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# The relationship between oral burns and oral squamous cell carcinoma: a systematic review

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**Background:** Micro-RNAs (miRNAs) have been found to play crucial roles in various biological processes and have been implicated in the development and progression of many diseases, including cancer. In recent years, several studies have suggested that miRNA may have a potential role in the relationship between oral burns and various. This systematic review aims to summarize the current evidence on the roles of miRNA in the relationship between oral burns and oral squamous cell carcinoma (OSCC).

**Materials and methods:** The present systematic review was performed using PubMed, Google Scholar, Science Direct, ProQuest, Ovid, and Embase from April 2024 to May 2024 following the "Preferred Reporting Items for Systematic Reviews" guidelines. The keywords, including "oral burn OR burning tongue OR burning mouth" AND "Oral squamous cell carcinoma" AND "miRNA."

**Results:** The study reviewed 9 publications, examining miRNA interactions common to oral burns and cancers. Among them, 5 studies focused on various burn types, while 4 addressed oral malignancies. Synthesizing these findings identified 5 shared miRNAs between burns and oral cancers. Regarding burn types, thermal burns were most mentioned, followed by carbon dioxide laser and chemical burns. For cancer, oral squamous cell carcinoma was predominant, with one study on tongue squamous cell carcinoma. Noteworthy miRNAs include hsa-miR-205, hsa-miR-18a, hsa-mir-23b, hsa-mir-203, and hsa-mir-150, each exhibiting distinct roles and expression patterns in burns and carcinogenesis.

**Conclusion:** Overall, the findings of this systematic review highlight the potential importance of miRNA in the relationship between oral burns and OSCC.

**Keywords:** burns, micro-RNA, oral burns, oral squamous cell carcinoma, systematic review

## Introduction

Oral squamous cell carcinoma (OSCC) presents a significant challenge to public health on a global scale, with an estimated 354 864 new cases and 177 384 fatalities documented in the year 2020[1]. Ranking as the sixth most prevalent form of cancer worldwide, its elevated mortality rates are primarily attributed to belated diagnoses and constrained therapeutic modalities[2]. Studies have highlighted the significance of risk factors like smoking, alcohol consumption, genetic influences, UV light exposure, human papillomavirus infections, and oral microbiota alterations in the progression of OSCC[3-5].

## HIGHLIGHTS

- Synthesizing these findings identified 5 shared miRNAs between burns and oral cancers.
- Regarding burn types, thermal burns were most mentioned, followed by carbon dioxide laser and chemical burns.
- For cancer, oral squamous cell carcinoma was predominant, with one study on tongue squamous cell carcinoma.
- Noteworthy miRNAs include hsa-miR-205, hsa-miR-18a, hsa-mir-23b, hsa-mir-203, and hsa-mir-150, each exhibiting distinct roles and expression patterns in burns and carcinogenesis.
- Overall, the findings of this systematic review highlight the potential importance of miRNA in the relationship between oral burns and OSCC.

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One potential risk factor for OSCC development that has garnered recent attention is oral burns which can stem from various sources like hot foods, beverages, smoking, or tobacco use, potentially leading to chronic damage to the oral mucosa[3]. Chronic exposure to oral burns has been linked to an increased risk of OSCC due to the inflammatory response and tissue damage[6]. Also, the oral mucosa's role in protecting against external insults and maintaining tissue health is crucial, and repeated burns can disrupt these functions, raising the likelihood of developing cancerous lesions[6].

Micro-RNAs (miRNAs) play crucial roles in various cellular processes, including gene expression regulation, chromatin remodeling, and protein translation[7]. Recent studies have highlighted the significant involvement of miRNAs in the relationship between burns and various cancers, impacting cancer initiation, progression, and metastasis[8]. Dysregulated expression profiles of miRNAs in OSCC tissues and cell lines have been linked to clinical outcomes, indicating their potential as biomarkers[9]. Moreover, miRNAs have been implicated in the response of oral tissues to burn injuries, influencing wound healing, tissue repair, and regeneration processes[8]. These findings underscore the multifaceted roles of miRNA in oral health, suggesting their importance as regulators of oncogenic pathways and tissue recovery mechanisms in the context of oral burns and cancer[10,11].

