Ekspresi MiRNA pada Manifestasi oral Gangguan Neuropsikiatri

(*MiRNAs Expression in Oral manifestations of Neuropsychiatric Disorders (Review)*)

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Abstrak

Penyakit psikologis telah terbukti menyebabkan lesi dan gejala di rongga mulut. Pasien psikiatri sering menunjukkan penyakit mulut yang ditandai dengan indikator klinis dan kebersihan mulut yang buruk, terkait dengan perubahan genetik dan metabolisme pada jaringan mulut, yang bertepatan dengan perubahan psiko-neurologis sebagai faktor yang berkontribusi. Etiologi psikosomatis pada penyakit mulut menginduksi perubahan epigenetik yang dapat dipilih sebagai biomarker kondisi patologis. microRNA (miRNA/miR) memainkan peran penting dalam proses biologis. Etiologi psikosomatis pada penyakit mulut menginduksi perubahan epigenetik yang dapat berfungsi sebagai biomarker untuk kondisi patologis. MicroRNA (miRNA/miR) memainkan peran penting dalam proses biologis. Enam belas studi dipilih berdasarkan relevansinya dengan topik dan kebaruan. Ekspresi MiRNA diatur dan telah ditemukan terkait dengan gangguan psikologis yang menyebabkan manifestasi oral. Studi ini menyelidiki peran biomarker potensial dari miRNA yang diekspresikan pada penyakit mulut yang terkait dengan gangguan psikologis.

Kata kunci: Biomarker, Gangguan neurologis, Gangguan psikologis, Manifestasi mulut, MicroRNA

Abstract

Psychological illnesses have been shown to induce lesions and symptoms in the oral cavity. Psychiatric patients frequently exhibit oral diseases characterized by clinical indicators and poor oral hygiene, linked to genetic and metabolic alterations in oral tissue, which coincide with psycho-neurological changes as contributing factors. The psychosomatic etiologies in oral diseases induce epigenetic alterations that can be chosen as the biomarker of pathologic condition. microRNA (miRNA/miR) plays crucial role in biological processes. Psychosomatic etiologies in oral diseases induce epigenetic alterations that may serve as biomarkers for pathological conditions. MicroRNA (miRNA/miR) plays a critical role in biological processes. Sixteen studies were selected based on their relevance to the topic and novelty. MiRNA expression is regulated and has been found to be associated with psychological disorders that cause oral manifestations. This study investigates the potential biomarker role of miRNAs expressed in oral diseases associated with psychological disorders.

Keywords: *Biomarker, MicroRNA, Neurological disorders, Oral manifestation, Psychological disorders*

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The oral cavity serves as a point of entry and a biological indicator, reflecting systemic changes in the body, such as weakened immune function or other related disorders. Patients with psychiatric disorders exhibit mental, physical, and social disabilities, leading to neglect in health habits and oral care. The impact of psychotropic medications on the oral cavity is influenced by hormonal changes, leading to vascular, muscular, and other physiological dysfunctions that result in tissue loss and disrupt homeostasis. The imbalance in psychological health may lead to a factor known as biopsychosocial. The International Classification of Functioning, Disability and Health (ICF) outlines the biopsychosocial model as a framework for understanding disease and disability. This model emphasizes the interrelatedness of three parameters: body functions, activities, and social participation (which is describe in the figure 1 below)[1].

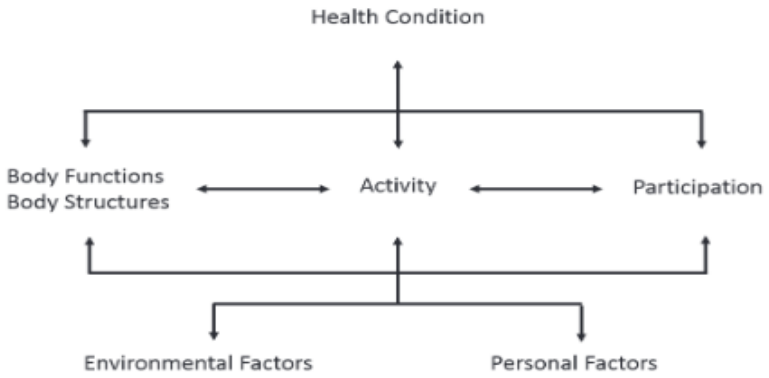

Figure 1. Frameworks of ICF, Mental, social, and psychological health are dependable towards systematic whole-body health and wellness [1].

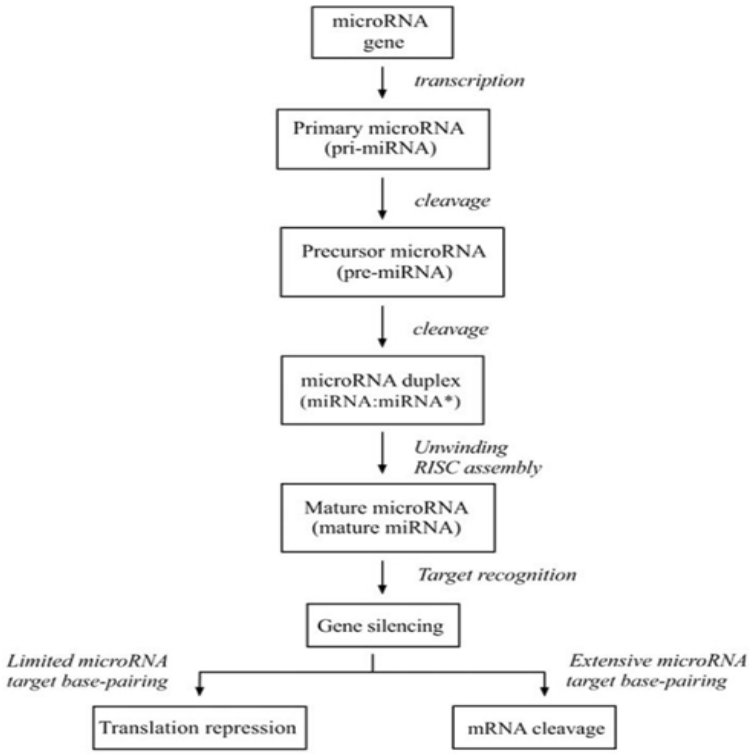

Figure 2. The Biogenesis of miRNA and silencing mechanism with mRNA targets [4].

