Ciencia Latina Revista Científica Multidisciplinar, Ciudad de México, México.
ISSN 2707-2207 / ISSN 2707-2215 (en línea), enero-febrero 2025,
Volumen 9, Número 1.

https://doi.org/10.37811/cl_rcm.v9i1

TRPV1 AS A MOLECULAR TARGET FOR THERAPEUTIC INTERVENTIONS IN STOMATOLOGY

TRPV1 COMO DIANA MOLECULAR PARA INTERVENCIONES TERAPÉUTICAS EN ESTOMATOLOGÍA

Paloma Montserrat Rosas Licona
Facultad de Ciencias Químicas de la Benemérita Universidad Autónoma de Puebla

Ana Delia Licona Ibarra
Clínica de Ortodoncia y Ortopedia Maxilar- Puebla de Zaragoza

Aurora Linares Campos
Facultad de Ciencias Químicas de la Benemérita Universidad Autónoma de Puebla

Laura Morales Lara
Facultad de Ciencias Químicas de la Benemérita Universidad Autónoma de Puebla

Victorino Gilberto Serafín Alatriste Bueno
Facultad de Ciencias Químicas de la Benemérita Universidad Autónoma de Puebla

DOI: https://doi.org/10.37811/cl_rcm.v9i2.17156

TRPV1 as a molecular target for therapeutic interventions in stomatology

Paloma Montserrat Rosas Licona[1]
rosaspaloma122@gmail.com
https://orcid.org/0009-0001-0025-4444
Facultad de Ciencias Químicas de la Benemérita Universidad Autónoma de Puebla
México

Ana Delia Licona Ibarra
analiconaibarra@hotmail.com
https://orcid.org/0009-0000-5507-8532
Clínica de Ortodoncia y Ortopedia Maxilar-Puebla de Zaragoza
México

Aurora Linares Campos
alinares_campos@hotmail.com
https://orcid.org/0009-0001-5774-5869
Facultad de Ciencias Químicas de la Benemérita Universidad Autónoma de Puebla
México

Laura Morales Lara
laura.morales@correo.buap.mx
https://orcid.org/0000-0001-5404-754X
Facultad de Ciencias Químicas de la Benemérita Universidad Autónoma de Puebla
México

Victorino Gilberto Serafín Alatriste Bueno
victorino.alatriste@correo.buap.mx
https://orcid.org/0000-0001-8680-5018
Facultad de Ciencias Químicas de la Benemérita Universidad Autónoma de Puebla
México

ABSTRACT

Transient receptor potential vanilloid 1 (TRPV1) is a cation channel involved in sensory perception in various tissues, including the oral cavity. This review article addresses its distribution in structures such as dental components, the oral mucosa, the trigeminal nerve, the tongue, and the salivary glands, highlighting its role in the modulation of nociception and inflammation. It also participates in tissue homeostasis and the response to chemical or thermal stimuli in oral physiology. Likewise, its role in various oral conditions, such as dentin hypersensitivity and oral squamous cell carcinoma, is analyzed since TRPV1 overexpression is associated with tumor progression. On the other hand, in the context of COVID-19, the possible relationship between TRPV1 and sensory alterations linked to the viral infection is discussed. Finally, therapeutic strategies based on the modulation of this receptor with enafis are addressed in the use of agonists and antagonists for the control of orofacial pain and the improvement of pathological conditions in the oral cavity.

Keywords: trpv1, oral cavity, sensitivity, nociception

[1] Autor principal
Correspondencia: rosaspaloma122@gmail.com

TRPV1 como diana molecular para intervenciones terapéuticas en estomatología

RESUMEN

El receptor de potencial transitorio vanilloide 1 (TRPV1) es un canal cationico involucrado en la percepción sensorial en diversos tejidos, incluidos aquellos que constituyen a la cavidad oral. Este artículo de revisión aborda su distribución en estructuras como los componentes dentales, la mucosa bucal, el nervio trigemino, la lengua y las glándulas salivales, resaltando su papel en la modulación de la nocicepción e inflamación. Así como su participación en la homeostasis tisular y la respuesta a estímulos químicos o térmicos en la fisiología oral. De igual forma, se analiza su papel en diversas afecciones orales, como la hipersensibilidad dentinaria y el carcinoma oral de células escamosas, puesto que la sobreexpresión a TRPV1 se asocia con la progresión tumoral. Por otro lado, en el contexto del COVID19, se discute la posible relación entre TRPV1 y alteraciones sensoriales vinculadas a la infeccion viral. Finalmente, se abordan estrategias terapéuticas basadas en la modulación de este receptor con enafis en el uso de agonistas y antagonistas para el control del dolor orofacial y la mejora de condiciones patológicas en la cavidad oral.

Palabras clave: trpv1, cavidad oral, sensibilidad, nocicepción

Artículo recibido 15 enero 2025

Aceptado para publicación: 19 febrero 2025

INTRODUCTION

Transient receptor potential (TRP) constitutes a superfamily of specialized proteins that comprise more than 30 subtypes in mammals (Chen *et al*., 2024). Its primary function is modulating membrane potential by increasing intracellular ion concentrations (Samanta *et al.,* 2018). They act as integrators of polymodal signals, responding to various environmental and physiological stimuli (Chen *et al.,* 2024). Considering the homology in their amino acid sequences, their structural characteristics, and the ligands with which they interact, mammalian TRP proteins are grouped into six main subfamilies (TRPC, TRPM, TRPA, TRPML, TRPP, and TRPV) as shown in Table 1.

Table 1. General classification of the mammalian TRP channel superfamily**.**

Subfamily	Name	Isoforms	Function
TRPC	Canonical	1-7	They are non-voltage-regulated channels that allow the entry of Ca^{2+} and Na^{+} in response to PIP_2 and IP_3. They contribute to cell signaling, proliferation, and neuronal and muscle modulation (Wen *et al*., 2020).
TRPM	Melastatin	1-8	They mediate the influx of Ca^{2+} and Mg^{2+} in response to changes in ion and lipid concentrations. It detects oxidative stress, endothelial permeability, and vascular tone (Huang *et al*., 2020).
TRPML	Mucolipin	1-3	They adjust the autophagy-lysosome system, influencing cancer progression and immune evasion (Santoni *et al.*, 2020).
TRPA	Ankyrin	1	It is in the dorsal root ganglia and trigeminal nerves. It has ankyrin repeats and is activated by extreme cold and electrophilic or non-covalent compounds (Nilius *et al*., 2012).

