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Review

The paradigm of miRNA and siRNA influence in Oral-biome

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ABSTRACT

Short nucleotide sequences like miRNA and siRNA have attracted a lot of interest in Oral-biome investigations. miRNA is a small class of non-coding RNA that regulates gene expression to provide effective regulation of post-transcription. On contrary, siRNA is 21–25 nucleotide dsRNA impairing gene function post-transcriptionally through inhibition of mRNA for homologous dependent gene silencing. This review highlights the application of miRNA in oral biome including oral cancer, dental implants, periodontal diseases, gingival fibroblasts, oral submucous fibrosis, radiation-induced oral mucositis, dental Pulp, and oral lichenoid disease. Moreover, we have also discussed the application of siRNA against the aforementioned disease along with the impact of miRNA and siRNA to the various pathways and molecular effectors pertaining to the dental diseases. The influence of upregulation and downregulation of molecular effector post-treatment with miRNA and siRNA and their impact on the clinical setting has been elucidated. Thus, the mentioned details on application of miRNA and siRNA will provide a novel gateway to the scholars to not only mitigate the long-lasting issue in dentistry but also develop new theragnostic approaches.

Abbreviations: miRNA, microRNA; siRNA, small-interfering RNA; GBD, Global Burden of Disease; OSCC, oral squamous cell carcinoma; Pri-miRNA, primary miRNA; RISC, RNA-induced silencing complex; HIF, Hypoxia inducing factor; MDR1, multidrug resistance mutation 1; ECE, Extracapsular extension; TPM1, tropomyosin; PTEN, phosphatase tensin homolog; ASO, antisense oligonucleotide; TSCC, tracheal squamous cell carcinoma; PKM2, pyruvate kinase type M2; ARHGEF3, Rho Guanine Nucleotide Exchange Factor 3; IGF1R, Rho Guanine Nucleotide Exchange Factor 3.; FGFR3, Fibroblast growth factor receptor 3; OTSCC, oral tongue squamous cell carcinoma; SOD2, Superoxide dismutase 2; KLF13, Kruppel Like Factor 13; UTR, untranslated region; HK2, hexokinase 2; MEC, MC-3 mucoepidermoid carcinoma; Sp1, specificity protein 1; DKK1, Dickkopf-1; Cdk, cyclin-dependent kinase; NRP1, Neuropilin 1; TGFβ, Transforming Growth factor beta; PDX, Patient derived xenograft; TNM, Tumor nodes and metastasis; RB1, retinoblastoma 1; HPV, Human Papillomavirus; CSC, Cancer Stem Cells; ALDH, Aldehyde dehrydrogenase; OSF, Oral submucous fibrosis; UBE2B, ubiquitin-conjugating enzyme E2B; PTPRS, protein tyrosine phosphatase receptor type sigma; OLP, oral lichen planus; CAFs, cancer-associated fibroblasts (CAFs); NF, normal fibroblasts; HOK, human oral keratinocyte; IGF-IR, Insulin-like growth factor-I receptor; LNM, lymph node metastasis; TKT, Transketolase; AK2, adenylate kinase-2; PPP, pentose phosphate pathway; CK14, cytokeratin-14; SACC, salivary adenoid cystic carcinoma; MAG, myelin-associated glycoprotein; LCP, lipid-calcium-phosphate; PDT, photodynamic therapy; PEG-PEI-Ce6, polyethylene glycol-polyethyleneimine-chlorin e6; EMT, epithelial to mesenchymal transition; DOX, doxorubicin; MSNP-PEI, mesoporous silica nanoparticles-polymer polyethyleneimine; ECE-1, endothelin-converting enzyme-1; Skp2, S phase kinase-interacting protein 2; TSCC, tongue squamous cell carcinoma; LAT1, L, type amino acid transporter 1; uPAR, urokinase-type plasminogen activator receptor; siHIKE, siRNA for HIKESHI; MHT, mild hypothermia; DSBs, double-strand breaks; 5-FU, 5-Fluorouracil; siIFITM1, IFITM1 siRNA; PICF, peri-implant crevicular fluid; Ti, Titanium; PEG, polyethylene glycol; PEI, polyethyleneimine; GO, graphene oxide; TNP, polyethyleneimine.; TLRs, Toll-like Receptor; PgLPS, *Porphyromonas gingivalis* lipopolysaccharide; HGFs, human gingival fibroblasts; GF, Gingival fibroblasts; NRFA1, nuclear receptor 4A1; DIGO, Drug-induced gingival overgrowth; PD, periodontal disease; OSF, Oral submucous fibrosis.; RIOM, Radiation-induced oral mucositis; DPSCs, dental pulp stem cells; TRAF, TNF receptor-associated factor; OLD, Oral lichenoid disease; OLP, Oral lichenoid planus.

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1. Introduction

Clinical oral biome is a technically oriented field concerned with the preclusion and management of oral diseases including diseases of the teeth and supporting structures [1]. With the rise in the aging population, the increase in the burden of diseases that are non-communicable (diabetes, chronic respiratory diseases, cancer, and cardiovascular diseases) has fractured the healthcare system. The Global Burden of Disease Study (GBD) 2017 [2] estimated that 3.5 billion people have been affected by oral diseases worldwide. Their recent findings showed evidence of untreated common oral conditions like untreated caries, extreme periodontitis and complete loss of the tooth. The oral health of the worldwide populations has been reported to be healthy however major problems has been found to be persisting in deprived communities of low and middle-income countries. The ultimate objective of the health authorities has been to break down the barriers existing between scientific oral research and global health.

The non-coding small RNAs with approximately 19–22 base pair in length are known as MicroRNAs (miRNAs). These miRNAs assists in the regulation of gene expression at the post-transcriptional level by repressing the mRNA of a target gene and thereby regulating mRNA translation via base pairing to partially complementary sites [3]. Oral cancer, which is mainly represented by oral squamous cell carcinoma (OSCC), is one of the most communal types of cancer globally. There is a report of rapid increase in the number of OSCC cases and poor prognosis caused by recurrences, lymph node metastasis, and late diagnosis even after the implication of prognosis therapies like visual inspection and innovations in diagnostics and therapeutic strategies [4]. Diagnosis of the diseases is the key player in tackling oral cancer that has to be given attention. For early detection of the diseases, recent investigations have been focussed on identifying the circular miRNAs as possible biomarkers. The miRNA and its variables can help in the development of new molecules for diagnostic and prognostic biomarkers for the early-stage diagnostics of oral cancer. On the other hand, the non-coding double-stranded RNA molecules with a length of around 20–24 bp are the small interfering RNAs (siRNAs), which mainly operates within the RNA interference pathway. The siRNA exhibits dysregulated expression during the progression and development of diseases like cancer. Owing to their highly specific nature of siRNAs, studies have reported their use in cancer diagnostics for identification of particular gene function and gene silencing for the development of new therapies.

The primary miRNA transcript (pri-miRNA) is synthesized from the microRNA gene using RNA polymerase II or III. The microprocessor complex DROSHA-DGCR8 (Pasha) assists in cleaving the pri-miRNA, which results in the synthesis of pre-miRNA. EXPORTIN 5 or Ran GTP then exports the resultant precursor miRNA hairpin (pre-miRNA) from the nucleus to the cytoplasm. Then, The RNase DICER in complex with TBRP protein cleaves the precursor-miRNA into miRNA –miRNA duplex in the cytoplasm. The developed miRNA strand is loaded into the RNA-induced silencing complex (RISC) with Argonaute 2 /Ago2 proteins, which silences the target mRNAs through mRNA degradation, translational repression, etc. The antiviral siRNA biogenesis pathway is triggered with the generation of siRNA duplexes from long double-stranded RNAs through cleavage by DICER where one strand of siRNA is integrated into RISC directly targeting RNA cleavage.

siRNAs mainly operate within the RNA interference pathway [5]. During the development and evolution of illnesses related to oral diseases, siRNA expression is dysregulated [6]. Recent studies have used siRNAs in dentistry due to their highly specific nature to identify a particular gene function and develop new therapies through gene silencing.