Patients with psychiatric disorders exhibit increased vulnerability to oral diseases. Social, environmental, and other external factors shape the brain. The brain's plasticity facilitates survival through molecular epigenetic modifications. MicroRNAs (miRNAs/miR) respond to significant biological processes and regulate gene expression in response to environmental exposure. miRNA is highly expressed in the brain and has the capability to integrate external factors, such as environmental inputs, to adjust gene expression. miRNA has been shown to be abnormally expressed, negatively impacting the conditioning ability of human behavior in social interactions, as observed in cases of dementia and autism[2].

Evidence suggests that a gene and transcriptional factors associated with stress are also implicated in obesity, potentially elucidating the molecular mechanisms by which miRNA sharing influences anxiety and metabolic disorders. miRNA is a type of non-coding RNA that regulates gene expression, consisting of sequences that are 20-25 nucleotides in length. miRNA binds to its target through short complementary sequences, leading to the attenuation of messenger RNA (mRNA) translation. MicroRNAs can be delivered via cargo, such as exosomes and other vesicles, to penetrate target cells and organs [3].

MicroRNAs (miRNAs) are highly conserved, single-stranded molecules that target mRNA to inhibit translation or facilitate mRNA degradation. The biogenesis of miRNA begins with a series of complex cleavage steps (Fig. 2). Upon transcription of the miRNA gene, primary microRNA (pri-miRNA) is produced. Nuclear cleavage results in the cleavage of pri-miRNA, leading to the formation of precursor microRNA (pre-miRNA). Pre-miRNA is transported to the cytoplasm via exportin-5, where it undergoes cleavage to form a microRNA duplex containing the mature miRNA. The duplex will dissociate, allowing the mature miRNA to associate with the RNA-induced silencing complex (RISC) effector on the strand. This complex will facilitate the identification of mRNA targets and the assessment of silencing or cleavage of mRNA.[4].

Rosa *et al*. demonstrate a study on miRNA expression influenced by microbiota colonies, which condition the limbic system and are associated with depression and anxiety, leading to mood fluctuations. In normal colonization, miR-185-5p and miR-182-5p exhibit decreased levels in the amygdala. These miRNAs are implicated in the regulation of stress and fear responses. Following the fear conditioning experiment on mice, the expression levels of miR-34b-5p, miR-34c-5p, and miR-34b-3p were found to be low, suggesting that these deletions contribute to anxiety resilience and the retention of fear-related memories[5].

Depression, anxiety, and psychological stress lead to alterations in neurotropics, disrupting the biological cycle of hormonal secretion. This disruption induces dysfunction in vascular and muscular systems, resulting in pain, burning sensations, and ulcerations. These factors can lead to the development of oral mucosal lesions and disorders, including oral lichen planus, recurrent aphthous stomatitis, and burning mouth syndrome[6]. Under stress conditions, the autonomic nervous system undergoes sympathetic and

parasympathetic changes, leading to an imbalance in the hypothalamic-pituitary-adrenal axis, which affects immune response through cytokine production. Stress increases the levels of salivary cortisol and reactive oxygen species, which contribute to the onset of lesions such as aphthous stomatitis.[7]. Collectively, microRNAs may serve as potential biomarkers and therapeutic targets for oral manifestations associated with psychological disorders.

METHOD

MicroRNA and oral manifestation with psychological disorders compromise multiple fields of molecular, oral and maxillofacial medicine, neurology, and psychology. A literature review of these abroad components is needed to be systematically choosing the articles. To limit the review, the oral manifestations were concreted to atypical odontalgia, bruxism, burning mouth syndrome, myofascial pain dysfunction, oral lichen planus, orofacial pain, recurrent aphthous stomatitis. The search of article performed using the databases of Google Scholar, Pubmed, ScienceDirect, and Scopus by using combination of "microRNA", "psychological disorders", "neurological disorders", "oral manifestation", "atypical odontalgia", "bruxism", "burning mouth syndrome", "myofascial pain dysfunction", "oral lichen planus", "orofacial pain", and "recurrent aphthous stomatitis" as keywords (Table 3).

Due the limitations of published interest study, there was not set for date and types of publication restriction. The relevancy of the further explanation and exploratory of the study, individual articles were retrieved manually to be added and elaborated the findings discussion. So the study selections are according into the criteria written in English or no imposing linguistic which constrained, related according to the interest keywords into the search engine, and with the time of study 10-year published. The review was performed based on PRISMA guidelines which described in figure 3.

The quality assessment of the included studies was performed the Database of Abstract of Reviews of Effects (DARE) method[8]. The criteria is consisting of five question: (i) was inclusion/ exclusion of the criteria in study reported; (ii) was the search of interest study adequate to be reviewed; (iii) was the included study's quality are done assessed; (iv) are the details sufficiently included in individual studies; (v) were the studies also assessed until synthesis data. After that, it will be interpreted by fulfilling "yes", "partial", "no" and the score described using level of agreement and kappa index[9] which described in the table 2.

Table 1. The Search Strategy

Database	Keywords
Google Scholars PubMed	("microRNA"[All field] OR "miR" [All field]) AND ("psychological disorders"[All field] OR "neurological disorders"[All field]) AND ("oral manifestation"[MeSh Subheading], AND "atypical odontalgia[All field]" OR "bruxism" [All field], OR "burning mouth syndrome" [All field],OR "myofascial pain dysfunction" [All field], OR"oral lichen planus" [All field], OR"orofacial pain" [All field], OR "recurrent aphthous stomatitis" [All field]
ScienceDirect	"microRNA" AND "psychological disorder" AND "oral manifestation" OR "atypical odontalgia" OR "bruxism" OR "burning mouth syndrome" OR "myofascial pain dysfunction" OR "oral lichen planus" OR "orofacial pain" OR"recurrent aphthous stomatitis"
Scopus	(ALL (microRNA) AND (psychological disorder) AND (oral manifestation))