TRPP	Polycystin	2, 3 y 5	They form complexes with polycystins, and their dysfunction is related to autosomal dominant polycystic kidney disease (Semmo *et al*., 2014).
TRPV	Vanilloids	1-4	They interact with vanilloid compounds and respond to temperature increases and pH changes. They play a key role in nociception (Zhang *et al.,* 2023).

Among the TRP protein subfamilies, transient receptors potential vanilloid (TRPV), particularly TRPV1, stand out for their relevance in detecting noxious stimuli and their fundamental role in specific physiological processes. TRPV1 comprises intracellular N-terminal and C-terminal regions and a transmembrane region, which includes six domains (S1-S6) that form the channel pore (Nadezhdin *et al*., 2021). Its activation allows the entry of Ca^{2+} into the cell, which causes membrane depolarization or starts signaling pathways (Zhang *et al*., 2023). While S5 and S6 are crucial for pore opening (Nadezhdin *et al*., 2021), the TRP domain, located after S6, is critical to subunit assembly and allosteric modulation of the channel (Liao *et al.,* 2013).

This receptor opens its cationic pore to enter Ca^{2+} by interacting with ligands. The most studied exogenous agonist for TRPV1 is capsaicin, the active ingredient in chili peppers (genus *Capsicum*) (Yang & Zheng, 2017). Likewise, it interacts with other organic molecules such as piperine (bioactive from pepper), cinnamodial (unsaturated dialdehyde terpenes, located in cinnamon), allicin (derived from garlic), monoterpenes such as eugenol (derived from eucalyptus), phytocannabinoids, myrcene and camphor (Andrei *et al.,* 2023).

To open their channel, TRPV1 also uses endogenous inflammatory mediators, such as anandamide and arachidonic acid metabolites (Elokely *et al*., 2016), and thermal stimulation. Molecular dynamics simulations show that TRPV1 remains closed at 30°C with a stable lower gate, while at 60°C, it undergoes changes that stimulate the channel (Zheng & Wen, 2019). This process can be modulated by divalent cations, which reduce the activation temperature by inducing structural changes in the extracellular region (Andrei *et al*., 2023). On the other hand, TRPV1 detects pH deviations with opening promotion, implying a proton permeation mechanism that can occur even in the presence of

physiological concentrations of Na^{+}, $Mg^{2+,}$ and Ca^{2+} (Hellwig *et al.,* 2004) due to a hydrophilic bridge that allows proton conductance and cation permeation (Hellwig *et al.,* 2004).

TRPV1 was initially identified in thinly myelinated and unmyelinated slow-conducting primary somatosensory afferent neurons of the dorsal root ganglia of the spinal cord (Andresen, 2019). However, subsequent research has shown that this receptor is widely distributed in other body cell types and tissues. It is essential to address its role in regions sensitive to stimuli that affect the receptor, such as the oral cavity. In this area, TRPV1 is in sensory afferent nerve fibers, such as Aδ and C fibers (Smutzer & Devassy, 2016). Furthermore, it is widely distributed in oral epithelial cells, where it plays a key role in the inflammatory response and the regulation of local homeostasis (Moayedi *et al.*, 2022). It has even been reported that in keratinocytes, TRPV1 contributes to sensory perception and the modulation of the immune system (Smutzer & Devassy, 2016).

Thus, TRPV1 plays an essential role in the response to external stimuli within the oral cavity, facilitating the maintenance of tissue balance (Takahashi *et al.,* 2020). Its activation releases neurotransmitters that amplify nociceptive signals to the central nervous system, intensifying thermal sensation and algesia in oral tissues (Arendt-Nielsen *et al.,* 2022). Therefore, understanding TRPV1-mediated pain modulation in oral diseases could lead to new therapeutic opportunities for managing such conditions.

Under this context, the present review article provides a global approach that includes studies on the specific localization of TRPV1 in oral cavity structures, such as dental components, epithelial tissue, cranial nerves, tongue, and salivary glands. Its link with painful conditions and its impact on inflammatory and hyperesthetic processes, as well as the relationship between TRPV1 and conditions such as cancer and COVID-19, are also addressed. Finally, the possible clinical and therapeutic applications are discussed, highlighting their relevance in developing new strategies for managing oral pain and inflammatory oral diseases.

METHODOLOGY

A bibliographic search of scientific information related to the expression of TRPV1 in the oral cavity was carried out through the Scopus and Pubmed databases. The analysis revealed 680 documents using the following search language: trpv1 AND (mouth OR cavity OR oral OR teeth OR buccal) AND (treatment OR COVID-19 OR cancer).

Regarding the exclusion criteria, presentations, reports, and conference papers were eliminated. Articles and reviews written in a language other than English were excluded, as were duplicate elements. From the above, the number of manuscripts was reduced to 278.

Subsequently, a second filter was carried out based on the title, omitting information that was not directly related to the topic of this review. Next, a third screen was applied based on the scope of the summaries with the eventual evaluation of the total content of the articles considering the effectiveness of the research presented in each of them. With this review, 27 articles were identified whose contributions support the topic in question. 23 documents were also included to complement the general information regarding TRPV1 and the oral cavity anatomy. The integration of these sources allows for a more detailed discussion of its molecular functions, associated signaling pathways, and potential clinical implications in oral health and disease.