Over all, by conducting a comprehensive systematic review, this study primarily aims to investigate the complicated relationship between oral burns, OSCC, and miRNAs. Also, through synthesizing and analyzing previous research findings, the objective is to explain the molecular mechanisms that connect oral burns to the development of OSCC, with a particular focus on the regulatory roles of miRNAs.

### Research questions

What are the common miRNAs between burn and OSCC?

How can the identified miRNAs serve as mediators between burn and OSCC?

What is the expression behavior (up- or down-regulation) of these miRNAs in burn and OSCC?

## Methods

### Study registration and reporting

This systematic review was carried out utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary Table S1, available at: http://links.lww.com/MS9/A772)[12]. This systematic review and meta-analysis study have been registered in the International Prospective Register of Systematic Reviews (PROSPERO) database. Given the nature of this investigation as a systematic review involving the scrutiny of previously published research, it is noteworthy that the acquisition of patient-informed consent and ethical approval was deemed unnecessary.

### Search methodology

The ongoing systematic review meticulously adhered to the "PRISMA" guidelines and was rigorously executed by systematically searching multiple databases such as PubMed, Google Scholar, Science Direct, ProQuest, Ovid, and Embase within the timeframe from April 2024 to February 2024[13]. The search procedure was executed by utilizing the following search terms and Boolean operators: "oral burn OR burning tongue OR burning mouth" AND "Oral squamous cell carcinoma" AND "miRNA." The retrieved publications were methodically stored, completely removing any duplicated records. Furthermore, in order to augment accuracy, distinct factors were integrated, such as tongue cell carcinoma and oral cancer.

### Inclusion and exclusion criteria

Our investigation encompasses all experimental studies conducted from 2000 to 2024 (April), examining the impact of oral burns on dysregulated miRNA expression within various oral malignancies, with particular attention given to OSCC. Indeed, In the present study, the inclusion criteria for selecting articles were as follows: studies related to oral cancer, burns in the oral cavity, or both simultaneously, as well as investigations examining miRNA changes during burns or OSCC. Studies that did not meet the specified criteria were excluded: (1) the absence of shared miRNA between oral burns and cancer in the publication, (2) studies primarily focused on bioinformatics, (3) those that did not have molecular assays, (4) articles including reviews, guidelines, or conference proceedings, and (5) duplicated articles across databases.

### Criteria for selection and data extraction

A meticulous and stringent selection process was undertaken, involving a thorough assessment of article titles, abstracts, and full texts, diligently carried out by two independent authors. Only articles containing human, animal, or cell line data, and specifically focusing on in vivo or in vitro studies presented in the English language, were deemed eligible. Publications such as reviews, guidelines, protocols, and conference abstracts were expressly omitted, with sole emphasis placed on original research studies. Initially, both authors scrutinized the full texts, selectively incorporating cases meeting the pre-established inclusion criteria. Articles considered relevant by both authors were subsequently included in the subsequent analysis. Also, Endnote software (V.21) was applied to references management. In cases of disagreement, a third researcher was consulted to facilitate resolution. A concise portrayal of the search process is provided in Fig. 1. The AMSTAR 2 checklist was completed to evaluate the study quality (Supplementary File S2, available at: http://links.lww.com/MS9/A773)[14].

## Results

The current investigation has collated a total of nine studies, encompassing miRNA interactions common to both oral burns and cancers. Among these, five studies specifically addressed various types of burns, while four articles delved into malignancies associated with the oral cavity. Consequently, through the synthesis of findings from these studies, 5 miRNAs have been identified as shared components between burns and oral cavity cancers (Table 1).