RESULT

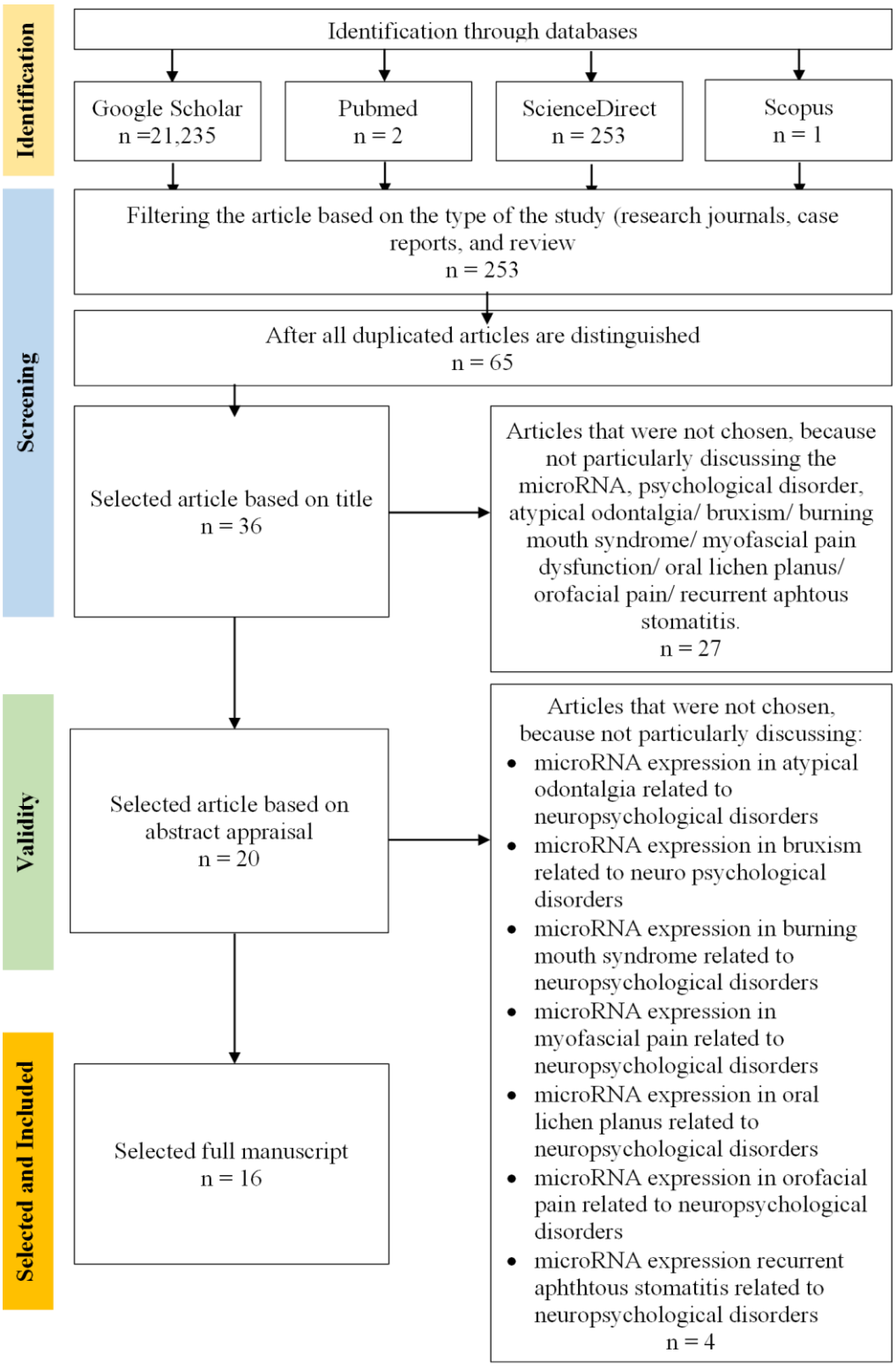

Figure 3. Schematic strategical literature searches of the study with PRISMA flow diagram

Table 2 Detailed Result of DARE assessment

No	Author	Inclusion and Exclusion	Search coverage	Assessment of Quality	Study Description	Synthesis of Study	Kappa Index	Level of Agreement
1.	Vali *et al*, 2023	Y	Y	Y	Y	Y	1.00	Almost perfect
2.	Wieckiewicz *et al*, 2020	Y	Y	Y	Y	Y	1.00	Almost perfect
3.	Kim *et al*, 2019	Y	Y	Y	Y	Y	1.00	Almost perfect
4.	Antolis *et al* , 2021	Y	Y	Y	Y	Y	1.00	Almost perfect
5.	Shrivastava *et al*, 2021	Y	Y	Y	Y	Y	1.00	Almost perfect
6.	Naghikani *et al*, 2019	Y	Y	Y	Y	Y	1.00	Almost perfect
7.	Bai *et al*, 2007	Y	Y	Y	Y	Y	1.00	Almost perfect
8.	Li *et al*, 2022	Y	Y	Y	Y	Y	1.00	Almost perfect
9.	Seif *et al*, 2022	Y	Y	Y	Y	Y	1.00	Almost perfect
10.	Mehdipour *et al*, 2018	Y	Y	Y	Y	Y	1.00	Almost perfect
11.	Byun *et al*, 2015	Y	Y	Y	Y	Y	1.00	Almost perfect
12.	Olga *et al*, 2023	Y	Y	Y	Y	Y	1.00	Almost perfect
13.	Sabina *et al*, 2022	Y	Y	Y	Y	Y	1.00	Almost perfect
14.	Dong *et al*, 2014	Y	Y	Y	Y	Y	1.00	Almost perfect
15.	Bao *et al*, 2023	Y	Y	Y	Y	Y	1.00	Almost perfect
16.	Cai *et al*, 2023	Y	Y	Y	Y	Y	1.00	Almost perfect

Y: Yes, N: Partial; N: No

Table 4. Summary of literatures miRNAs expression in oral manifestation of neuropsychological disorder