The review focuses on all aspects of dental diseases utilizing miRNAs and siRNAs as biomarkers and therapeutics to develop new therapies and use them for the clinical management of dental diseases.

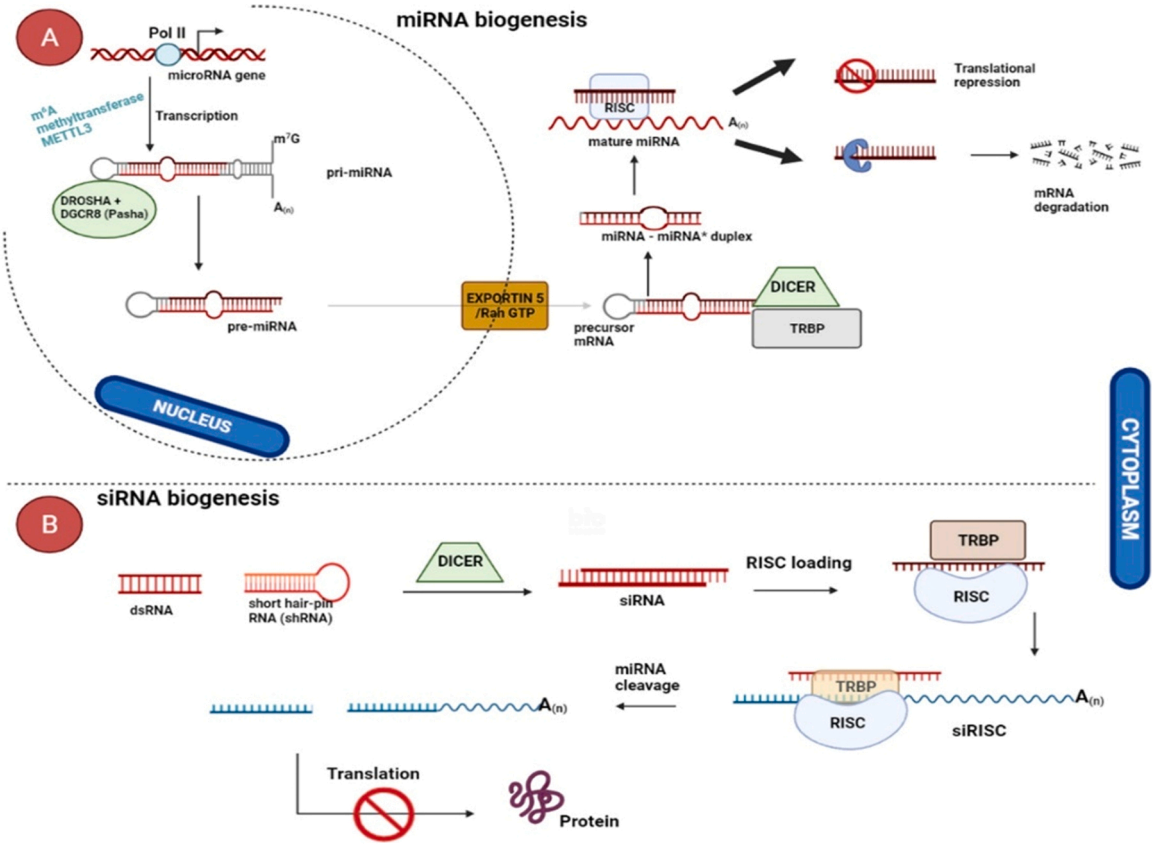

Fig. 1. Schematic diagram showing the biogenesis of miRNA and siRNA.

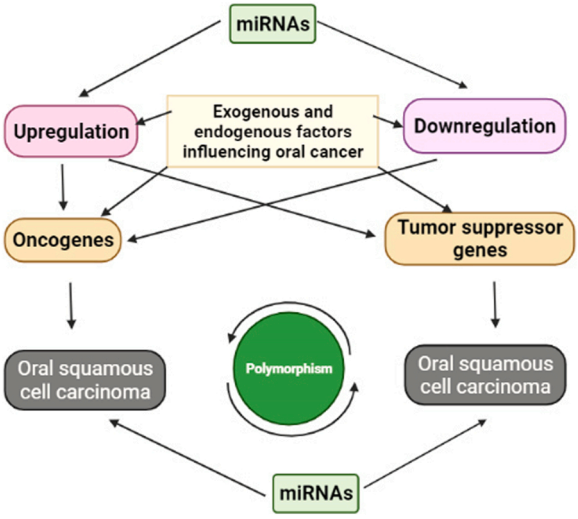

Fig. 2. Schematic diagram presenting the role of miRNA in oral cancer progression.

(Figs. 1–10).

2. Oral cancer

In recent times, the statistics intending to highlight the overall ranking of oral cancer on a global platform has awakened serious health concerns due to lack of proper treatment, non-invasive markers, poor prognostic measures, and reinfection cases leading to augmenting mortality and morbidity. While holding the thirteenth rank in the list of fatal cancers, oral cancer has established a major clinical challenge against patient survival. miRNAs facilitate epigenetic regulation in the form of either tumour-suppressive miRNAs or carcinogenic miRNAs, supported by the advent of multifaceted technological advancements [7]. However, the urgent need of the hour demands more therapeutic candidates for the futuristic application of genetically modified strategies acquiring the power to effectively combat the malignancy. The hunt has led to the development of designing and delivery of siRNAs targeting oncogenic sites and further silencing the target within the cytoplasm of the oral cancer cell [8]. This report elucidates the potential for the theragnostic utilities of miRNAs and siRNAs which are deregulated at differential levels of oral cancer progression. The molecular pathway adopted by miRNAs including miR-184, miR-24, miR-196a, miR-223, miR-200b-3p, miR-31, miR-31–5p, miR-187–5p, miR-483–5p, miR-494, miR-1246, miR-494–3p, miR-20a, hsa-miR-4484, miR-181, miR-455–5p, miR-375, miR-148a, miR-1254, miR-155, miR-21, miR-133a, miR-133b, miR-138, miR-98, miR-211, miR-100, miR-222, miR-125b, miR-142–5p, miR-203, miR-145, miR-127–3p, miR-143, miR-373–3p, miR-137, miR-193a-3p, miR-7, miR-338, miR-639, miR-219 and siRNAs including si-HIF1α, si-MDR1, si-ECE, si-Skp2, si-LAT1, si-u-PAR, si-BRCA2, si-Slug, si-survivin, si-IFITM1, si-HUR, si-TWIST, si-TKT, si-Ak2, si-CIP2As, si-MDR25mer, si-Ck14 and si-Notch4 has been reviewed in detail corresponding to their role in cellular biological processes like metastasis, proliferation, invasion, apoptosis and differentiation in OSCC.