### Types of burns and cancer

Within this research, the predominant mentions of burns included thermal burns with three instances, followed by carbon dioxide laser burns and chemical burns, each noted once. Moreover, in terms of cancer findings, three studies were

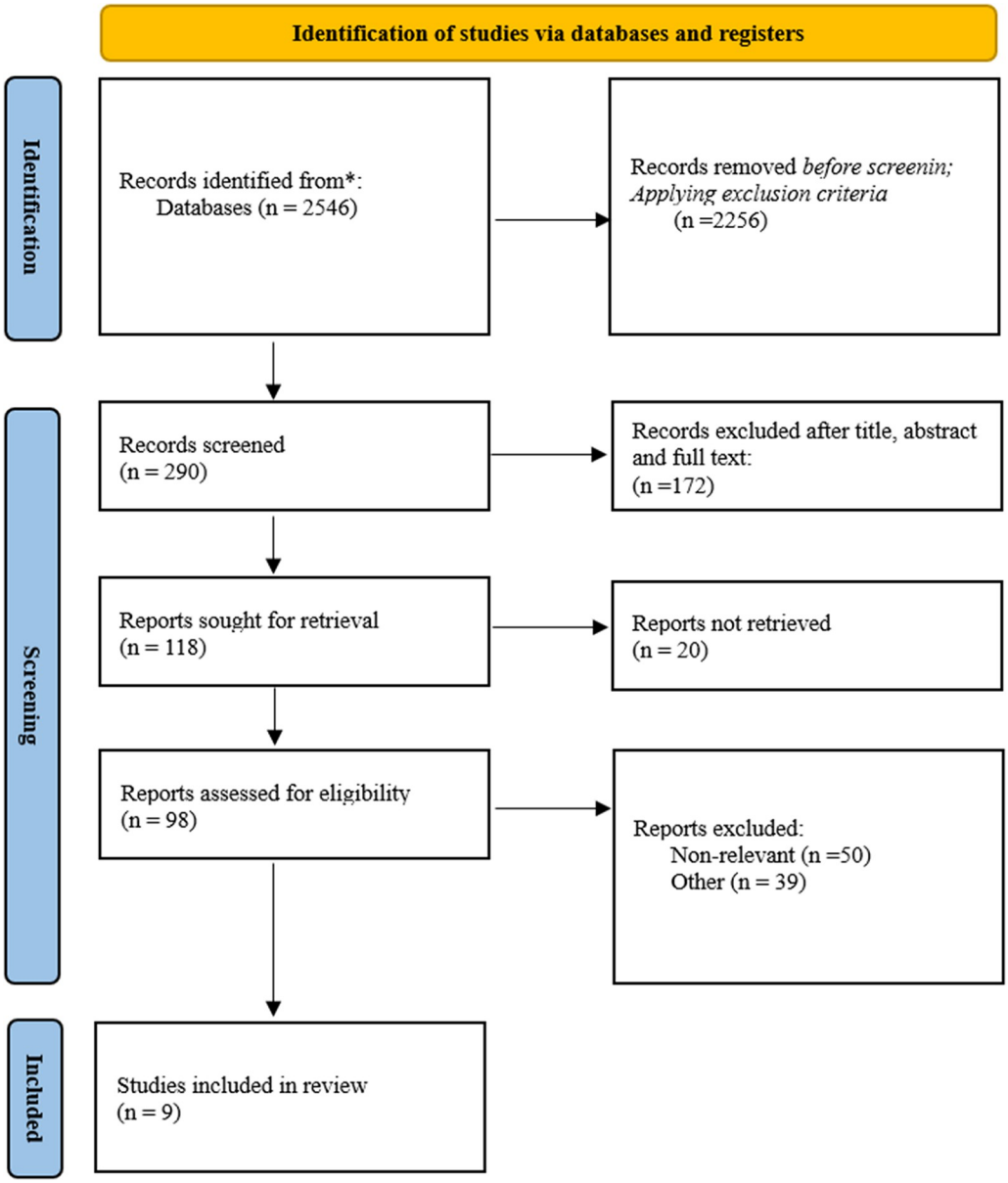


**Figure 1.** Flowchart of the search strategy.

dedicated to oral squamous cell carcinoma, while one study focused on tongue squamous cell carcinoma (Fig. 2).