No	Title	Author(s) and Published Year	Study Design	Source and Method	Marker	Result	Oral Disease Type
1	miRNA contributes to neuropathic pains[10]	Vali *et al*, 2023	Scope Review	Leinders *et al* (2016), observing the white blood cell (WBC) with miR-132-3p expression in 30 patients and 30 healthy controls that showing chronic pain	miR-132-3p	miR-132-3p found 2.6 fold increase in WBC of neuropathic pain	Neuropathic Pain (Atypical Odontalgia)
				Sakai and Suzuki (2013) performed rat in vivo experiment by investigating miR-21 that involved in neuropathic pain	miR-21	miR-21 expression modulate the pain in chronic neuropathic pain	
				Yan *et al* (2018) investigated miR-32-5p in post spinal ligation causing neuropathic pain	miR-32-5-p	miR-32-5p found promoting neuropathic pain	
2	Generic basis of sleep bruxism and sleep apnea-response to a medical puzzle[11]	Wieckiewicz *et al*, 2020	Cross sectional study	The authors presented to analyze the single nucleotide polymorphism in 100 caucasian group (74 with sleep bruxism and 28 patients with sleep apnea) and 125 healthy group as a control.	miR-504	miR-504 is found to be targeting rs686 od dopamine receptor gene DRD1	Bruxism
3	Profiling of Salivary Exosoma MicroRNAs in Burning Mouth Syndrome Patients[12]	Kim *et al*, 2019	Cross sectional study	The authors assessed 15 patients salivary exosomal miRNAs with next generation sequencing to observe the microRNA expression	28 miRNAS expressed in salivary BMS patients	Upregulated miRNAs: miR-1273h-5p, miR-1273a, miR-1304-3p, miR-4449, miR-1285-3p, miR-6802-5p, miR-1268a, miR-1273d, miR-1273f, and miR-423-5p Downregulated miRNAs: miR-27b-3p, miR-16-5p, miR-186-5p, miR-142-3p, miR-141-3p,	Burning Mouth Syndrome

						miR-150-5p, miR-374a-5p, miR-93-5p, miR-29c-3p, miR-29a-3p, miR-148a-3p, miR-22-3p, miR-27a-3p, miR-424-5p, miR-19b-3p, miR-99a-5p, miR-548d-3p, and miR-19a-3p	
4	Molecular genetics and epigenetics of temporomandibular disorders[13]	Antolis *et al* , 2021	Scope review	The authors summarized that miR-140 is expressed in temporomandibular joint.	miR-140	The expression of miR-140 controls bone homeostasis for bone remodeling, the loss expression causing the TMD	Myosfacial Pain Dysfunction due Temporomandibular Joint Disorder
5	Review article – A comprehensive review on biomarkers associated with painful temporomandibular disorders[14]	Shrivastava *et al*, 2021	Scope Review	The authors summarized miRNAs which expressed in painful TMD are miR-221-3p, miR-140-5p, miR-101a-3, and miR-21-5p.	miR-221-3p, miR-140-5p, miR-101a-3p, and miR-21-5p	miR-221-3p expression has downregulated in degenerative joint disease, miR-140-5p has a role in TMJ degenerative changes,	
6	Effect of dry needling on miR-939 and miR-25 serum levels in myofascial pain syndrome with shoulder girdle myofascial trigger points[15]	Naghikani *et al*, 2019	Case control study	The authors performed dry needling to treat mucopolysaccharidosis and assess miR-939 and miR-25 serum level in 25 myofascial trigger points patients	miR-939 and miR-25	miR-939 and miR-25 upregulated after the treatment indicating the less painful in patients	
7	Downregulation of selective microRNAs in trigeminal ganglion neurons following inflammatory muscle pain[16]	Bai *et al*,2007	In vivo study	The authors explored the treatment in inflammatory pain by giving Freund's adjuvant (CFA) into rat masseter muscle one-side and quantified the miRNA in trigeminal ganglion.	miR-10a, miR-29a, miR-98, miR-99a, miR-124a, miR-134, miR-183	miR-29a, miR-98, miR-99a, miR-124a, miR-134, miR-183 were found rebound higher after the treatment.	
8	The functional mechanism of microRNA in oral lichen planus[17]	Li *et al*, 2022	Scope Review	The authors summarized miR-123, miR-647, miR-31 as the pathogenesis of erosive OLP, miR-122 for apoptosis in keratinocytes, miR-21 and miR-125b allowing leading into malignant. Additionally, the authors continued for search in miR-214, miR,146a, miR-155, miR-27a/b, and miR-26a/b.	miR-123, miR-647, miR-31, miR-122, miR-21, miR-125b, miR-214, miR-146a, miR-155, miR-27a/b, miR-26a/b	miR-214 is found downregulated in OLP by targeting CD44, miR-146a is upregulated by targeting STAT1, IFN-γ, IL-2 in $CD4^+$ T reg cells, miR-155 is shown upregulated by targeting SOCS1 in erosive OLP, miR-27a/b is downregulated by targeting TGF-β, p53, p63, Smad, and miR-26a/b shown downregulated targeting PKCδ/ CD38.	Oral Lichen Planus
9	The expression of salivary microRNAs in oral lichen planus: searching for a	Seif *et al*, 2022	Scope Review	The authors summarized 8 miRNAs which are expressed in OLP.	miR-155, miR-4484, miR-21,	The upregulated miRNAs are: miR-155, miR-	

	prognostic biomarker[18]				miR-142-3p, miR-125a, miR-137, miR-320a, miR-27b	4844, miR-21, miR-142-3p The downregulated miRNAs are: miR-125a, miR-137, miR-320a, miR-27b.	
10	Diagnostic and prognostic relevance of salivary microRNA-21, -125a, -31 and, -200a levels in patients with oral lichen planus – a short report[19]	Mehdipour *et al*, 2018	Cross sectional study	The authors performed an exploration from 30 patients with OLP and quantified the expressed miR-21, miR-125a, miR-31 and miR-200a.	miR-21, miR-125a, miR-31, and miR-200a	MiR-21 and miR-31 are shown upregulated and miR-125b and miR-200a down regulated in OLP	
11	Diagnostic profiling of salivary exosomal microRNAs in oral lichen planus patients[20]	Byun *et al*, 2015	Case control study	The authors observed exosomal salivary miRNA in patients OLP and quantified miR-4484, miR-1246, and miR-1290.	miR-4484, miR-1246, and miR-1290	miR-4484 is upregulated and targeting lymphoblastoid cell lines.	
12	Genetics of musculoskeletar and neuropathic orofacial pain: a narrative review[21]	Olga *et al*, 2023	Scope review	The authors summarized the serum miRNAs in Trigeminal Neuralgia causing Orofacial Pain.	miR-132-3p, miR-146-5p, miR-155-5p, miR-384.	miR-132-3p, miR-146-5p, miR-155-5p, miR-384 expressed to be related with trigeminal neuralgia by targeting genes for proliferation and migration of Schwan cells, proliferation, regeneration, and apoptosis.	Orofacial Pain caused by Trigeminal Neuralgia
13	Expression and biological functions of miRNAs in chronic pain: a review on human studies[22]	Sabina *et al*, 2022	Narrative review	The authors summarized the miRNAs expressed in Orofacial Pain	miR-126-3p, miR-155-5p, miR-21-5p	miR-126-3p and miR-155-5p are overexpressed	Orofacial Pain
14	Decreased microRNA-125a-3p contributes to upregulation of p38 in rat trigeminal ganglions with orofacial inflammatory pain[23]	Dong *et al*, 2014	*In vivo* study	The authors observed miR-125a-3p expression in orofacial inflammatory pain.	miR-125a-3p	miR-125-5p is negatively correlated orofacial inflammatory pain and targeting p38 MAPK.	Orofacial Pain
15	Identification and functional analysis of serum specific miRNA in recurrent aphthous stomatitis patients with excess-heat or yin-deficiency[24]	Bao *et al*, 2023	Cross sectional study	From 90 patients were selected and after being treated with Traditional Chinese Medicine and observed the expressed miRNA in RAS	miR-20-5p	miR-20-5p is expressed in RAS	Recurrent Aphthous Stomatitis
16	Characterization of immune landscape and development of a novel N7-methyguanin-related gene signature to aid therapy in recurrent aphthous stomatitis[25]	Cai *et al*, 2023	In vitro study	The authors are performed using N7-methylguanin/ m7G gene in RAS. Then found the binding target gene of m7G in RAS with expressed miRNAs through Protein-Protein Interaction (PPI)	miR-423-3p, miR-10-25p, miR-218-5p	There are interactions among miR-423-3p, miR-10-25p, miR-218-5p and m7G.	