Study have shown the exhibition of overexpression of oncogenic miRNA-21 in OSCC with inhibited levels of tropomyosin (TPM1) and phosphatase tensin homolog (PTEN) to inhibit apoptosis in the cancer cells. An inverse relation was established by the 3'-UTR binding of TPM1 and PTEN with the miRNA [9]. MicroRNA profiling was conducted in 10 cases of TSCC by transfecting miR-21 antisense oligonucleotide (ASO), depicting that inhibition of miR-21 led to anchorage-independent growth, reduced survival, alleviated proliferation and apoptosis of the TSCC cells in nude mice. Thus, based on the findings in vitro models, insights into the therapeutic applications of miR-21 was focused as a

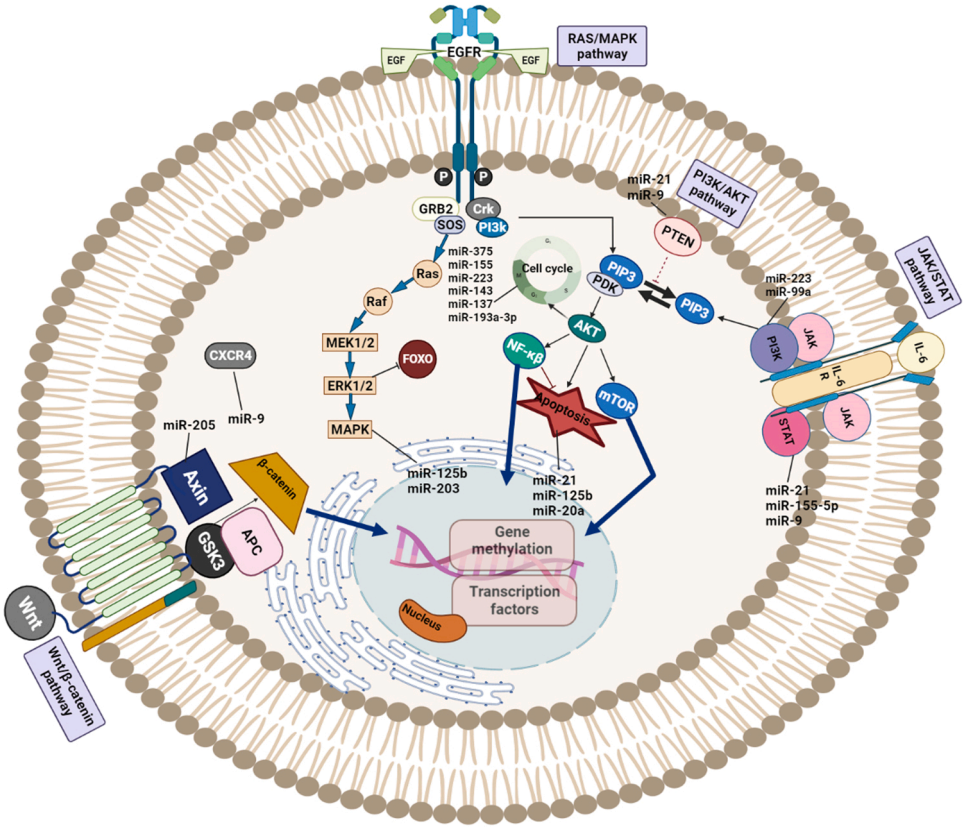

Fig. 3. The signalling cascade mediated by miRNA for oral cancer.

prognostic tool [9].

The downregulation of tumour suppressor miR-133a and miR-133b in TSCC cells in vitro by targeting a transcript of pyruvate kinase type M2 (PKM2) has been reported as a potential oncogene in solid cancers. The screening of the aberrant expression of these miRNAs in micro dissected cells extracted from the tongue carcinoma showed a 12.5-fold decrease in mature miR-133a and 5.3-fold reduction in miR-133b as compared with normal epithelial cells, moreover the morphological changes were found to be induced by these miRNAs [10]. Further analysis confirmed that miR-133a and miR-133b precursors reduced proliferation by regulating the intrinsic apoptotic machinery. The inverse relation between miR-133b and miR-133a with PKM2 indicates that overexpression of this oncogenic transcript has the potential to induce malignancy and inhibit apoptosis of the SCC cells [10].

By targeting RhoC and ROCK2 in their 3'-UTR regions via the Rho GTPase signaling pathway, miR-138 is linked to increased metastatic potential in OSCC and reduces invasion and migration in TSCC cell lines [11]. The inverse relation is validated upon enhanced levels of Rho and ROCK1 induced by the miR-138 knockdown via the anti-miR-138 PNA. An additional target, ARHGEF3 elevated the GTPase activity of Rho GTPases. Further, bioinformatic analysis in this study validated that miR-138 acts as a miRNA that suppresses tumors by modulating the expression of the oncogenic targets Rho and ROCK2. The overexpression of these oncogenic targets has the potential to augment cellular stress and subsequently alter cell morphology [11].

Studies have reported the downregulation of miR-98 in OSCC cell lines and tissues for anti-cancerous effect. Studies have highlighted their role as potential tumour suppressor miRNAs that have prevented colony formation, migration, invasion, and proliferation of OSCC cells by aiming the Insulin-like growth factor 1 receptor (IGF1R) in 19 samples of primary OSCC tissues obtained from SCC-25 and Tca-8113 cell lines. Hence, miR-98 can act as a significant therapeutic target against tumorigenicity and carcinogenic growth in OSCC cells [12].

The oncogenic potential of miR-211 was exhibited as its overexpression leading to migration, proliferation, and anchorage-independent colony formation of OCC by induced translational repression of targeted mRNA LacZ associated with the β-galactosidase activity. The in-vitro study exhibited an alleviated levels of miR-211 expression in comparison to NHOKs, whereas SAS cells reported a 45% reduction in β-galactosidase activity validating the inverse relation with the LacZ gene. Further analysis will provide insights into the ability of miR-211 to surpass biological regulations and induce vascular invasion and metastasis in OSCC cells [13].

Henson et al. transfected exogenous OSCC cell lines (NHOK) with miR-100 acting as an effective tumor suppressor miRNA, causing repression of proliferation and tumorigenesis while regulating target and non-target gene expression. More than 130 genes were modified by 1.8-fold or more by miR-100, which can control the expression of 700 genes. ID1, EGR2, MMP13, and FGFR3 were all downregulated in miR-100 transfected cells, with MMP13 protein levels dropping by more than 2-fold and FGFR3 levels dropping by 1.8-fold. As a result, miR-100 may have the potential to be used as a prognostic tool [14].

miR-222 has been identified as an oncogenic miRNA candidate that leads to tumour initiation, metastasis, cell invasion, and proliferation of oral tongue squamous cell carcinoma (OTSCC) by targeting the 3'-UTR regions of MMP1 and SOD2 in OTSCC. Hsa-miR-222 regulates the expression of the aforementioned genes and has the potential to increase metastasis through SOD2-dependent upregulation of MMPs via direct cis-regulatory mechanisms targeting MMP1 mRNA and indirect trans-regulatory mechanisms targeting the MMP1 gene via targeting SOD2. Thus, the reduction in invasion upon ectopic transfection of hsa-miR-222 serves as a therapeutic target in tumorigenesis [15].

miR-125b acts as a tumor-suppressing by regulating gene expression by 1.8 folds and inhibiting cell proliferation in NHOK cells of OSCC cell lines. The in vitro transfection of miR-125b downregulated the KLF13 gene and up-regulated CXCL11 and FOXA1 [14]. RISC processes mRNA mimics to deliver synthetic small double-stranded molecules acting as identical substitutes for miR-125b that caused mitigated levels of carcinogenesis, thereby facilitating the role of miR-125b as a therapeutic target [14].