### *Types of identified miRNAs*

#### Hsa-miR-205

Building upon prior evidence, hsa-miR-205 has been observed to target numerous mRNAs, including the Androgen Receptor itself, thus counteracting epithelial-to-mesenchymal transition (EMT) and the mitogen-activated protein kinase (MAPK) signaling pathways[22]. Additionally, historical texts have depicted the miRNA as a tumor suppressor[23]. Our present findings corroborate these notions, indicating a down-regulation of hsa-miR-205 during burns[16]. Interestingly, a parallel down-regulation of hsa-miR-205 is observed during the onset of OSCC, suggesting a potential association between reduced hsa-miR-205 expression and poorer prognosis among OSCC patients[15].

#### Hsa-miR-18a

hsa-miR-18a plays pivotal roles in cell proliferation, growth, apoptosis, and survival, targeting genes central to these processes and influencing cellular destiny and tissue homeostasis. Furthermore, it is involved in fostering tumor angiogenesis by targeting genes within angiogenic signaling pathways. Additionally, hsa-miR-18a may modulate immune response pathways, potentially contributing to immune-related disorders or diseases[24,25]. In the present study, our evidence indicates

**Table 1**

**Shared components between burns and oral cavity cancers**

| miRNA | Cancer type | Up- or Down-regulation during cancer | Burn type | Up- or Down-regulation during burn | Mechanism of action |
|---|---|---|---|---|---|
| hsa-miR-205 | Oral squamous cell carcinoma[15] | Down-regulated | Thermal injuries[16] | Down-regulated | Promotion of EMT |
| hsa-miR-18a | Oral squamous cell carcinoma[17] | Up-regulation | Fractional CO2 laser[18] | Up-regulation | Tumor Vasculogenesis |
| hsa-mir-23b | Tongue squamous cell[19] | Up-regulation | Thermal injuries[20] | Up-regulation | Immune suppression |
| hsa-mir-203 | Oral squamous cell carcinoma[21] | Down-regulated | Thermal injuries[16] | Down-regulated | Promotion of EMT |
| hsa-mir-150 | Oral squamous cell carcinoma [134] | Down-regulated | Chemical burn [135] | Down-regulated | Promotion of EMT |

a consistent behavior of hsa-miR-18a in both burns and carcinogenesis, with heightened expression levels observed in laser burns tissue, followed by subsequent elevation in cancerous tissue[17,18].

## Hsa-miR-23b

hsa-miR-23b acts as a suppressor of EMT by inhibiting the phosphoinositide 3 kinase (PI3K)–protein kinase B (AKT) signaling pathway[26]. hsa-mir-23b plays a critical role in regulating normal physiological functions, cellular differentiation, and cellular immunity. Consequently, any disruption to the homeostasis of hsa-mir-23b adversely affects the normal physiological functions of cells, leading to the onset of diseases. hsa-mir-23b can elicit a complex array of responses by directly targeting multiple transcripts. Specifically, alterations in the expression of hsa-mir-23b are closely intertwined with various transcription factors such as Transforming growth factor β1-activated kinase 1 binding protein (TAB) 2&3, NF-kB, tumor suppressor P53, estrogen receptor (ER)-α, MAPK, activated protein activation (AP)-1, reactive oxygen species, and chemokine ligand7[27]. Additionally, the findings of this study indicate an up-regulation of this miRNA in both burns and OSCC[19,20]. Nevertheless, in one of the findings, it was observed that hsa-mir-23b experienced down-regulation subsequent to burns[16].

## Hsa-miR-203

Previously, it has been reported that elevated hsa-miR-203 expression correlates with poorer prognosis and may serve as a novel predictive marker for prostate cancer[28]. Notably, while