DISCUSSION

MicroRNAs expression in Atypical Odontalgia

Comorbid psychiatric disorders negatively impact orofacial pain. Orofacial pain is characterized by persistent discomfort in the dentoalveolar region, often manifesting as chronic dental pain without identifiable pathogenic signs. Trigeminal neuralgia can be diagnosed in conjunction with neuropathic pain in atypical odontalgia. A study in Okayama demonstrated that 82.1% of patients with orofacial pain are attributed to trigeminal neuralgia. Atypical odontalgia is characterized primarily by continuous throbbing pain and stabbing sensations, rather than paroxysmal pain types. Atypical odontalgia is associated with psychological comorbidity. Conditions such as depression, anxiety, and a low likelihood of bipolar disorder and schizophrenia[26].

miRNAs play a role in regulating neuropathic pain, including trigeminal neuropathic pain, which is a contributing factor to atypical odontalgia. MicroRNAs also modulate immune responses and neuronal activity. miR-132-3p is found to be highly expressed in patients compared to healthy individuals. The nerve injury, indicative of blood-nerve barrier impairment, demonstrates an elevated expression of miR-21. The putative target gene of miR-21 is the RECK gene, which is suppressed and downregulated the Mmp9 gene while upregulating the Tgfb gene. This indicates the pain-mimicking behavior of miR-21 in neuropathic conditions. miR-21 plays a significant role in neuropathic pain and pain-like behavior, as evidenced by its target genes and the associated effects on expression. miR-32-5p is downregulated in trigeminal ganglia, contributing to neuropathic pain through the regulation of the Cav3.2 calcium channel in the central nervous system, thereby modulating and sustaining neuropathic pain [10,27]. Chronic pain associated with miR-21 and miR-32-5p expression clinically shown targeting of MMP-9, resulting in blood-nerve barrier disruption, and favorably regulated TGF-β through the RECK pathway.

MicroRNAs expression in Bruxism

Bruxism involves the activity of masticatory muscles, characterized by either phasic/rhythmic or tonic/non-rhythmic contractions, and is not classified as a movement disorder. Critical clinical signs for diagnosing bruxism, according to the International Classification of Sleep Disorders, include audible tooth grinding, abnormal tooth wear, and associated symptoms such as jaw muscle pain, fatigue, headaches, and jaw locking during wakefulness. This sleep disorder provides evidence that autonomic nervous systems are in a disordered state, leading to bruxism. Electroencephalography in bruxism patients reveals cortical disturbances accompanied by tachycardia as clinical indicators, along with elevations in sympathetic tone related to neurotransmitters, and the involvement of central dopaminergic or serotonergic mechanisms in the genesis of bruxism. The single nucleotide polymorphism (SNP) is a genetic factor associated with the etiology of bruxism. miR-504 has been identified as an expressed miRNA in bruxism through its binding to the 3' untranslated region (3'UTR) of the rs686 SNP in the DRD1 gene, which encodes the dopamine receptor D1. This receptor is responsible for neuropsychiatric disorders[11]. Thus, it will lead the important role of miR-504 expression in dopamine receptor due the alteration of allele sequence, causing bruxism. The interplay of environmental external stressors influences the genetic predisposition which indicate the interaction in bruxism's etiology-the calcium signaling, GABAergic systems, and the expressed microRNAs-that potentially to be therapeutic targets.

MicroRNAs expression in Burning Mouth Syndrome

Burning mouth syndrome, as defined by the International Classification of Headache Disorders, third edition, beta version (ICDH-III-β), is characterized by dysesthesia or a burning sensation that persists as a chronic medical condition, accompanied by certain clinical signs occurring for at least 2 hours per day over a duration of 3 months. There are two forms: essential and idiopathic BMS. The causative factors of BMS include local, systemic, psychological, neurological, and idiopathic origins. Anxiety is prevalent in BMS, with an odds ratio of 2.64 (95% confidence interval). Depression is also more prevalent in BMS. The two risk factors are comorbid in the context of BMS[28]. A study demonstrated that genetic polymorphism contributes to various chronic diseases, as evidenced by the clinical signs of increased production of interleukin-1β, a pro-inflammatory cytokine, in patients with burning mouth syndrome (BMS). The gamma-aminobutyric acid receptor (GABAa-receptor) in peripheral tissue is altered in burning mouth syndrome (BMS), indicating that the neuropathic pathogenesis of BMS is associated with changes in GABAa-receptor density. The density of epithelial nerve fibers and axons in the tongue is reduced in patients with burning mouth syndrome (BMS). This also indicates the etiology of burning mouth syndrome (BMS), with the trigeminal nerve contributing to its development[29].