The role of miR-142–5p was exhibited for the promotion of OSCC tumorigenesis in SAS and HSC-M3 cells obtained from 70 patients by targeting pTEN through the PI3K/AKT pathway. The induced proliferation is inhibited by suppressing pTEN responsible for dephosphorylating PIP3 to PIP2 and inactivating AKT [16]. Cells transfected with miR-142–5p mimics enhanced proliferation and cell invasion, whereas siRNA-induced suppression of PTEN inhibited proliferation. The inverse relation was validated by overexpression of miR-142–5p and

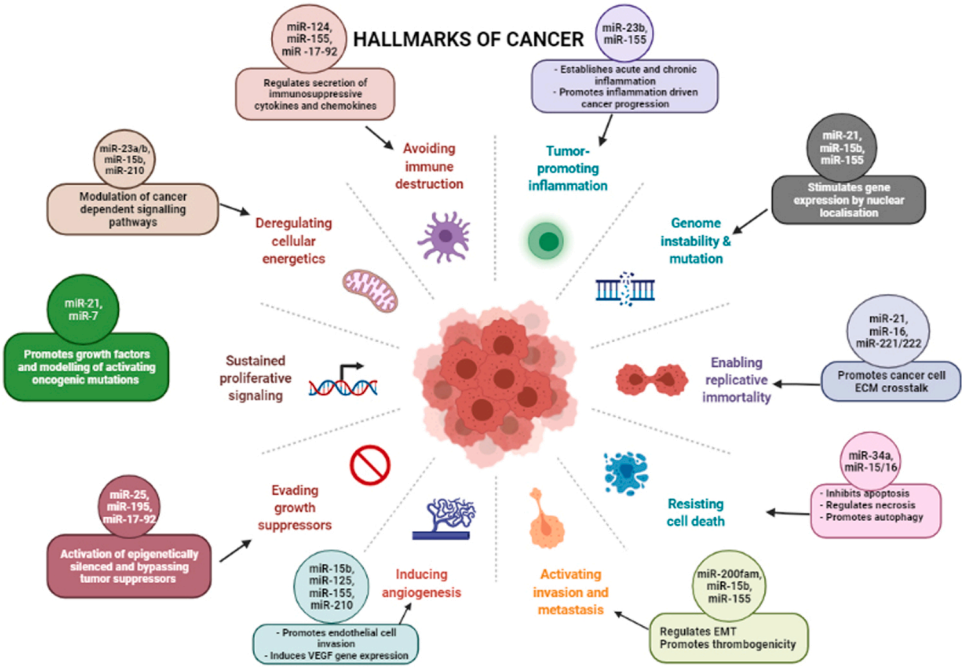

Fig. 4. Influence of miRNA on cancer hallmarks.

downregulation of PTEN as an essential therapeutic target in OSCC [16].

The KB and NHOK human oral cancer cells were used for the evaluation of the molecular mechanisms of miR-203 as a tumour suppressor. Overexpression of miR-203 induced down-regulation of Yes-1 gene, as a potential oncogene of the Yamaguchi avian sarcoma virus and augmented nuclear condensation and apoptotic population of KB cells. miR-203 was downregulated by 8 folds in KB cells as compared to NHOK cells and inhibited proliferation and induced apoptosis of KB cells by targeting the 3'-UTR of the Yes-1 gene. Hence, miR-203 serves as a significant prognostic biomarker [17].

miR-143 is frequently associated with augmented glucose metabolism, cell invasion, proliferation, and growth in OSCC by downregulation in Tca8113 cells while analysing in vitro expression in 15 humans with normal oral tissues and 15 humans with tissues of oral cancer. The expression of miR-143 is inversely related to the upregulation of hexokinase 2 (HK2) mRNA by direct binding at 3'-UTR of HK2. Thus, the aberrant expression of miR-143 attenuates glycolysis by inhibiting glucose metabolism and plays a suppressive role in OSCC, indicating possible means of the therapeutic target [18].

The role of miR-127–3p with the arrest of the cell cycle in MC-3 mucoepidermoid carcinoma (MEC) cells and reduced specificity protein 1 (Sp1) expression are linked to the cell cycle, p21, cyclin D1, and p27, it was found to enhance the expression of proteins [19]. MEC, which is derived from the salivary gland, originates from the oral cavity. The overexpression of 127–3p significantly increased cells in the G_1 phase for G_1/S cell cycle arrest in vitro. The regulation of the Sp1 transcription factor upregulated cyclin-dependent kinase inhibitor 1 A. Hence, they serve as prognostic targets by inducing anti-proliferative activity against human MEC [19].

miR-145 was suppressed in OSCC for inhibiting proliferation, colony formation and subsequently induced G_1 phase arrest and apoptosis in Tca8113 cells by targeting Cdk6 as well as c-Myc. The downregulation of cell-cycle regulatory genes c-Myc and Cdk6 produced cell cycle arrest at the G1 phase in cells transfected with miR-145 mimics. The downregulation of miR-145 in OSCC cells suggested a potential oncosuppressor and a therapeutic biomarker against the pathogenesis of OSCC [20].

The miR-373–3p is upregulated in TSCC to promote EMT-induced metastasis and cancer progression through the Wnt/β-Catenin pathway and targets Dickkopf-1 (DKK1), E-cadherin, and CK18 [21]. Wnt signaling is associated with the disassembly of activated β-catenin dissociates from E-cadherin through upregulating EMT biomarkers and negatively regulating DKK1. Thus, the aforementioned targets were downregulated in vitro causing the overexpression of miR-373–3p for inducing enhanced cell viability, invasion, and proliferation and a therapeutic biomarker against the pathogenesis [21].

The functional role of miR-137 against OSCC where it acted as potential tumour suppressors, by downregulating in OSCC cells and induced aberrant DNA methylation. miR-137 was downregulated for reduced cell growth causing downregulation of Cdk6 or E2F factor 6 genes in immortalized oral keratinocyte line. As a result, overexpression of miR-137 inhibited cell development via the G0-G1 arrest and caspase-mediated death, making it essential in cancer [22]. Moreover, miR-193–3p was downregulated in OSCC cell lines through tumour-specific hypermethylation causing reduced cell growth through the downregulation of cyclin-dependent kinase (Cdk6) or E24 transcription factor in the same cell. Another target Bcl-2 was detected upon transfecting the cells with miR-193–3p causing tumour regression via cell cycle arrest and associating the potential of miR-193–3p as a prognostic biomarker against OSCC [22].

miR-7 is characterized as a tumour suppressor in TSCC by directly binding with the 3'-UTR of insulin-like growth factor 1 (IGF1R) and inducing stimulation of Akt (protein kinase B) for suppressed cell proliferation and cell-cycle arrest in oral cancer cells in-vitro. An enhanced apoptotic rate through the IGF1R/Akt signalling pathway was exceeded by regulation occurring post-transcriptional of IGF1R. Hence, miR-7 can be utilized as a therapeutic target in TSCC cells [23].

Overexpression of miR-338 elicited anti-proliferative activity and inhibited metastasis, colony formation, invasion, and migration in OSCC through downregulation of the inversely correlated target, Neuropilin 1 (NRP1). NRP1 is a co-receptor for vascular endothelial growth factor whose expression causes proliferation, metastasis, immunity, and angiogenesis. Thus, highlighting the therapeutic role of miR-338 from OSCC samples [24].