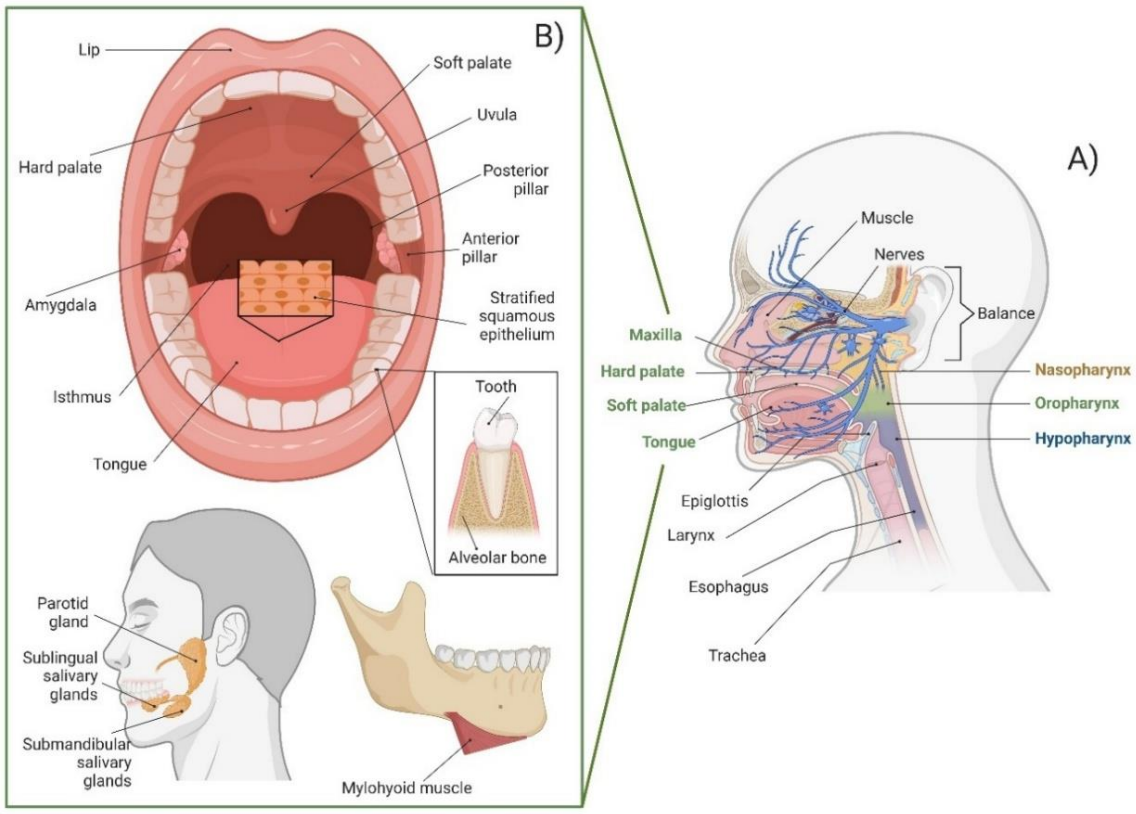
RESULTS AND DISCUSSION

This is how the oral cavity is constructed.

The stomatognathic system is a morphofunctional unit made up of bone, muscular, nervous, and glandular structures articulated at the craniofacial level (Zieliński *et al.,* 2021) (Figure 1A). It can integrate with the digestive, respiratory, and phonatory systems and participate in the sensory perception of taste, touch, and balance (Gualdrón-Bobadilla *et al.,* 2022).

Within this system is the oral cavity (Figure 1B), which is internally lined by the mucosa, composed of stratified squamous epithelium and is kept hydrated thanks to the secretion of the submandibular and sublingual salivary glands (McKnight *et al.,* 2024). The oral cavity is primarily made up of the tongue. It is delimited by the alveolar processes with teeth in the anterior and lateral region, while posteriorly, it communicates with the oropharynx through the isthmus of the fauces (Xia, 2023). The roof constitutes the hard palate in the anterior portion and the soft palate in the posterior portion, from which the uvula extends. At the same time, the floor is formed by the mylohyoid muscles (Devine & Zur, 2021).

Figure 1. Anatomical representation of the stomatognathic system and the oral cavity. A) Lateral view of the stomatognathic system, highlighting the segmentation into nasopharynx, oropharynx, and hypopharynx. B) Detailed view of the oral cavity, showing its main structures. Also included are the salivary glands, mylohyoid muscle, and the alveolar bone architecture associated with the dentition.



TRPV1: A key receptor in dental health

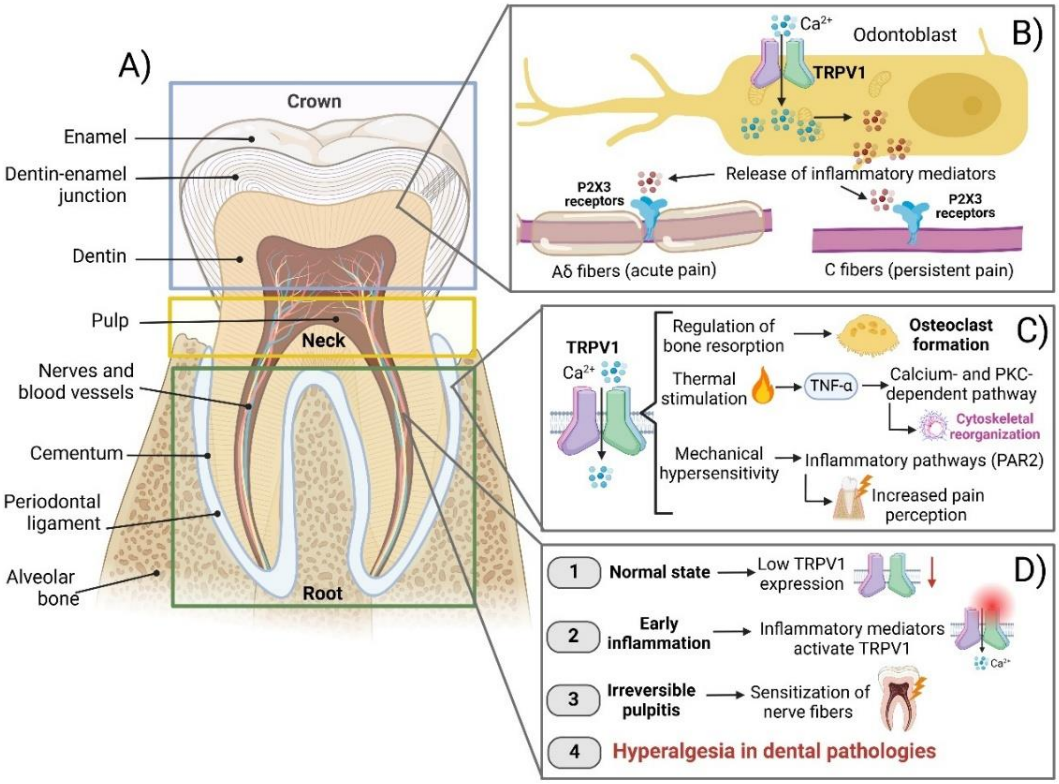
Teeth are key structures within the oral cavity, essential for chewing and digestion. Dental anatomy (Figure 2A) comprises three main sections: the crown, the neck, and the root. Due to mineralization processes, the crown has enamel, the outermost layer (Lacruz *et al.*, 2017). This structure protects dentin, a tissue structured by odontoblasts, with a yellow tone that is exposed when the enamel wears away (Lacruz *et al.*, 2017). According to Kamakura (2015), the dental neck connects the crown with the root, located at the junction between the enamel and the cementum. The pulp is located inside the tooth and is described as a vascularized tissue with nerve fibers extending to the root through the canal. Finally, the root connects to the alveolar bone through the periodontal ligament, a tissue that contains nerves and blood vessels.