As a multifactorial disorder, the etiology of BMS is also dependent on genetic factors. Numerous studies have reported that miRNAs modulate pain disorders, particularly in regulating GABAa ligand expression. A study conducted in Korea demonstrated the expression of miRNAs in 15 patients with BMS, utilizing saliva as a medium for quantification. Saliva contains genetic proteins that are analogous to those found in plasma. The study also indicated the use of salivary exosomes for the detection of miRNAs. Twenty-eight miRNAs have been identified as contributors to the etiology of complex regional pain syndrome (CRPS). The upregulated miRNAs in BMS include miR-1273h-5p, miR-1273a, miR-1304-3p, miR-4449, miR-1285-3p, miR-6802-5p, miR-1268a, miR-1273d, miR-1273f, and miR-423-5p. Conversely, the downregulated miRNAs are miR-27b-3p, miR-16-5p, miR-186-5p, miR-142-3p, miR-141-3p, miR-150-5p, miR-374a-5p, miR-93-5p, miR-29c-3p, miR-29a-

3p, miR-148a-3p, miR-22-3p, miR-27a-3p, miR-424-5p, miR-19b-3p, miR-99a-5p, miR-548d-3p, and miR-19a-3p[12].

The expression of miR-1237h in relation to the mRNA binding of chemokines (CXC motif) ligand 12 (CXCL12) in gastric cancer[30]. miR-1273a is associated with the G protein signaling 22 gene (RGS22), miR-1237d is linked to the Kinesin family member 1B gene (KIF1B), and miR-1237f corresponds to the sterol carrier protein 2 (SCP2) gene. The family of miR-1237 is upregulated in patients with BMS[31]. Another study revealed that certain miRNAs, specifically miR-29c-3p and miR-19b-3p, are upregulated in various neuronal disorders and play a significant role in cognitive functions as biomarkers for Alzheimer's disease. In the study by Kim *et al*., the team demonstrated that these two miRNAs are downregulated in BMS. In another case, miR-142-3p is shown to be highly expressed in multiple sclerosis, whereas in the BMS study, it is downregulated. This suggests that miR-142-3p may function as a neuroprotective agent by targeting glutamatergic synaptic neurons and synapses while mediating IL-β[12]. The overexpressed microRNA which released in peripheral blood of BMS patients may indicate the marker of the disease. microRNAs release influencing the pain pathways and simultaneously increase the pain intensity and psychological distress.

MicroRNAs expression in Myofascial Pain Dysfunction

Pain dysfunction in maxillofacial musculature is closely associated with temporomandibular disorder (TMD). TMD, being a multifactorial disease, is influenced by genetic factors. The expression of miRNA is significant in the chondrocytes of patients with temporomandibular disorders (TMD). miR-140, expressed in the temporomandibular joint (TMJ), regulates articular remodeling and bone homeostasis. Its low suppression is associated with susceptibility to temporomandibular disorders (TMD), which can lead to degenerative changes and musculature pain[13]. miR-221-3p has been observed to target Ets-1, a transcription factor that regulates matrix metalloprotease, which is responsible for remodeling and tissue degradation in cartilage. The degenerative changes in the cartilage matrix of the temporomandibular joint (TMJ) are also characterized by the expression of miR-101a-3p and miR-21-5p[14]. Myofascial pain, which is associated with complex regional pain syndrome, involves the downregulation of miR-939 and miR-25. The downregulation of miR-939 correlates with an increase in inflammatory mediators, including vascular endothelial growth factors, TNFa, and NF-κB. Additionally, miR-25 plays a role in cell proliferation via the Wnt pathway and targets VEGF in patients with chronic pain[15]. Another study demonstrated that the expression levels of miR-29a, miR-98, miR-99a, miR-124a, miR-134, and miR-183 were elevated following treatment with complete Freund's adjuvant (CFA) in the trigeminal ganglion under conditions of inflammatory muscle pain [16]. miRNAs which expressed in chronic pain and alleviated by preferred treatment may differs the level of expression, regulates the gene target, and the outcomes. The upregulating pain biomarker in musculoskeletal can be recommended to be the therapeutic target in myofascial pain disorder.

MicroRNAs expression in Oral Lichen Planus

Oral lichen planus (OLP) is a chronic inflammatory disease of the oral mucosa, influenced by factors such as genetics and psychological stress. A case report by Sufiawati *et al*. (2022) examined six patients with Oral Lichen Planus (OLP) using the Depression Anxiety Stress Scale (DASS)-21. Among these patients, three exhibited moderate anxiety, while the others were classified as having severe anxiety levels. In patients with depression level 5, one exhibited moderate stress while the others experienced mild stress. Psychological stress leads to dysregulation in immune processes by causing an imbalance in neuroendocrine and neuroimmune disorders within epithelial tissues[32].

The genetic factors involved in oral potentially malignant disorders (OPMD) of oral lichen planus (OLP) indicate that the development of this autoimmune disease, mediated by T cells, is regulated by miRNA. The expression of miR-214 confirms that low levels of miR-214 directly target CD44, which is associated with the progression of OLP. miR-146a is upregulated and targets STAT1, IFN-γ, and IL-2 to regulate the OLP in conjunction with the forkhead box P3 (FOXP3) inflammation mediator within the T-regulatory cell axis. miR-155 targets suppressor of cytokine signaling 1 (SOCS1) through negative regulation, leading to the deregulation of endothelial nitric oxide synthase in OLP. miR-27 expression is implicated in the proliferation of myocytes, neuroblastoma cells, and T cells. In OLP, miR-27 is implicated in the proliferation of oral keratinocytes and the apoptosis of basal epithelial cells. miR-26 is expressed in oral lichen planus (OLP), where it inhibits IL-6, TNF-a, and NF-κB in inflammatory responses. It also suppresses the vitamin D receptor pathway in the oral keratinocyte microenvironment and inhibits protein kinase C-delta (PKCδ), an apoptosis regulator, in CD38, contributing to inflammation in OLP[17].

Another study indicated that atrophic and erosive oral lichen planus expressed miR-155 and exosomal miR-4484. These two upregulated miRNAs each target specific genes, with miR-155 playing a role in the expression of proinflammatory cytokines. Additionally, the function of downregulated miR-125a is expressed in OLP16. miR-4484 is associated with the expression of matrix metalloproteinase 21 (MMP-21) and shows a correlation with lymphoblastoid cell lines[31,18]. Additionally, there is an upregulation in the expression of miR-21 and miR-142-3p. miR-21 contributes to genomic instability, whereas miR-142-3p promotes keratinocyte proliferation in oral lichen planus (OLP). The downregulation of miR-137 and miR-320a contributes to dysregulation in the cell cycle and angiogenesis in OLP16. In the OLP condition, the dysplastic type exhibited lower expression of miR-31, which became upregulated during the transformation to OSCC[19]. MicroRNAs which expressed in OLP conditions, may exhibit the

imbalance of its expression level. The upregulated miRNAs in OLP (miR-7a-3p, miR-21-3p, miR-100-5p) correlating to OLP severity. miRNAs bind the target of mRNA in cytokine regulations. Several microRNAs (miR-93 and miR-412-3p) also exhibit the interplay of pathogenesis in transformation into OSCC condition.