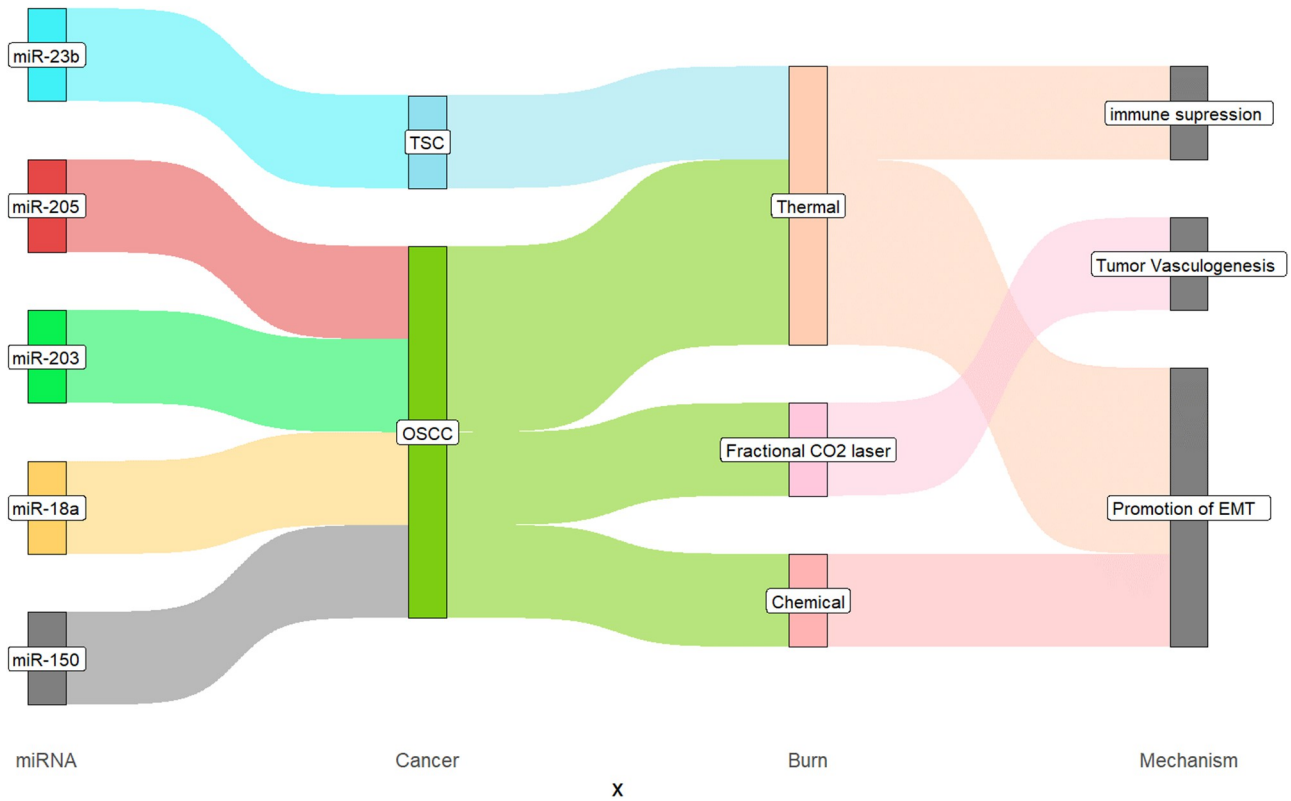


**Figure 2.** Logical flow results extracted using senky plot.

hsa-miR-203 levels diminish in hematologic malignancies and prostate cancer, they are modulated in ovarian, bladder, and colorectal cancers. Furthermore, excessive miR-203 expression in metastatic prostate cell lines within the brain or bone has been shown to induce EMT by effectively inhibiting cell proliferation, migration, and invasion[29]. In our study, the evidence suggests consistent miR-203 expression patterns in both burns and squamous cell carcinoma, with decreased levels noted in burns and OSCC tissues[16,21].