Of these dental structures, TRPV1 expression has been identified in odontoblasts (Figure 2B), suggesting its participation in sensory transduction (Okumura *et al.*, 2005). In this context, the "hydrodynamic receptor" theory stands out, which postulates the action of odontoblasts as

mechanosensors capable of detecting changes in fluid pressure within the dentinal tubules, which contributes to the perception of dental pain (Wen *et al.*, 2017). When enamel is worn or damaged, dentin exposure can intensify this response and promote the activation of TRPV1. After its stimulation, inflammatory mediators, such as ATP, are released, which acts as a paracrine signal by binding to purinergic P2X3 receptors (Hossain *et al.*, 2019) (Figure 2B). P2X3 is predominantly located in Aδ fibers (myelinated, responsible for acute and rapid pain) and C (unmyelinated, associated with dull and persistent pain). It is crucial in transmitting nociceptive signals to the central nervous system (Hossain *et al.*, 2019). Thus, TRPV1 allows the integration of signals that influence dental hypersensitivity.

Regarding other regions, Sooampon *et al.* (2013) mention that TRPV1 is also located in human periodontal ligament cells (Figure 2C), where its interaction by capsaicin modulates the homeostasis of the osteoprotegerin (OPG)/receptor activator of nuclear factor kappa B ligand (RANKL) axis. This mechanism alludes to the regulation of bone resorption by TRPV1 based on the formation of osteoclasts. Regarding thermal stimulation, the expression of TNF-α is induced through a calcium and protein kinase C (PKC)-dependent pathway in a process that requires reorganization of the cytoskeleton. Osada *et al.* (2022) identified that TRPV1 and acid-sensitive ion channels are stimulated in response to acidification of the periodontium caused by tooth movement. The above contributes to mechanical hypersensitivity by stimulating inflammatory signaling pathways, such as that mediated by protease-activated receptor 2 (PAR2). Therefore, TRPV1 sensitization could intensify pain perception during orthodontic treatment. Gibbs *et al.* (2012) determined that in the dental pulp, the expression of TRPV1 is relatively low. However, its regulation by inflammatory mediators can increase thermal sensitivity and enhance nociceptive transmission (Figure 2D). The above favors the development of hyperalgesia in pathological states such as irreversible pulpitis, where inflammation and hyperemia sensitize nociceptive fibers, which is exacerbated by the release of neuropeptides that amplify the algesic signal. On the other hand, TRVP1 is found to a limited extent in neurons that innervate the pulp compared to those of the periodontal ligament, which suggests a difference in the ability to detect stimuli between both tissues. This distribution could influence the variability of odontogenic pain perception.

Figure 2. TRPV1 expression in dental tissues and its involvement in sensory transduction and pain perception. (A) Anatomy of the tooth, composed of crown, neck, and root. The enamel, dentin, pulp, and periodontal ligament stand out. (B) In odontoblasts, TRPV1 mediates the release of inflammatory mediators in response to thermal and mechanical stimuli, activating purinergic receptors (P2X3) in Aδ and C fibers. (C) TRPV1 regulates bone resorption in the periodontal ligament and participates in mechanical hypersensitivity through PAR2-dependent inflammatory pathways. (D) In the dental pulp, its expression is low under normal conditions but increases in the presence of inflammation, favoring hyperalgesia in pathologies such as irreversible pulpitis.

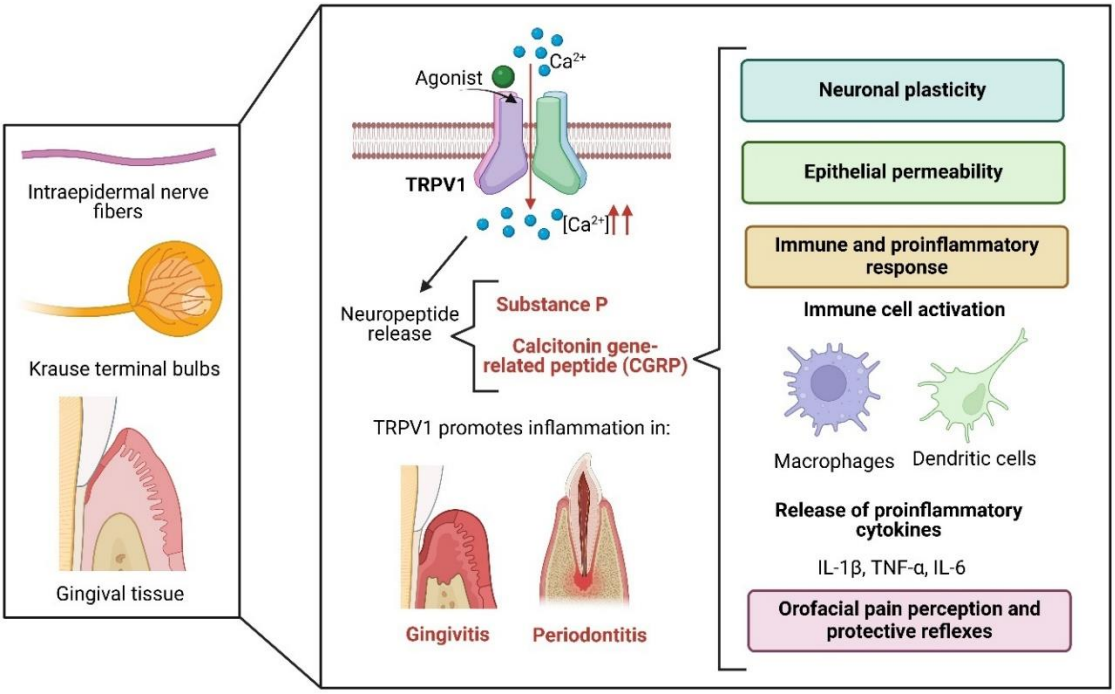


TRPV1 is a bridge between sensation, inflammation, and immunity in the oral cavity

TRPV1 expression in the oral cavity encompasses various epithelial tissues and neuroanatomical structures (Takahashi *et al.*, 2020). Moayedi *et al.* (2022) highlight its location in intraepidermal nerve fibers and the terminal bulbs of Krause (Figure 3). In these areas, TRPV1 facilitates stimulus detection and is involved in ionic balance and modulation of epithelial permeability. Also, it triggers the release of proinflammatory neuropeptides (substance P and calcitonin gene-related peptide), essential for maintaining the oral microenvironment. Also, its role in neuronal plasticity alludes to a contribution to physiological adaptation through sensitization and desensitization of primary afferent fibers. Consequently, a modulated response to thermal fluctuations and exposure to pathogens is generated (Takahashi *et al.*, 2020). In this way, neuronal plasticity can influence orofacial pain perception, protective reflexes, and mucosal homeostasis. Even according to the information collected by Takahashi

et al. (2020), in gingival tissue, TRPV1 exerts a protective function of the epithelial barrier. It has also been linked to the progression of periodontal diseases, including gingivitis and periodontitis. This is because TRPV1 promotes the activation of macrophages and dendritic cells, favoring the release of proinflammatory cytokines such as IL-1β, TNF-α, and IL-6.