MicroRNAs expression in Orofacial Pain

The International Association for the Study of Pain (IASP) characterized chronic pain as being significantly associated with emotional factors. Orofacial pain, as a component of chronic pain, is classified according to its etiological factors, which include dentoalveolar issues, mucosal diseases, bony pathologies, sinusitis, salivary gland disorders, musculoskeletal conditions, neuropathic pain, vascular problems, and other categories[7]. Clinical symptoms of orofacial pain are characterized by pain and discomfort in the maxillofacial region. Orofacial conditions are consistently associated with long-term correlations to depression, anxiety, and subsequent psychological impairment[33].

The biogenetics of orofacial pain is discussed in relation to the mechanisms and causes of temporomandibular disorders (TMD), trigeminal neuropathic pain (PTTN), and trigeminal neuralgia (TN). Levels of miR-132-3p, miR-145-5p, miR-155-5p, and miR-384 are elevated during the progression of TN. These miRNAs target Schwann cells in processes such as proliferation, migration, regeneration, and apoptosis[21]. Patients with orofacial conditions also experience headaches or migraines for 15 days per month over a duration exceeding 3 months. miR-155-5p directly targets the nuclear factor-E2 related factor 2 (Nrf2) gene, leading to its downregulation and influencing neuroimmunity in TN progression. miR-126-3p, miR-34-a-5p, and miR-375 have been identified as overexpressed in migraine cases. miR-34a-5p and miR-382-5p are implicated in neurogenic inflammation, cellular degranulation, and vasodilation associated with migraines[22]. miRNAs expressed in the orofacial region include miR-125a-3p, found in the trigeminal ganglion, which is involved in pain transduction processes such as nerve impulse transmission, synaptic transmission, and action potential regulation. miR-125a-3p exhibits a negative correlation with p38 mitogen-activated protein kinase (MAPK) in orofacial pain, which is involved in neuronal network sensitization and the neuroimmune response[23].

The interference innervation in trigeminal nerve due injury is corresponding to the microRNAs' expression. miR-6954-3p is proven to be downregulated inducing the elevation of voltage-gated sodium channel β2 subunit (SCN2B), this condition lead into orofacial neuropathic pain. miR-6954-3p will complicates the networks trigeminal neuralgia. The pain signaling pathway is proposedly under the competing endogenous RNA (ceRNA) to be formed (by interactions miRNA with mRNA target)[34,35].

MicroRNAs expression in Recurrent Aphthous Stomatitis

Recurrent aphthous stomatitis is an ulcerative lesion of the oral mucosa. The lesion presents as a self-limiting ulcer that is recurrent, occurring in nonkeratinized mucosa, accompanied by a burning sensation and prodromal symptoms lasting over one day. Numerous studies have demonstrated that stress and anxiety are implicated in the role of RAS and contribute to lesion promotion. Psychological stress induces immunoregulatory activity, evidenced by an increased number of leukocytes at sites of inflammation[36]. A study demonstrated the expression of miR-20b-5p in RAS, indicating its potential role as a biomarker for the regulation of hypoxia inducible factor 1 (HIF1) and signal transducer and activator of transcription 3 (STAT3). The single nucleotide polymorphism in the STAT3 gene is linked to RAS[24].

Cai *et al*. (2023) demonstrated the protein-protein interaction (PPI) to elucidate the transcription factors-microRNA-messenger RNA network in the 7-methylguanosine (m7G) gene of RAS. Three miRNAs are expressed: miR-423-3p, miR-10b-5p, and miR-218-5p. m7G plays a significant role in stabilizing transfer RNA (tRNA). miR-10b-35p is a novel entity in RAS, functioning in immune regulation and targeting transcription factors such as m7G, apurinic/apyrimidinic endonuclease 1 (APEX1) involved in DNA repair, SRY-box transcription factor 10 (SOX10) relevant to embryonic development and tissue formation, and the aryl hydrocarbon receptor (AHR) gene, which regulates immune responses, cellular differentiation, and stem cell development[25].

The ceRNA is hypothesized to arise via the interaction of miRNA or other non-coding RNAs with the mRNA targets of the pro-inflammatory cytokines IL-6 and IL-18 in RAS patients. The cancer susceptibility 2 (CASC2) gene is a proposed target gene implicated in the pathophysiology of RAS during the heightened inflammatory phase.

The expression of miRNAs in oral diseases associated with neuropsychological disorders has the potential to reveal new biomarkers, enhancing the understanding of pathogenesis, target gene studies, and molecular targeted therapies. This study's examination of microRNA expression may lead to diverse opportunities for the management of various oral diseases in both research and clinical practice.

REFERENCES

1. Norderyd, Johanna. *et al.* A biopsychosocial approach to functioning, oral health and specialist dental health care in children with disabilities - Swedish and international perspectives. (2017).
2. Popa, N., Boyer, F., Jaouen, F., Belzeaux, R. & Gascon, E. Social Isolation and Enrichment Induce Unique miRNA Signatures in the Prefrontal Cortex and Behavioral Changes in Mice. *iScience* **23**, (2020).

3. Meydan, C., Shenhar-Tsarfaty, S. & Soreq, H. MicroRNA Regulators of Anxiety and Metabolic Disorders. *Trends Mol Med* **22**, 798–812 (2016).

4. MacFarlane, L.-A. & Murphy, P. R. MicroRNA: Biogenesis, Function and Role in Cancer. *Curr Genomics* **11**, 537 (2010).

5. Rosa, J. M., Formolo, D. A., Yu, J., Lee, T. H. & Yau, S. Y. The Role of MicroRNA and Microbiota in Depression and Anxiety. *Front Behav Neurosci* **16**, (2022).

6. Suresh, K. V *et al.* Oral mucosal diseases in anxiety and depression patients: Hospital based observational study from south India. *J Clin Exp Dent* **7**, 95–104 (2015).