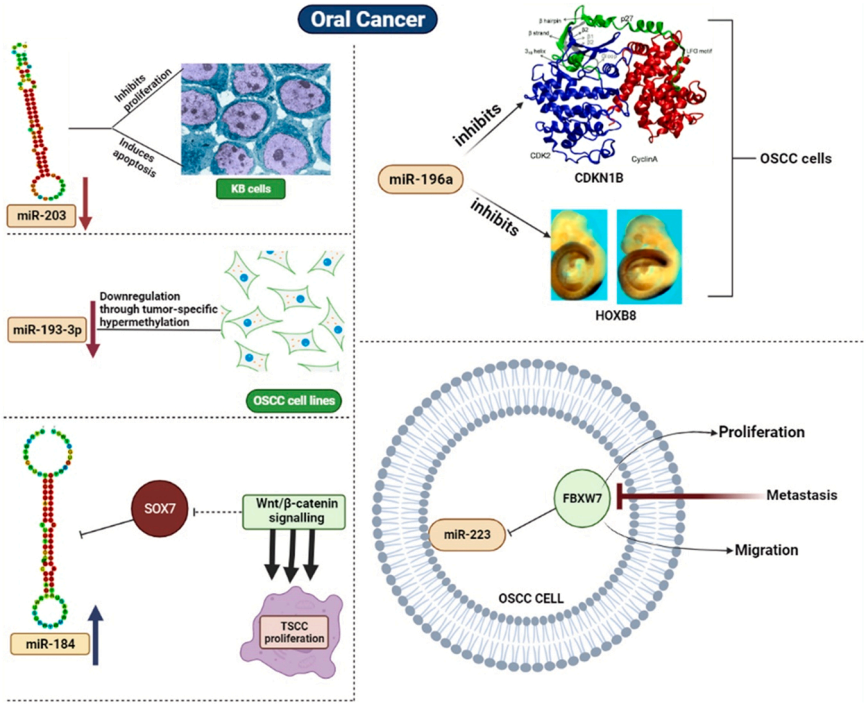

Fig. 5. Influence of miRNA as a biomarker for diagnosis of oral cancer.

miR-639 is known to be a miRNA that suppresses tumours and modulates the expression of TGF-β through EMT in TSCC cell lines, SCC-9 and CAL27. MicroRNA analysis disclosed that miR-639 was down-regulated in TGFβ transfected cells, and transfection induces metastasis and proliferation whereas the transfection by miR-639 mimics effectively blocked EMT in the aforementioned cells. The silencing of FOXC1 inhibited metastasis by blocking TGF-β in SCC9 cells and overexpression of miR-639 served as a therapeutic target [25].

miR-219 played a critical role in suppressing carcinogenesis in TSCC by protein kinase CI (PRKCI) which inherits the potential to induce tumorigenesis against the tumour-suppressive effects of miR-219 in SCC-15 and CAL-27 cells. Overexpression of miR-219, inversely related with the expression of the oncogenic target PRKCI, alleviated cell proliferation, invasion, migration, and colony formation of TSCC cells. Thus, this miRNA also serves as an essential prognostic marker [26].

Wong et al. initially determined a transformed expression of circulating miRNAs in oral cancer. Enhanced hsa-miR-184 levels were detected in both TSCC cells and patient plasma with decreased plasma levels of miR-184 post tumour resection promoting apoptosis and hindered cell proliferation in TSCC cell lines [27]. Moreover, miR-184 promotes TSCC proliferation by targeting the *SOX7* gene as a potential therapeutic target for TSCC treatment [28]. In another investigation, miR-184 was found to be elevated in tumour tissue samples compared to marginal tissue samples, which were linked to the patients' clinic-pathological characteristics. MiR-184 therefore seems to be a viable predictive and diagnostic biomarker in TSCC. [29].

The levels of miR-24 were higher in the plasma, OSCC tissues, and OSCC cell lines relative to controls. The inhibition of miR-24 and exogenous miR-24 expression indicated the growth-promoting role of miR-24 and p57 as its downstream target [30]. The upregulation of miR-184 in OSCC in patients suggested its potential as an OSCC biomarker [31].

In an investigation, higher miR-196 levels were present in OSCC tissue compared to control mucosa, with plasma miR-196a levels distinguishing patients from controls. Furthermore, the expression of miR-196 was dependent on enhanced oncogenesis. Enhanced expression of miR-196a and TT genotype of miR-196a2 gene was responsible for anti-dependent prediction associated with minimal patient survival. It is noteworthy that only the events leading to the high expression of miR-196a, thereby excluding the correlation with 196b, it was allied to nodal metastasis, tumor reformation, and fatal outcomes [32]. However, over-expression of both miR-196a and miR-196b in oral cancer and their association with lymph node metastasis was reported in another study. Moreover, miR-196 inhibited NME4 expression and further activated p-JNK, suppressed TIMP1, and augmented MMP1/9 to enhance the invasion and migration of cells and invasion without disturbing cell growth [33]. miR-196a inhibited the expression of HOXB8 and p27 (CDKN1B) in OSCC, whereas the inhibitor of miR-196a reduced cell proliferation [34]. In addition, analysis of miR-196 levels in patient plasma samples showed that for the early diagnosis of oral cancer, the combined quantification of circulating miR-196a and miR-196b levels serves as a potential plasma biomarker [35].

A study reported higher expression of miR-223 and increased the amount of miR-223 circulating levels in oral cancer patients than in controls, thereby rendering the functional aspect of miR-223 as a tumor suppressor by leading to the inhibition of cell proliferation and causing the induction of apoptosis [36]. Furthermore, miR-223 binds to the *TCF7L2* gene, reducing the invasion, migration, and metastasis ability of OSCC via the Wnt/β-catenin signalling pathway both in vivo and in vitro. Thus, circulating miR-223 paves way for more insights into its application as a potential biomarker for diagnosis and an attractive therapeutic target for metastasis in OSCC [37].

According to Sun et al., MiR-200b-3p expression was considerably elevated in the plasma of OSCC patients compared to healthy controls. In addition, amplified miR-200b-3p expression was linked to a poor prognosis. Even though the exact function of miR-200b-3p in OSCC has yet to be identified, these findings suggest that it plays a significant part in its development. Despite this, plasma miR-200b-3p detection has good sensitivity and specificity, suggesting it could be used as a non-invasive biomarker for OSCC [38].

The upregulated levels of miR-31 in patients with OSCC relative to sex and age-matched individuals in control, with significant reduction post tumour resection indicating their origin from tumour tissues [39]. Salivary miR-31 levels were significantly high in oral carcinoma patients at all the clinical stages, comprising tiny tumours. Salivary miR-31 had a higher level of miR-31 than plasma, signifying that salivary miR-31 is a more sensitive diagnostic for oral cancer. Salivary miR-31 in patients with oral carcinoma was significantly reduced after tumour excision, identical to that of plasma miR-31 [40]. Oral keratinocytes are immortalized for early-stage oral carcinogenesis is linked to the elevation of miR-31 in the oral premalignant epithelium [41]. In addition, miR-31 targets SIRT3 in OSCC cells to drive invasion, disruption of the activity of the mitochondria, and increased oxidative stress in oral carcinoma [42]. These data suggest that salivary and plasma miR-31 could be used

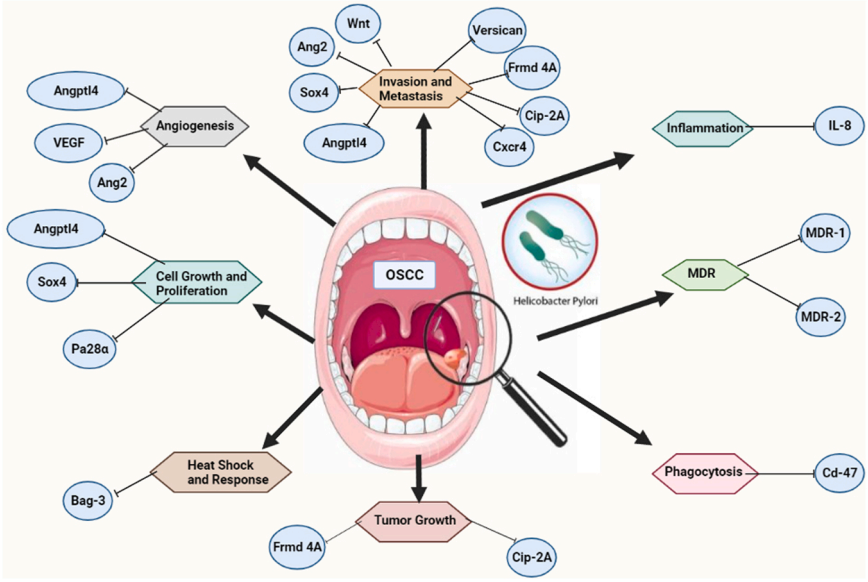

Fig. 6. Therapeutic intervention of siRNA for modulating cancer hallmarks.

as a biomarker for early identification and postoperative monitoring of oral cancer.