Figure 3. TRPV1 in intraepidermal nerve fibers, terminal bulbs of Krause, and gingival tissue. TRPV1 induces the release of proinflammatory neuropeptides, promoting inflammation and periodontal pathologies through immune activation and the release of proinflammatory cytokines.



Nerve bundles with TRPV1 are abundantly distributed in the lamina propria of circumvallate, foliate, and fungiform papillae, with branches penetrating the taste buds (Kido *et al.*, 2017). Although TRPV1 immunoreactivity within taste cells is limited, it is strongly expressed in the surrounding epithelium, promoting peripheral sensory uptake (Kido *et al.*, 2017). In fact, according to Roper (2014), TRPV1 favors the detection of thermal and chemical stimuli on the tongue by modulating the response to pungent compounds such as capsaicin. This effect is achieved by associating the tissue with the afferent fibers of the trigeminal nerve with the consequent transmission of nociceptive signals to the central nervous system. Its sensory role is enhanced by interaction with TRPA1 receptors from a synergistic response to irritants. Furthermore, the strong expression of TRPV1 at the top of the palatal wrinkles, structures that protrude into the oral cavity, suggests the receptor's involvement in guiding food to the larynx (Kido *et al.*, 2017). Subsequently, in the afferent fibers of the trigeminal nerve, TRPV1 triggers

central and peripheral sensitization (Saunders *et al.,* 2013). This mechanism favors orofacial hyperalgesia and the development of chronic pain in conditions such as trigeminal neuralgia and temporomandibular dysfunction (Roper, 2014). Thus, cooperation with sensory proteins (TRPA1 and acid-sensitive ion channels) in these nerves increases the nociceptive response and synaptic plasticity in trigeminal neuronal networks (Saunders *et al.*, 2013).

Regarding its presence in salivary glands, TRPV1 regulates the function of ion channels and aquaporin transporters (Takahashi *et al.,* 2020). However, its involvement in salivary secretion does not seem to be direct through the transcellular pathway (Choi *et al.,* 2014). It has been observed that high concentrations of capsaicin (100 µM) reduce transepithelial resistance, inducing a possible effect on paracellular permeability (Choi *et al.,* 2014). Likewise, it plays a relevant role in the innate immune response, acting as a mediator in the detection of oral pathogens and in triggering pro-inflammatory pathways (Tynan *et al.,* 2019). Its intervention in tissue remodeling makes it a determining factor in the healing of epithelial wounds, ensuring oral tissue's structural and functional restoration after mechanical or infectious aggression (Takahashi *et al.,* 2014).

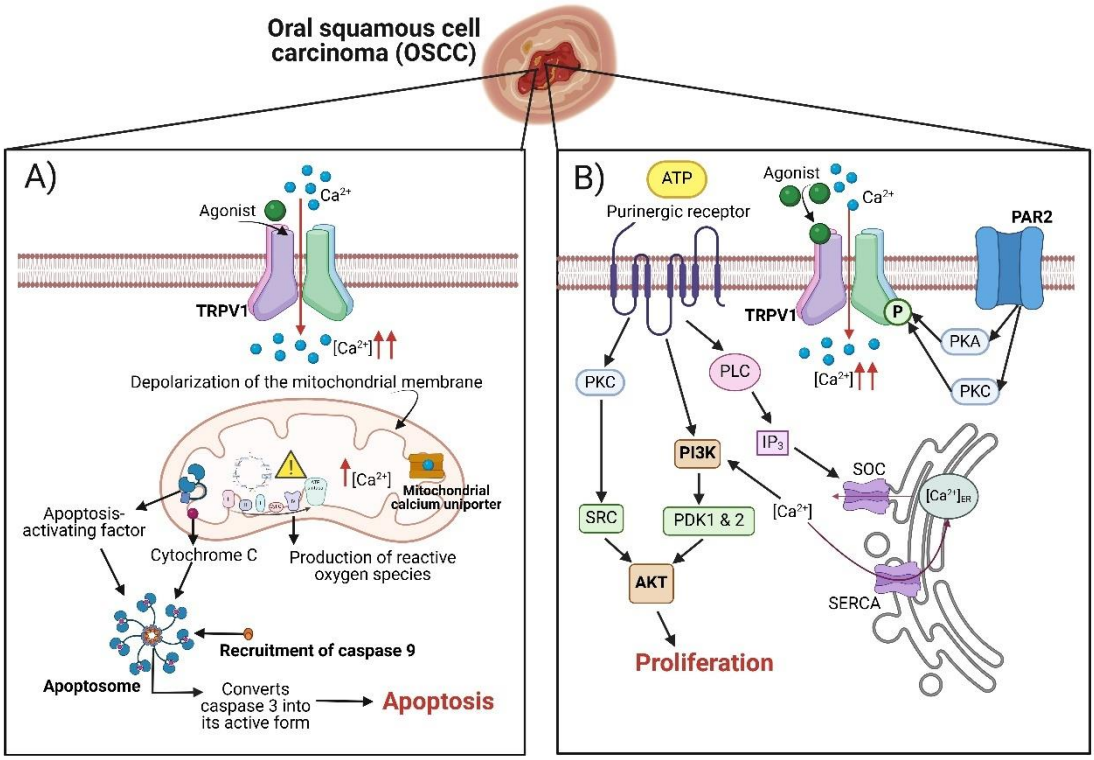
The duality of TRPV1 in oral cancer: cytotoxicity or tumor resistance

Marincsák *et al.* (2009) documented the overexpression of TRPV1 in oral squamous cell carcinoma (OSCC) through the significant increase in mRNA and protein levels compared to healthy epithelial tissue. At the molecular level, the interaction of TRPV1 by agonists unleashed a massive influx of intracellular Ca^{2+}, recruiting effector caspases and the release of cytochrome c from mitochondria, promoting apoptosis in tumor cells (Zhai *et al.,* 2020) (Figure 4A). Nevertheless, TRPV1-induced cytotoxicity is highly dependent on the agonist concentration and tumor context since sustained activation of the channel can unleash survival mechanisms mediated by the PI3K/Akt pathway (Figure 4B), inducing cell proliferation and resistance to apoptosis (Zhai *et al.,* 2020).