### Hsa-miR-150

hsa-miR-150 demonstrates versatile functions across various physiological and pathological states. In the realm of immune-related ailments, it plays a pivotal role in modulating B cell function, immune equilibrium, and disease advancement, thereby serving as a diagnostic indicator and prognostic determinant[30,31]. During heart failure, hsa-miR-150 contributes to cardio protection by mitigating maladaptive remodeling post-myocardial infarction and regulating distinctive noncoding RNA and gene profiles in cardiomyocytes[32,33]. Furthermore, its interaction with long noncoding RNA, MIAT, and downstream target Hoxa4 is crucial in ischemic heart failure, unveiling a novel regulatory pathway in cardiac safeguarding. Overall, miR-150's repertoire spans immune regulation, cardioprotection, and modulation of gene expression across diverse pathological contexts[34]. Additionally, hsa-miR-150 plays a notable role in cancer, particularly in OSCC. Studies reveal its down-regulation in nasopharyngeal carcinoma, leading to suppressed cell proliferation, G1/S cell cycle arrest, and inhibited tumorigenesis[35]. Moreover, in OSCC, hsa-miR-150 regulates malignant progression by interacting with LINC00657, influencing epithelial-mesenchymal transition, cell motility, and invasion, underscoring its potential as a diagnostic marker and pivotal factor in tumor evolution. These insights underscore the pivotal involvement of hsa-miR-150 in cancer, including its contribution to OSCC advancement and its promise as a therapeutic target[36]. Furthermore, our data also indicates a decrease in expression of this miRNA during chemical burns and OSCC[34,37].

## Discussion

Burn injuries represent a widely acknowledged global health concern with substantial societal ramifications. These injuries encompass damage to the skin and underlying tissues, typically stemming from exposure to fire, electricity, radiation, or chemical agents. Notably, they inflict severe pain and can precipitate adverse physical and psychological repercussions on affected individuals. Burn injuries can have profound physical and emotional impacts, often giving rise to a range of psychological challenges, with anxiety being a prominent issue[38]. Furthermore, managing such wounds presents formidable challenges owing to the pronounced and prolonged systemic dysfunction they induce[39]. Based on evidence, burns and cancer are integral components of a larger puzzle, where burns-induced hyperplasia can potentially lead to cancer development in affected areas[40]. On one hand, the oral cavity, especially in rodents, is frequently exposed to various incendiary agents like chemicals, which could predispose to future complications[41]. In this regard, the present study aimed to investigate the correlation between burns and OSCC, focusing on identifying miRNAs. Overall, the findings suggest that burns are associated with at least five miRNAs implicated in OSCC development. Additionally, it appears that the EMT mechanism, mediated by these miRNAs, plays a pivotal role in this association.

This study highlights evidence suggesting that various burns in the oral cavity can contribute to the development of OSCC. In this context, De *et al* have noted in their review that chemical burns, which can induce cellular abnormalities like hyperplasia in oral tissues, may be associated with precancerous changes. For example, the simultaneous occurrence of chemical burns in the mouth has been linked to conditions such as leukoplakia on the buccal mucosa, which could signal early signs of malignancy[42]. Furthermore, cellular and molecular studies indicate that burns in the oral cavity can promote malignancies through multiple mechanisms. Chemical burns, in particular, pose a heightened risk by directly damaging tissues and triggering epigenetic changes. Harmful chemicals can cause DNA damage, leading to genetic mutations that drive uncontrolled cell growth. Additionally, these chemicals may silence tumor suppressor genes through epigenetic modifications like abnormal DNA methylation and histone alterations. For instance, irregular methylation of promoter regions in essential genes can push cells toward malignancy[43]. Additionally, Chronic inflammation resulting from chemical burns also creates a favorable environment for cancer development. This inflammation can activate cancer-related signaling pathways, such as the PI3K/Akt pathway, which supports the growth and survival of cancer cells[44]. Moreover, oxidative stress induced by chemical exposure generates free radicals that damage biomolecules like DNA and RNA, further accelerating carcinogenesis[45].

Furthermore, our results indicate that five miRNAs, including hsa-miR-205, hsa-miR-18a, hsa-mir-23b, hsa-mir-203, and hsa-mir-150, may significantly influence cancer arising from burns in oral cave. Moreover, the findings suggest that alterations in these factors during burns and cancer are consistent. In this context, past evidence indicates that many natural and pathological processes in the body are mediated by miRNAs[46]. Additionally, Shukla *et al* have highlighted through bioinformatic analysis that burns can significantly disrupt the body's miRNA profile[47]. Suszynska *et al* have also shown that these miRNA alterations are noticeable during cancer[48]. Furthermore, specific miRNAs act as either onco-mirs or tumor suppressors, regulating target genes crucial in cancer development[49]. Hence, the overlap in miRNA profile changes between burns-induced cancer and other cancer types may reflect shared underlying oncogenic pathways, such as cell cycle regulation, apoptosis, and DNA repair[50,51]. Additionally, Rawi *et al*, in their 2021 systematic review, demonstrated that miR-205 is dysregulated during the development of OSCC, which aligns with the findings of our study[52]. Furthermore, Nakamura *et al* (a meta-analysis) reported that elevated levels of miR-150 in the bloodstream could serve as a highly accurate predictor for the occurrence of OSCC[53].