7. Alrashdan, M. S. & Alkhader, M. Psychological factors in oral mucosal and orofacial pain conditions. *Eur J Dent* **11**, 548 (2017).

8. Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews. (1995).

9. McHugh, M. L. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)* **22**, 276 (2012).

10. Vali, R. *et al.* miRNA contributes to neuropathic pains. *Int J Biol Macromol* **253**, 126893 (2023).

11. Wieckiewicz, M. *et al.* Genetic basis of sleep bruxism and sleep apnea—response to a medical puzzle. *Sci Rep* **10**, 1–14 (2020).

12. Kim, K.-Y., Byun, J.-S., Jung, J.-K. & Choi, J.-K. Profiling of Salivary Exosomal Micro RNAs in Burning Mouth Syndrome Patients. *J Oral Med Pain* **44**, 25–30 (2019).

13. Antolis, M., Langit, K. S., Gultom, F. P. & Auerkari, E. I. Molecular genetics and epigenetics of temporomandibular disorder. *J Phys Conf Ser* **1943**, (2021).

14. Shrivastava, M., Battaglino, R. & Ye, L. A comprehensive review on biomarkers associated with painful temporomandibular disorders. *Int J Oral Sci* **13**, (2021).

15. Naghikhani, M., Nasrabadi, H. T., Soleimanirad, J., Joghataei, M. T. & Arablu, A. M. Effect of Dry Needling on miR-939 and miR-25 Serum Levels in Myofascial Pain Syndrome With Shoulder Girdle Myofascial Trigger Points. *Crescent Journal of Medical and Biological Sciences* **6**,.

16. Bai, G., Ambalavanar, R., Wei, D. & Dessem, D. Downregulation of selective microRNAs in trigeminal ganglion neurons following inflammatory muscle pain. *Mol Pain* **3**, 13–16 (2007).

17. Li, Y. *et al.* The Functional Mechanism of MicroRNA in Oral Lichen Planus. *J Inflamm Res* **15**, 4261–4274 (2022).

18. Seif, S. *et al.* The expression of salivary microRNAs in oral lichen planus: Searching for a prognostic biomarker. *Pathol Res Pract* **234**, 153923 (2022).

19. Mehdipour, M. *et al.* Diagnostic and prognostic relevance of salivary microRNA-21, -125a, -31 and -200a levels in patients with oral lichen planus - a short report. *Cellular Oncology* **41**, 329–334 (2018).

20. Byun, J. S., Hong, S. H., Choi, J. K., Jung, J. K. & Lee, H. J. Diagnostic profiling of salivary exosomal microRNAs in oral lichen planus patients. *Oral Dis* **21**, 987–993 (2015).

21. Olga, A. *et al.* Genetics of musculoskeletal (TMD) and neuropathic orofacial pain : a narrative review . Genetics of musculoskeletal (TMD) and neuropathic orofacial pain : a narrative review. 1–16 (2023).

22. Sabina, S. *et al.* Expression and Biological Functions of miRNAs in Chronic Pain : A Review on Human Studies. (2022).

23. Dong, Y., Li, P., Ni, Y., Zhao, J. & Liu, Z. Decreased MicroRNA-125a-3p Contributes to Upregulation of p38 MAPK in Rat Trigeminal Ganglions with Orofacial Inflammatory Pain. **9**, 5–12 (2014).

24. Bao, J. *et al.* Identification and Functional Analysis of Serum Specific miRNAs in Recurrent Aphthous Stomatitis Patients with Excess-heat or Yin-deficiency. *Clinical Complementary Medicine and Pharmacology* **3**, 100079 (2023).

25. Cai, X. *et al.* Characterization of immune landscape and development of a novel N7-methylguanine-related gene signature to aid therapy in recurrent aphthous stomatitis. *Inflammation Research* **72**, 133–148 (2023).

26. Tizzoni, R., Tizzoni, M. & Clerici, C. A. Atypical odontalgia and trigeminal neuralgia: psychological, behavioral and psychopharmacological approach in a dental clinic – an overview of pathologies related to the challenging differential diagnosis in orofacial pain. *F1000Res* **10**, (2021).

27. Korczeniewska, O. A., Kohli, D., Benoliel, R., Baddireddy, S. M. & Eliav, E. Pathophysiology of Post-Traumatic Trigeminal Neuropathic Pain. *Biomolecules* **12**, 1–17 (2022).

28. Galli, F., Lodi, G., Sardella, A. & Vegni, E. Role of psychological factors in burning mouth syndrome: A systematic review and meta-analysis. *Cephalalgia* **37**, 265–277 (2017).

29. Savage, N. W. & Abetz, L. M. Burning mouth syndrome and psychological disorders. *Aust Dent J* **54**, 84–93 (2009).

30. Wang, Y. C. *et al.* miR-1273h-5p suppresses CXCL12 expression and inhibits gastric cancer cell invasion and metastasis. *Open Medicine* **17**, 930 (2022).

31. Ivashchenko, A., Berillo, O., Pyrkova, A. & Niyazova, R. Binding Sites of miR-1273 Family on the mRNA of Target Genes. *Biomed Res Int* **2014**, (2014).

32. Sufiawati, I., Megawati, A., Al Farisyi, M. & Putra, I. N. G. J. A Case Series of Psychological Stress Evaluation as a Risk Factor for Oral Lichen Planus. *Case Rep Dent* **2022**, (2022).

33. Karamat, A., Smith, J. G., Melek, L. N. F. & Renton, T. Psychologic Impact of Chronic Orofacial Pain: A Critical Review. *J Oral Facial Pain Headache* **36**, 103–140 (2022).

34. Liu, F. *et al.* MicroRNA-6954-3p Downregulation Contributes to Orofacial Neuropathic Pain in Mice Via Targeting Voltage-Gated Sodium Channel β2 Subunit Protein. *J Pain* **25**, (2024).

35. Fang, Z. H. *et al.* Interactions Among Non-Coding RNAs and mRNAs in the Trigeminal Ganglion Associated with Neuropathic Pain. *J Pain Res* **15**, 2967 (2022).

36. Gallo, C. de B., Mimura, M. A. M. & Sugaya, N. N. Psychological Stress and Recurrent Aphthous Stomatitis. *Clinics (Sao Paulo)* **64**, 645 (2009).