infection via histological analysis (A) Schematic representation of the experimental protocol for *C. albicans* infection in mice. (B) Visual comparison of tongue appearance between control and *C. albicans*-infected mice (indicated by the arrow). Histological analysis of tongue tissues stained with Hematoxylin and eosin (H&E) staining (C) and Periodic acid-Schiff (PAS) staining (D) (indicated by the square). *C. albicans*, *Candida albicans*.

role in mediating pain responses. Our study provides evidence that TRPV1 contributes to pain perception and inflammatory responses across species, reinforcing its potential as a therapeutic target for infection-induced pain management. Peripheral nerve research is challenging due to the lack of suitable models for detailed spatial and quantitative analysis. Zebrafish embryos offer a unique advantage in studying peripheral nerves, as techniques like immunohistochemistry and WISH allow simultaneous assessment of both localization and expression levels of

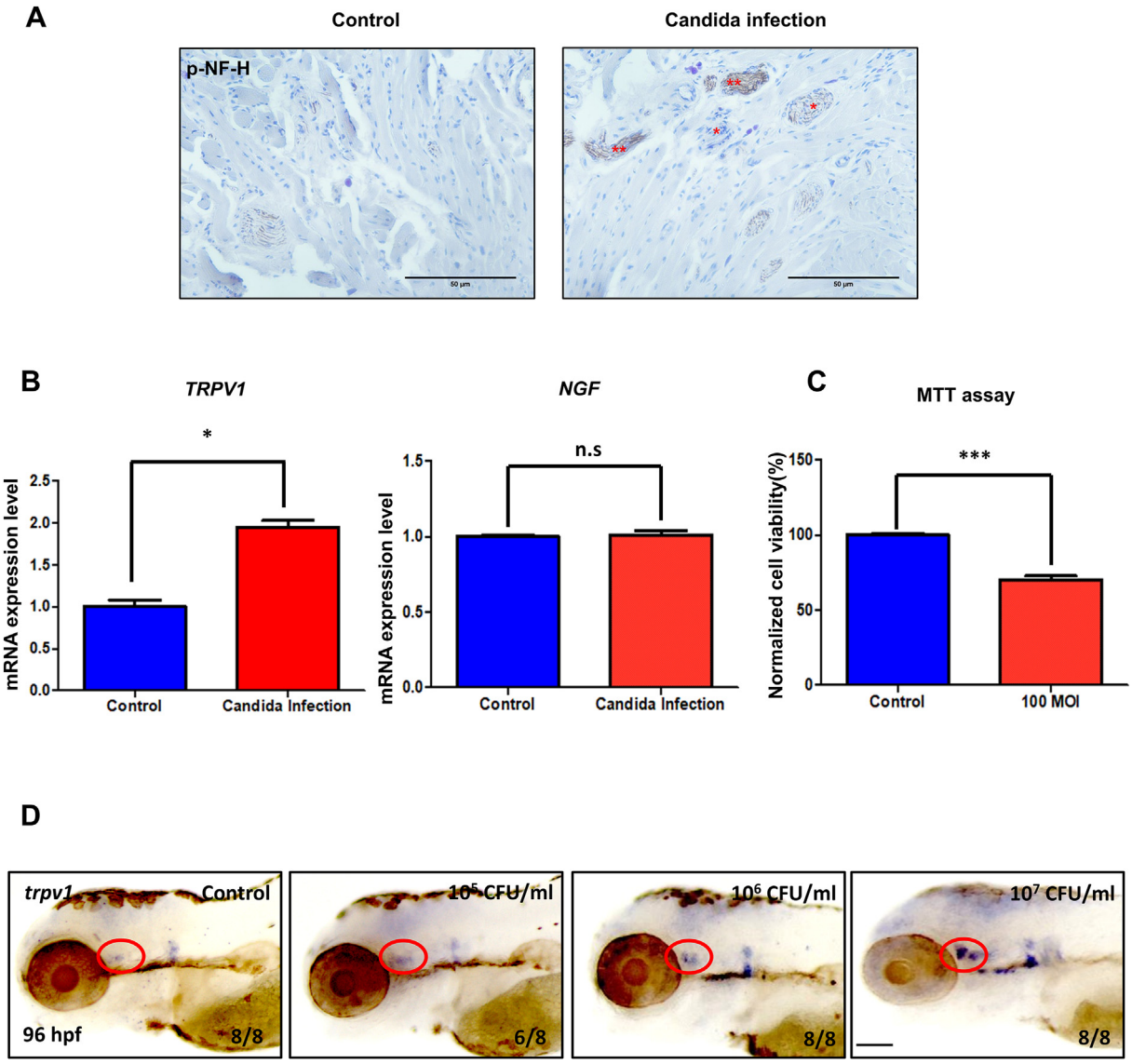

Figure 4 Induction of trigeminal neuron damage by *C. albicans* infection (A) Immunohistochemical analysis of p–NF–H in tongue tissues. Scale bars, 50 μm. (B) Quantitative RT-PCR analysis of TRPV1 and NGF expression in the *C. albicans*-infected group compared to the control. (* indicates significance at $P < 0.05$). (C) MTT assay results with *C. albicans* at a MOI of 100 compared to the control group (* indicates significance at $P < 0.001$). (D) In situ hybridization of trpv1 in zebrafish embryos exposed to 10^5 CFU/mL, 10^6 CFU/mL, and 10^7 CFU/mL concentrations of *C. albicans* at 96 hpf. Scale bars, 0.2 mm, *C. albicans*, *Candida albicans*. p–NF–H, Phosphorylated neurofilament heavy chain. RT-PCR, Reverse transcription polymerase chain reaction. TRPV1, Transient receptor potential vanilloid 1. MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide. trpv1, Zebrafish ortholog, TRPV1. NGF, Nerve growth factor. MOI, Multiplicity of infection. CFU, Colony-forming unit.

target proteins. This model provides a comprehensive and efficient approach to exploring peripheral nerve function and pathology, making zebrafish embryos a valuable tool for advancing peripheral nerve research.

Our findings highlight TRPV1 as a promising therapeutic target for managing *C. albicans*-induced burning sensations in the oral cavity. While nystatin effectively alleviated symptoms through its antifungal action, it did not provide relief for all patients, suggesting the presence of treatment-resistant cases. For these patients, therapies directly targeting TRPV1 could offer an alternative approach to addressing persistent symptoms. Although this study demonstrates the potential link between TRPV1 activation and infection-related neuropathic pain, it did not investigate TRPV1-targeted treatments. Future research exploring the efficacy of TRPV1 inhibitors, either as standalone therapies or in combination with antifungal agents, could simultaneously address pain and facilitate nerve recovery. Additionally, the long-term effects of *C. albicans* infection and its treatment on TRPV1 expression and nerve integrity remain unexplored. Follow-up studies are necessary to evaluate the durability of therapeutic outcomes and understand the broader implications of infection-induced neuropathy. Developing targeted

therapies that integrate these insights could significantly enhance outcomes for patients suffering from infection-related neuropathic pain.

Declaration of competing interest

The authors have no conflicts of interest to disclose related to this work.

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