Hypersensitization of TRPV1 in oral cancer is associated with an increase in mechanical and chemical pain, correlating with the increased expression of TRPV1 in trigeminal ganglion neurons that innervate the tumor (Sawicki *et al.,* 2022). The opening of TRPV1 in the tumor microenvironment is controlled by the PAR2 receptor (Figure 4B), leading to sensitization of the channel through phosphorylation by protein kinases A and C (PKA and PKC) (Scheff *et al.*, 2022). In preclinical models, PAR2 inhibition

has been shown to reduce capsaicin aversion in behavioral assays, suggesting a functional interaction between these receptors in the perception of OSCC-induced pain (Scheff *et al*., 2022).

Figure 4. Expression and function of TRPV1 in oral squamous cell carcinoma (OSCC). (A) Activation of TRPV1 by agonists increases intracellular Ca^{2+}, promoting mitochondrial depolarization, production of reactive oxygen species, and apoptosis. (B) In contrast, TRPV1 can generate survival pathways mediated by PI3K/Akt in a specific tumor context, favoring cell proliferation. PAR2 receptor regulates TRPV1 sensitization through phosphorylation by protein kinases, influencing tumor progression and pain perception in OSCC. Phospholipase C (PLC), Inositol 1,4,5-trisphosphate (IP_3), Store-Operated Calcium Channels (SOC), Ca^{2+}-Sarcoplasmic/Endoplasmic Reticulum ATPase (SERCA), Phosphatidylinositol 3-kinase (PI3K), Phosphoinositide-dependent Kinase 1 & 2 (PDK1 & 2), Proto-oncogene Tyrosine-protein Kinase Src (SRC), Protein Kinase B (AKT). Created in



TRPV1 has been proposed as a diagnostic biomarker due to its early overexpression in precancerous lesions and in the epithelium surrounding the tumor (Marincsák *et al.*, 2009). As a treatment, intratumoral administration of capsazepine can reduce tumor size without affecting healthy tissues, suggesting that TRPV1 antagonists could effectively inhibit the neoplastic progression of OSCC (Gonzales *et al.*, 2014). As a perspective, TRPV1 modulation could offer a targeted analgesic approach to patients with OSCC, minimizing chemical hypersensitivity without compromising normal sensory function (Sawicki *et al*., 2022).

Oral neuroinflammation due to COVID-19 and the role of TRPV1

SARS-CoV-2 infection has been related to various sensory alterations, including oral hypersensitivity and loss of taste, sparking interest in its molecular mechanisms (Nanjo *et al.*, 2019). Since TRPV1 is presented in sensory neurons in this area, a probable connection is established between the dysfunction of these receptors and the alterations observed in patients with COVID-19 (Maaroufi, 2021).

The S protein of SARS-CoV-2 can interact with TRPV1 through ankyrin repeat binding motifs (Maaroufi, 2021). The above could alter the functionality of TRPV1, affecting the transmission of sensory signals in the oral cavity and contributing to the dysgeusia observed in infected patients (Tsuchiya, 2023). Furthermore, since TRPV1 is involved in the inflammatory response, facilitating the release of IL-6 and TNF-α, it exacerbates inflammatory processes and generates oral hypersensitivity (Takahashi *et al.*, 2020). Other studies have shown that respiratory viruses such as respiratory syncytial virus and measles can induce the overexpression of TRPV1 in epithelial cells and neurons, evoking a similar mechanism in SARS-CoV-2 infection (Omar *et al*., 2017).

As mentioned above, modifications in TRPV1 in the oral mucosa are linked to the immune response. TRPV1 activation has been shown to play a crucial role in generating adaptive immune responses, suggesting that its dysfunction affects the effectiveness of the response against the virus (Tynan e*t al.*, 2019). In this sense, the possibility of using TRPV1 agonists as adjuvants in vaccines against SARS-CoV-2 is raised (Maaroufi, 2021). Since TRPV1 is associated with the regulation of lung inflammation, it could be related to the multisystem symptomatology of COVID-19, including effects at the cardiovascular and neuronal level (Omar *et a*l., 2017; Liviero *et al.*, 2021; Tsuchiya, 2023). These findings highlight the relevance of TRPV1 in the oral pathophysiology of COVID-19 infection and raise new therapeutic perspectives to mitigate its effects in the oral cavity.

Therapeutic perspectives on TRPV1 in the treatment of oral disorders

The TRPV1 receptor has emerged as a promising therapeutic target in managing orofacial pain and oral inflammation. Its activation by agonists such as capsaicin and resiniferatoxin induces progressive neuronal desensitization, reducing nociceptive excitability and modulating neurogenic inflammation (Smutzer & Devassy, 2016). The application of capsaicin has been shown to modulate the release of pro-inflammatory neuropeptides, allowing the management of neuropathic pain associated with

peripheral hypersensitization (Chen *et al.*, 2024). Likewise, resiniferatoxin, with greater potency and lower systemic toxicity than capsaicin, has shown potential in the selective ablation of nociceptive fibers without compromising general neuronal function (Smutzer & Devassy, 2016).

On the other hand, TRPV1 antagonists have gained relevance in developing anti-inflammatory and analgesic treatments, particularly in managing hyperalgesia in patients with oral lesions. In the context of periodontal pathology, the inhibition of TRPV1 by capsazepine has shown positive effects in regulating bone resorption (Sooampon *et al*., 2013). However, its clinical application requires further refinement, given that some antagonists have shown adverse effects on the regulation of intracellular calcium (Smutzer & Devassy, 2016). This is due to the broad expression of TRPV1 in the nervous system and other peripheral tissues (Smutzer & Devassy, 2016).

TRPV1 activation and blockade have been investigated as strategies to influence immune responses in infectious and inflammatory diseases. This process enhances T cell and macrophage responses through neuropeptide release in peripheral nociceptors (Tynan *et al.*, 2024). This suggests its possible usefulness in optimizing local immune responses, including those directed against oral pathogens. On the contrary, the inhibition of TRPV1 can modulate inflammatory responses in oral tissues, having therapeutic potential in periodontal diseases and pathological processes of the oral mucosa (Sooampon *et al.*, 2013). The study of TRPV1 as a therapeutic target offers an alternative route for treating oral conditions in patients with pharmacological restrictions. Nevertheless, TRPV1 modulation may have dual effects depending on the pathological context (Chen *et al.*, 2024). That is why developing therapeutic strategies based on this receptor requires a deeper understanding of its effects on immune balance and inflammation. Designing drugs specific for TRPV1 in the oral cavity could represent a significant innovation in regenerative dentistry and pain medicine.