When compared with normal controls, the expression of miR-31–5p was reported to be higher in both oral cancer tissues and sera of patients. Moreover, serum miR-31–5p levels were suggestively higher in pre-operative patients relative to post-operative patients. The ability of serum miR-31–5p levels to distinguish oral cancer patients from healthy controls and track oral cancer recurrence implies that miR-31–5p could be used as a standalone diagnostic biomarker. The ability of miR-31–5p mimics and a miR-31–5p inhibitor in vitro have been studied, and they represent the involvement of miR-31–5p in enhancing the propagation of oral cancer cells [43]. Others [44,45] have also demonstrated miR-31–5p's tumour-promoting role in oral cancer. Antagonizing miR-31–5p with lower p-AKT and elevated PTEN expression levels resulted in tumour regression in oral cancer patients and PDX models, showing that miR-31–5p could be used as a therapeutic target in oral cancer via the PTEN/AKT pathway [43].

An upregulated level of miR-187 in both plasma and OSCC patients enhanced oncogenic phenotype via colony formation that is independent of anchorage and cell migration. Decreased plasma level of miR-187 in OSCC patient's post-surgical resection for a better prognosis, which implies an oncogenic role of miR-187 in oral cancer. As a result, plasma miR-187 could be utilized as a diagnostic and predictive factor for OSCC patients who have had ablation surgery [46].

An upregulated expression of miR-483–5p in both tumour serum and tissue of OSCC patients relative to healthy controls associated with tumour nodal metastasis (TNM) stage and lymph nodal metastases, indicating poorer prognosis. Thus, miR-483–5p acts as a possible candidate for the prognostic and diagnostic biomarker of OSCC [47]. There was significant upregulation of miR-494 in OSCC patients relative to controls [50,4849] and the clinical stage of illness and TNM classification did not affect changes in miR-494 expression. Thus, miR-494 acts as a potential biomarker for OSCC diagnosis but not OSCC progression [48]. miR-494 was significantly under-expressed in OSCC compared to normal tongue tissues and is known for repression of HOXA10 expression ultimately leading to inhibited cell proliferation in oral cancer [51].

However, absence of differential expression of miR-494 between healthy oral mucosa and OSCC tumour specimens [50]. These contradictory results suggest that further study is required to establish the exact nature of miR-494 expression and potential as a biomarker in OSCC tumour tissue. In SAS OSCC cells, ectopic expression of miR-494–3p enlarged the population of senescence-associated-galactosidase while downregulating Bmi1 and the expression of retinoblastoma 1 (RB1) and p16(INK4a). Furthermore, an inverse relationship between Bmi1 and miR-494–3p expression in OSCC tissues shows that miR-494–3p improves OSCC cell radio-sensitivity by promoting cellular senescence through Bmi1 downregulation. As a result, miR-494–3p may be used as a therapeutic target in OSCC [52].

The upregulation of miR-1246 in tumour tissues and cell lines of oral cancer relative to controls significantly correlated with TNM stage, nodal status, and tumour grade [53]. miR-1246 expression acts as an independent prognostic factor of poor patient survival [53,54]. In addition, miR-1246 is significantly upregulated in oral cancer stem cells (OCSC) and enhances cancer stemness and chemoresistance by targeting CCNG2. Furthermore, the modulation of DENN/MADD Domain Containing 2D (DENND2D) by high amounts of miR-1246 in exosomes from oral cancer cell lines enhanced cell motility and invasion [55]. Thus, miR-1246 is a potential prognostic biomarker and promising therapeutic candidate to prevent the relapse of cancer and suppress metastasis in OSCC.

miR17 and miR-20 were significantly downregulated in TW2.6 MS-10 as compared to the low-migration-ability TW2.6 cells. Levels of expression of the miR-17–92 cluster were inversely correlated with movement ability in OSCC lines and miR-20a and miR-17 were the dominant effectors of the miR-17–92 cluster that suppressed the migration ability of OSCC. While elevated levels of miR-17 and miR-20a augmented endurance, both of them are known to undergo negative regulation at the TNM stage. Moreover, both miR-20a and miR-17 target directly and downregulate integrin β8 to inhibit cell migration in OSCC, showing promise as potent biomarkers for OSCC [56].

In comparison to non-progressive leukoplakia and normal oral mucosa, miR-181b levels were considerably elevated in progressive leukoplakias, and OSCCs clustered together. The upregulation of miR-181b expression plays a significant role in carcinogenic conversion by elevation in lesion severity during progression from leukoplakia to oral carcinoma [57]. miR-181 overexpression was correlated with vascular invasion, lymph node metastasis, poor survival rate, and cell migration however showed a null effect on the anchorage-independent colony formation in the experimental OSCC cells. Moreover, plasma levels of both miR-181a and miR-181b were high OSCC patients and together distinguished between malignant and non-malignant states [58]. The

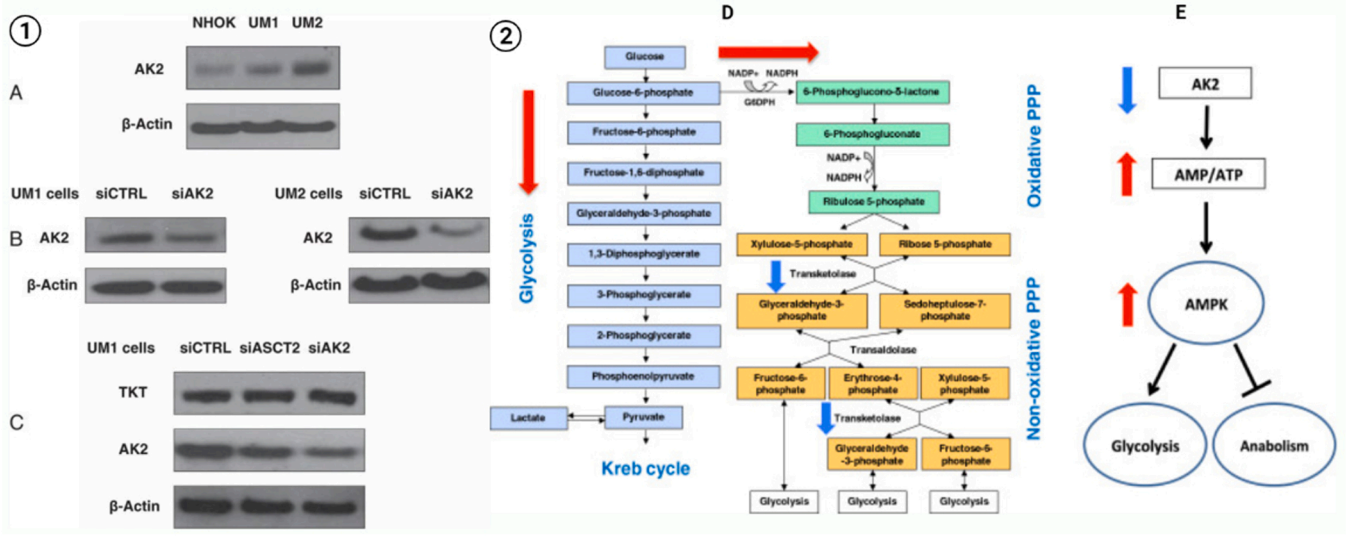

Fig. 7. (1) siRNA knockdown of AK2 expression in UM1 and UM2 oral cancer cells 2) A schematic diagram of possible metabolic network adaptations in survived UM1 and UM2 oral cancer cells after siRNA silencing of TKT or AK2.
Reproduced and adapted from ref [126].

levels of miR-181a and miR-181d expression in OSCC cells were hindered by HPV16 transfection, whose alteration is correlated with growth independent of anchorage and cancer stem cell (CSC) phenotype of the transfected cells. Moreover, abolition of malignant and cancer stemness-promoting effects of HPV16 in HPV16-transfected OSCC cells was achieved by silencing of miR-181a/d target genes K-ras and ALDH1 [59]. While more research is required to comprehend the exact function of miR-181 in oral cancer, it appears to show possibility as a diagnostic biomarker in OSCC and a therapeutic target in HPV-positive OSCC.