Additionally, EMT emerged as a major mechanism through which miRNAs could mediate the occurrence of OSCC post-burns in this study. EMT occurs during normal embryonic growth, tissue remodeling, organ fibrosis, and wound healing, where epithelial cells can dynamically transition into a mesenchymal phenotype. However, in tumor progression with metastatic spread and the generation of tumor cells with

stem cell-like properties playing a significant role in cancer therapy resistance, EMT has a role[54]. Furthermore, Weber *et al* have also indicated that burns in thermal burn wounds are both EMT-dependent myofibroblast formation and re-epithelialization of keratinocytes. TGF-β is a key cytokine involved in many wound healing elements, including EMT induction through multiple pathways[55]. Additionally, numerous pieces of evidence have also suggested that this process during cancer correlates with a poor prognosis in cancer patients[56]. Therefore, these results suggest that a deeper understanding of EMT mechanisms and its role in cancer progression could facilitate improvements in cancer management and prevention of this deadly disease. For this purpose, further research on this topic is needed to provide the best strategies for managing high-risk cancers such as OSCC.

### *Limitations*

This investigation marks the inaugural systematic review delving into the influence of burn on the OSCC incidence, centering on the role played by miRNAs. Consequently, it is imperative to acknowledge that certain constraints are inherent in this study. Initially, our scrutiny exclusively embraced literature in the English language from the year 2000 onward, potentially introducing a degree of bias in the results. Moreover, the generally reduced quality of the studies included may have also predisposed some bias in the outcomes. Additionally, given the lack of direct research on this topic, our study gathered data from studies focusing on burns and cancer. Consequently, this approach may have resulted in the loss of some data.

### *Implication for clinical practice*

Overall, miRNAs could serve as reliable indicators for predicting, diagnosing, and anticipating different types of cancers. In light of our findings, it can be inferred that measuring these miRNAs in the oral cavity could predict the onset of various carcinomas. Additionally, since cancer development is multifaceted, uncovering even a fraction of the cancer puzzle through miRNA assessment could promise effective therapeutic strategies.

### *Recommendation for future studies*

Although the negative impact of burn on oral carcinoma has been validated, certain aspects in this area remain ambiguous. Therefore, the following research directions are suggested for further investigation: (1) investigating direct associations between various other ncRNAs and OSCC stemming from burns; and (2) delving into additional miRNAs that could play a significant role in enhancing the healing process of oral burn wound.

## Conclusion

In summary, our findings identified five miRNAs – hsa-miR-205, hsa-miR-18a, hsa-mir-23b, hsa-mir-203, and hsa-mir-150 – that suggest a potential link between cancer development and burns in the oral cavity. This association seems to be mediated through three processes: EMT, angiogenesis, and immune suppression. Also, Furthermore, our findings indicate the presence of coordinated behavior among these miRNAs in both cancer occurrence and burns.

## Ethical approval

This systematic review and meta-analysis study have been registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42024568867) (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=568867). Ethics approval was not required for this systematic review.

## Consent

This study is a systematic review and does not require ethical approval and consent.

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None.

## Author's contribution

Study concept and design by all authors; data acquisition by all authors; data interpretation by all authors; drafting the manuscript by all authors; revision of the manuscript by all authors; the final version of the manuscript is approved by all authors.

## Conflicts of interest disclosure

None.

## Research registration unique identifying number (UIN)

None.

## Guarantor

Bahar Farhadi.

## Provenance and peer review

Not commissioned, externally peer-reviewed.

## Data availability statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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