CONCLUSIONS

The TRPV1 receptor plays a key role in the oral cavity by participating in sensory transduction, inflammation, and tissue homeostasis. Its expression in various structures, such as dental components, oral mucosa, cranial nerves, and salivary glands, highlights its importance in pain perception, immune response, and modulation of pathophysiological processes. This receptor is associated with oral squamous cell carcinoma's progression and sensory alterations in viral infections such as COVID-19.

This evidence positions TRPV1 as a potential therapeutic target in stomatology, with applications in the design of strategies for managing inflammatory diseases in the oral cavity.

REFERENCES

Andrei, C., Zanfirescu, A., Nițulescu, G. M., Olaru, O. T., & Negreș, S. (2023). Natural active ingredients and TRPV1 modulation: focus on key chemical moieties involved in ligand-target interaction. *Plants*, 12(2), 339.

Andresen, M. C. (2019). Understanding diverse TRPV1 signaling–an update. F1000Research, 8.

Arendt-Nielsen, L., Carstens, E., Proctor, G., Boucher, Y., Clavé, P., Albin Nielsen, K., ... & Reeh, P. W. (2022). The role of TRP Channels in Nicotinic provoked Pain and Irritation from the oral cavity and Throat: translating Animal Data to humans. Nicotine and Tobacco Research, 24(12), 1849-1860.

Chen, J., Sun, W., Zhu, Y., Zhao, F., Deng, S., Tian, M., ... & Gong, Y. (2024). TRPV1: The key bridge in neuroimmune interactions. *Journal of Intensive Medicine*.

Choi, S., Shin, Y. H., Namkoong, E., Hwang, S. M., Cong, X., Yu, G., & Park, K. (2014). TRPV1 in salivary gland epithelial cells is not involved in salivary secretion via transcellular pathway. *The Korean Journal of Physiology & Pharmacology: Official Journal of the Korean Physiological Society and the Korean Society of Pharmacology*, 18(6), 525.

Devine, C., & Zur, K. (2021). Upper Airway Anatomy and Physiology. *Diagnostic and Interventional Bronchoscopy in Children*, 17-37.

Elokely, K., Velisetty, P., Delemotte, L., Palovcak, E., Klein, M. L., Rohacs, T., & Carnevale, V. (2016). Understanding TRPV1 activation by ligands: Insights from the binding modes of capsaicin and resiniferatoxin. *Proceedings of the National Academy of Sciences*, 113(2), E137-E145.

Gibbs, J. L., Melnyk, J. L., & Basbaum, A. (2011). Differential TRPV1 and TRPV2 channel expression in dental pulp. *Journal of dental research*, 90(6), 765-770.

Gonzales, C. B., Kirma, N. B., Jorge, J., Chen, R., Henry, M. A., Luo, S., & Hargreaves, K. M. (2014). Vanilloids induce oral cancer apoptosis independent of TRPV1. *Oral oncology*, *50*(5), 437–447.

Gualdrón-Bobadilla, G. F., Briceño-Martínez, A. P., Caicedo-Téllez, V., Pérez-Reyes, G., Silva-Paredes, C., Ortiz-Benavides, R., ... & Bermúdez, V. (2022). Stomatognathic system changes in obese patients undergoing bariatric surgery: a systematic review—Journal *of Personalized Medicine*, *12*(10), 1541.

Hellwig, N., Plant, T. D., Janson, W., Schäfer, M., Schultz, G., & Schaefer, M. (2004). TRPV1 acts as proton channel to induce acidification in nociceptive neurons. *Journal of Biological Chemistry*, *279*(33), 34553-34561.

Huang, Y., Fliegert, R., Guse, A. H., Lü, W., & Du, J. (2020). A structural overview of the ion channels of the TRPM family. *Cell Calcium*, 85, 102111.

Hossain, M. Z., Bakri, M. M., Yahya, F., Ando, H., Unno, S., & Kitagawa, J. (2019). The role of transient receptor potential (TRP) channels in the transduction of dental pain. *International journal of molecular sciences*, *20*(3), 526.

Kamakura, S. (2015). Tooth and tooth-supporting structures. *Advances in Metallic Biomaterials: Tissues, Materials and Biological Reactions*, 99–122.

Kido, M. A., Yoshimoto, R. U., Aijima, R., Cao, A. L., & Gao, W. Q. (2017). The oral mucosal membrane and transient receptor potential channels. *Journal of Oral Science*, 59(2), 189-193.

Liao, M., Cao, E., Julius, D., & Cheng, Y. (2013). Structure of the TRPV1 ion channel determined by electron cryo-microscopy. *Nature*, 504(7478), 107–112.

Liu, M., Jia, X., Liu, H., He, R., Zhang, X., & Shao, Y. (2022). Role of TRPV1 in respiratory disease and association with traditional Chinese medicine: A literature review. *Biomedicine & Pharmacotherapy*, *155*, 113676.

Liviero, F., Campisi, M., Mason, P., & Pavanello, S. (2021). Transient receptor potential vanilloid subtype 1: potential role in infection, susceptibility, symptoms and treatment of COVID-19. *Frontiers in Medicine*, 8, 753819.

Lacruz, R. S., Habelitz, S., Wright, J. T., & Paine, M. L. (2017). Dental enamel formation and implications for oral health and disease. *Physiological reviews*, *97*(3), 939–993.

Maaroufi, H. (2021). Interactions of SARS-CoV-2 spike protein and transient receptor potential (TRP) cation channels could explain smell, taste, and/or chemesthesis disorders—arXiv *preprint arXiv*:2101.06294.

Marincsák, R., Tóth, B. I., Czifra, G., Márton, I., Rédl, P., Tar, I., ... & Bíró, T. (2009). Increased expression of TRPV1 in squamous cell carcinoma of the human tongue. *Oral diseases*, 15(5), 328-335.

McKnight, C. A., Diehl, L. J., & Bergin, I. L. (2024). Digestive Tract and Salivary Glands. In *Haschek and Rousseaux's Handbook of Toxicologic Pathology* (pp. 1-148). Academic Press.

Moayedi, Y., Michlig, S., Park, M., Koch, A., & Lumpkin, E. A. (2022). Localization of TRP channels in healthy oral mucosa from human donors. *eneuro*, *9*(6).

Nadezhdin, K. D., Neuberger, A., Nikolaev, Y. A., Murphy, L. A., Gracheva, E. O., Bagriantsev, S. N., & Sobolevsky, A. I. (2021). Extracellular cap domain is an essential component of the TRPV1 gating mechanism. *Nature communications*, 12(1), 2154.