Oral submucous fibrosis (OSF) is a possibly malignant disorder of OSCC. An overexpression of hsa-miR-455–5p in OSF cells relative to normal controls [60]. The ubiquitin-conjugating enzyme E2B (UBE2B) boosted anchorage-independent growth and proliferative abilities of oral cancer cells by upregulating miR-455–5p in tumour tissues and OSCC cells lines [61]. Furthermore, a connection between miR-455–5p expression and stage, nodal status, and overall survival in patients suggests that it could be used as a predictive biomarker in OSCC [61]. To influence OSCC cell growth and proliferation, miR-455–5p directly targeted protein tyrosine phosphatase receptor type sigma (PTPRS). As a result, miR-455–5p appears to be a promising therapeutic target in OSCC [62].

miR-375 was down regulated in tumour tissues of patients with poor prognosis relative to those having favourable prognosis [63]. miR-375, a tumour suppressor whose under expression in oral cancer cells causes the expression of CIP2A in an uncontrolled manner and subsequently extends the stability of MYC to promote cancerous phenotypes [64]. In late-stage OSCC, miR-375 expression was downregulated, resulting in a bigger tumour size and an invasion pattern that is of non-cohesive type [65]. In addition, four anti-cancer drugs namely etoposide, trichostatin A, 5-fluorouracil, and doxorubicin is reported to enhance the expression of miR-375 and its primary transcript pri-miR-375 in tongue cancer cells CAL 27 and SCC-25 [66]. In TSCC tissues and cell lines, miR-375 expression was downregulated, and low miR-375 expression was linked to a deprived prognosis in TSCC patients. Furthermore, ectopic production of miR-375 hindered cell cycle progression and proliferation in TSCC cell lines by suppressing Sp1 expression, which resulted in cyclin D1 downregulation [67]. MiR-375 downregulation in tissues with progression from normal to oral lichen planus (OLP) and then to OSCC suggested that miR-375 regulates this premalignant development by directly binding to the 3' UTR of KLF5, causing downregulation of KLF5, a transcription factor that promotes upregulation of genes that elicit cell proliferation and tumorigenesis while inhibiting apoptosis [68]. Several other researchers have revealed significant downregulation of miR-375 occurs in oral cancer [69–77] and have reported the role of miR-375 in repressing glycolysis [69], reducing cell proliferation [69,73,75], decreasing tumor growth [69,72], suppression of cell migration [70,73,75] and invasion [70,73], inducing cell cycle arrest, increasing apoptosis [72,73], enhancing radiosensitivity [72,78] and decreasing cell viability [73]. Studies have also linked miR-375 downregulation with a higher threat of malignant transformation [71], higher incidence of lymph node metastasis [72], and poor survival [72,75]. Researchers have reported several mechanisms of miR-375 action [69,70,72,73,78]. miR-375 has been suggested as a promising diagnostic biomarker [69,74,76,77,79], prognostic indicator [71] and therapeutic target [69,70,72,73,78] in oral cancers.

By directly targeting WNT10B, a considerable downregulation of miR-148a in cancer-associated fibroblasts (CAFs) compared to normal fibroblasts (NFs) resulted in miR-148a restoration in CAFs for declined migration and invasion of oral cancer cells (SCC-25) [80]. Furthermore, study found that miR-148a expression was significantly lower in SCC 9 cells (human OSCC cell line) compared to human oral keratinocyte (HOK) cells. Its overexpression inhibited cell survival, migration, and invasion, possibly by directly targeting HLA G [81]. Similar to non-cancerous tissues and HOK cells, miR-148a downregulation in OSCC cells was compared to non-cancerous tissues and HOK cells, and its overexpression suppressed proliferation, migration, and invasion in SCC-15 cells, causing a negative correlation with lymph node metastasis and TNM stage. miR-148a appears to inhibit OSCC progression by suppressing the ERK/MAPK pathway by targeting Insulin-like growth factor-I receptor (IGF-IR) [82]. These studies indicate the tumor suppressor role of miR-148a in oral cancer and its potential as a target for the treatment of oral cancer.

When compared to normal tissues, the levels of miR-1254 were considerably reduced in OSCC tissues. Furthermore, miR-1254 expression was lesser in OSCC patients with lymph node metastasis (LNM) compared to those lacking LNM, as well as in late stages (Stages III and IV) compared to early stages (Stages I and II). Overexpression of miR-1254 inhibited cancer cell proliferation and invasion, and miR-1254 appeared to limit OSCC progression by directly targeting and partially downregulating CD36, suggesting that miR-1254 restoration could be a possible therapeutic approach [83]. Chen et al. demonstrated that quercetin conquers cell proliferation and invasion in OSCC via the miR-1254/CD36 cascade in vitro in human OSCC CAL-27 cells [84].

The expression of miR-155 is upregulated in OSCC, and miR-155 downregulates tumor suppressor CDC73 to enhance cell viability and decrease apoptosis in OSCC cells [85]. The miR-155 activity was upregulated significantly in oral cancer cell lines and OSCC tumor tissues for increased proliferation of OSCC cells in vitro with histologic grade of

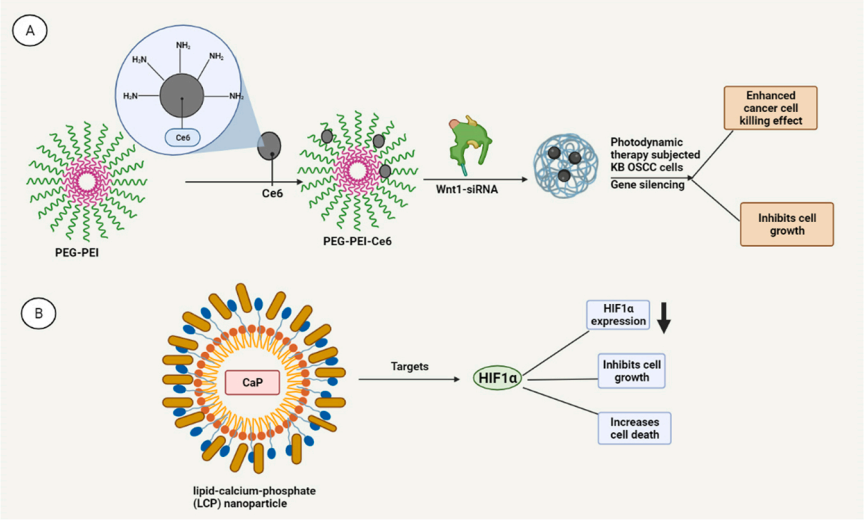

Fig. 8. Delivery of siRNA for oral cancer regression.