Nanjo, Y., Okuma, T., Kuroda, Y., Hayakawa, E., Shibayama, K., Akimoto, T., ... & Takahashi, K. (2022). Multiple Types of Taste Disorders among Patients with COVID-19. *Internal Medicine*, 61(14), 2127-2134.

Nilius, B., Appendino, G., & Owsianik, G. (2012). The transient receptor potential channel TRPA1: from gene to pathophysiology. Pflügers Archiv-European Journal of Physiology, 464, 425-458.

Okumura, R., Shima, K., Muramatsu, T., Nakagawa, K. I., Shimono, M., Suzuki, T., ... & Shibukawa, Y. (2005). The odontoblast as a sensory receptor cell? The expression of TRPV1 (VR-1) channels. *Archives of histology and cytology*, *68*(4), 251-257.

Omar, S., Clarke, R., Abdullah, H., Brady, C., Corry, J., Winter, H., ... & Cosby, S. L. (2017). Respiratory virus infection up-regulates TRPV1, TRPA1 and ASICS3 receptors on airway cells. *PloS one*, 12(2), e0171681.

Osada, A., Hitomi, S., Nakajima, A., Hayashi, Y., Shibuta, I., Tsuboi, Y., ... & Shinoda, M. (2022). Periodontal acidification contributes to tooth pain hypersensitivity during orthodontic tooth movement. *Neuroscience Research*, *177*, 103-110.

Roper, S. D. (2014). TRPs in taste and chemesthesis. *Mammalian Transient Receptor Potential (TRP) Cation Channels: Volume II*, 827–871.

Samanta, A., Hughes, T. E., & Moiseenkova-Bell, V. Y. (2018). Transient receptor potential (TRP) channels. *Membrane protein complexes: Structure and function*, 141-165.

Santoni, G., Santoni, M., Maggi, F., Marinelli, O., & Morelli, M. B. (2020). Emerging role of mucolipins TRPML channels in cancer. *Frontiers in Oncology*, 10, 659.

Saunders, C. J., Li, W. Y., Patel, T. D., Muday, J. A., & Silver, W. L. (2013). Dissecting the role of TRPV1 in detecting multiple trigeminal irritants in three behavioral assays for sensory irritation. *F1000Research*, 2.

Sawicki, C. M., Janal, M. N., Nicholson, S. J., Wu, A. K., Schmidt, B. L., & Albertson, D. G. (2022). Oral cancer patients experience mechanical and chemical sensitivity at the site of the cancer. *BMC cancer*, *22*(1), 1165.

Scheff, N. N., Wall, I. M., Nicholson, S., Williams, H., Chen, E., Tu, N. H., ... & Schmidt, B. L. (2022). Oral cancer induced TRPV1 sensitization is mediated by PAR2 signaling in primary afferent neurons innervating the cancer microenvironment. *Scientific reports*, 12(1), 4121.

Semmo, M., Köttgen, M., & Hofherr, A. (2014). The TRPP subfamily and polycystin-1 proteins. Mammalian Transient Receptor Potential (TRP) *Cation Channels: Volume I*, 675-711.

Smutzer, G., & Devassy, R. K. (2016). Integrating TRPV1 receptor function with capsaicin psychophysics. *Advances in Pharmacological and Pharmaceutical Sciences*, 2016(1), 1512457.

Sooampon, S., Phoolcharoen, W., & Pavasant, P. (2013). Thermal stimulation of TRPV1 up-regulates TNFα expression in human periodontal ligament cells. *Archives of Oral Biology*, *58*(7), 887–895.

Takahashi, N., Matsuda, Y., Yamada, H., Tabeta, K., Nakajima, T., Murakami, S., & Yamazaki, K. (2014). Epithelial TRPV1 signaling accelerates gingival epithelial cell proliferation. *Journal of Dental Research*, *93*(11), 1141-1147.

Takahashi, N., Tsuzuno, T., Mineo, S., Yamada-Hara, M., Aoki-Nonaka, Y., & Tabeta, K. (2020). Epithelial TRPV1 channels: expression, function, and pathogenicity in the oral cavity. *Journal of Oral Biosciences*, 62(3), 235-241.

Tsuchiya, H. (2023). COVID-19 oral sequelae: persistent gustatory and saliva secretory dysfunctions after recovery from Covid-19. *Medical Principles and Practice*, 32(3), 166.

Tynan, A., Tsaava, T., Gunasekaran, M., Bravo Iñiguez, C. E., Brines, M., Chavan, S. S., & Tracey, K. J. (2024). TRPV1 nociceptors are required to optimize antigen-specific primary antibody responses to novel antigens. *Bioelectronic Medicine*, 10(1), 14.

Wen, H., Gwathmey, J. K., & Xie, L. H. (2020). Role of transient receptor potential canonical channels in heart physiology and pathophysiology. Frontiers in Cardiovascular Medicine, 7, 24.

Wen, W., Que, K., Zang, C., Wen, J., Sun, G., Zhao, Z., & Li, Y. (2017). Expression and distribution of three transient receptor potential vanilloid (TRPV) channel proteins in human odontoblast-like cells. *Journal of Molecular Histology*, *48*, 367-377.

Yang, F., & Zheng, J. (2017). Understand spiciness: mechanism of TRPV1 channel activation by capsaicin. *Protein & cell*, 8, 169-177.

Xia, M. (2023). Oral and Maxillofacial Anatomy. In *Anesthesia for Oral and Maxillofacial Surgery* (pp. 7–26). Singapore: Springer Nature Singapore.

Zhai, K., Liskova, A., Kubatka, P., & Büsselberg, D. (2020). Calcium entry through TRPV1: a potential target for the regulation of proliferation and apoptosis in cancerous and healthy cells. *International journal of molecular sciences*, 21(11), 4177.

Zheng, W., & Wen, H. (2019). Heat activation mechanism of TRPV1: New insights from molecular dynamics simulation. *Temperature*, *6*(2), 120-131.

Zhang, M., Ma, Y., Ye, X., Zhang, N., Pan, L., & Wang, B. (2023). TRP (transient receptor potential) ion channel family: Structures, biological functions and therapeutic interventions for diseases. *Signal Transduction and Targeted Therapy*, *8*(1), 261.

Zieliński, G., Filipiak, Z., Ginszt, M., Matysik-Woźniak, A., Rejdak, R., & Gawda, P. (2021). The organ of vision and the stomatognathic system—Review of association studies and evidence-based discussion. *Brain Sciences*, *12*(1), 14.