OSCC [86]. The upregulation of miR-155 in oral cancer [49,87–91] and its role in enhancing proliferation [88–90], cell cycle progression [89, 91], invasion, migration [88], and cisplatin resistance [92], and decreasing apoptosis [89–91]. Zargar et al. showed the application of miR-155 sponge as a therapeutic intervention in tongue cancer [91]. miR-155 inhibitor-loaded exosomes reverse chemoresistance in cis^{Res} OSSC 3D tumor spheroid model and xenograft mouse model [93]. Thus, miR-155 seems to be an attractive potential prognostic and diagnostic biomarker and a promising therapeutic target for oral cancer.

Exogenous miR-100 and miR-125b alleviated cell proliferation and subsequently regulated the expression of target and non-target genes in OSCC cell lines. Together, they elicited a synergistic effect by altering cell cycle progression, differentiation, proliferation, and immune response upon their co-transfection [14]. Both miR-21 and miR-142–5p targeted PTEN through their overexpression and induced enhanced proliferation in OSCC cells [9,16]. Cell cycle arrest in the G_1 phase was manifested in miR-127–3p [19], miR-145 [20] and miR-7 [23]. Tumor-specific hypermethylation was common in miR-137 and miR-203 relating to the downregulation of the mentioned miRNAs in OSCC [22]. miR-145 [20] and miR-137 [22] share a common target, Cdk6. miR-137 and miR-193a are categorized under tumor suppressors that target Cdk6 and E24 transcription factors leading to their epigenetic silencing during oral carcinogenesis in OSCC [22]. (Tables 1 and 2).

The expression levels of TWIST1, Slug, E-cadherin, and glyceraldehyde-3-phosphate dehydrogenase were correlated in a recent study highlighting the enhancement of EMT owing to the molecular action of lysophosphatidic acid (LPA) towards the development of OSCC [105]. LPA-induced cancer cell invasion was analysed in-vitro for augmented levels of EMT factors, TWIST1 and Slug siRNA in YD-10B cells, and negative expression of E-cadherin. Thus, PA-induced oral carcinoma and cell invasion was inhibited by TWIST and Slug siRNA possess inherited the ability to serve as novel biomarkers against OSCC [105].

OCC survives from siRNA silencing of the targeted oncogenes by adopting substitutional metabolic pathways. Transketolase (TKT) and adenylate kinase-2 (AK2) siRNA were allowed to transfect UM1 and UM2 oral cancer cells from NHOK cell lines [106]. TKT catalyses the pentose phosphate pathway (PPP) for the synthesis of ribose-5-phosphate whereas Akt is also an important component of cellular metabolism and the knockdown of these siRNAs induced lactate production. The aforementioned cells dodged siRNA-induced TKT knockdown, by higher secretion of lactate using glucose and glutamine and survived from the siRNA silencing of AK2. This is a challenging point that hinders the therapeutic potential of these siRNAs against oral cancer [106].

A novel strategy was applied with RNAi by careful designing of a peptide 599 possessing two combinatorial therapeutic derivatives, an endosome fusogenic peptide sequence and the other including residues of nona D-arginine allowing cationic cell penetration serving the purpose of effective delivery of siRNA into the therapeutic target, CIP2A, a potential oncoprotein. This approach had successfully delivered 18-fold higher levels of siRNA effectively silencing the target gene and resulting in reduced cell invasion and anchorage-dependent growth thereby offering a new therapeutic technique against oral cancer [8].

A study investigated the fundamentals of cytokeratin-14 (CK14) expression while it is associated with invasion induced by salivary adenoid cystic carcinoma (SACC) [107]. A cohort of 121 patients manifested a 28% positive invasion from SACC and an 80% drop in the cumulative invasion of cells sourcing from SACC recurrence, metastasis, and poor prognosis of the patients. Cell migration was induced by 2D monolayer culture of Ck14 thereby confirming that Ck14 fostered collective invasion of SACC [107].

A similar investigation shed light on the aberrant expression of Notch4 siRNA, playing a critical role in tumorigenesis through targeting myelin-associated glycoprotein (MAG) in the tissue samples of OSCC [108]. Sixty patient samples were tested, and the expressions of si-Notch4 and MAG were critically analysed for further insights into the induced proliferation and migration in HSC-3 cells of OSCC cell lines. siRNA enhances metastasis by significantly upregulating self-expression levels and MAG, suppressing the migratory and proliferative potential of the metastatic OSCC as effective treatment options against aggressive malignancy [108].

A lipid-calcium-phosphate (LCP) nanoparticle-based delivery of HIF1α siRNA to the cytoplasm of sigma receptor-expressing photodynamic therapy (PDT)-subjected SCC4 and SAS oral cancer cells was performed which decreased HIF1α expression, increased cell death, and inhibited cell growth. Murine xenograft models showed accumulation of concentrated HIF1α siRNA and reduced HIF1α expression upon combinatorial therapy. Thus, this study suggests that nanoparticle-based HIF1α siRNA delivery in combination with PDT could potentially be used for the treatment of OSCC as a possible therapeutic method [109]. In a similar investigation, Wnt-1 siRNA was delivered to the cytoplasm of PDT-subjected KB OSCC cells by using polyethylene glycol-polyethyleneimine-chlorin e6 (PEG-PEI-Ce6) nanoparticles. This combinatorial approach hindered Wnt/β-catenin signaling and vimentin expression, essential for epithelial to mesenchymal transition (EMT) causing inhibition of cell growth and greater cell death, which shows the promise of such a siRNA-mediated therapeutic strategy for OSCC [110].

Moreover, co-delivery doxorubicin (DOX), a chemotherapy drug, and MDR1 siRNA to KBV cells (human oral squamous carcinoma DOX-resistant cell line), using mesoporous silica nanoparticles-polymer polyethyleneimine (MSNP-PEI) caused downregulation in *MDR1* gene expression and induction of apoptosis in KBV cells post-delivery. Co-delivery in murine xenograft models caused a substantial decrease in

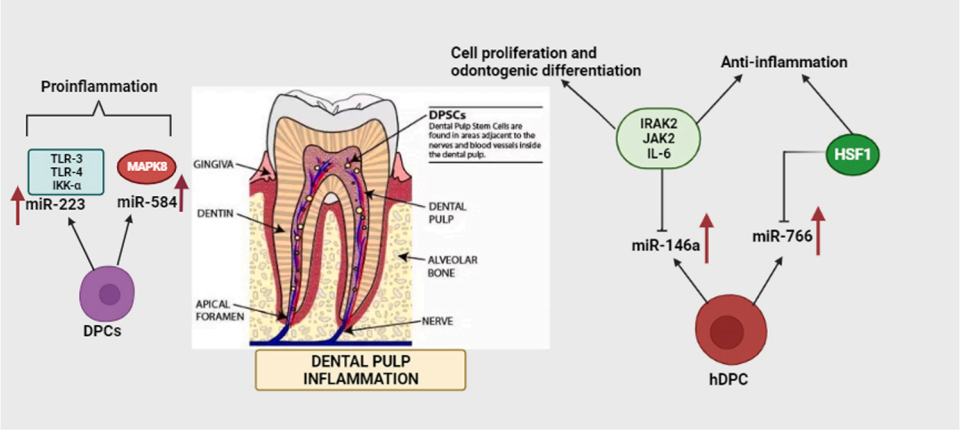

Fig. 9. Influence of miRNA as biomarker for diagnosis of the dental pulp.

tumor size and a slower tumor growth rate [111]. In another investigation, co-delivery of TH287, an MTH1 inhibitor, and MDR1 siRNA into CAL-27 OSCC cells using hyaluronic acid-based mesoporous silica nanoparticles significantly reduced tumor burden in OSCC [112].

Awano et al. reported that ECE siRNA treatment decreased endothelin-converting enzyme-1 (ECE-1) expression which reduced SCC cell proliferation. Thus, the modulation of the endothelin system in oral SCC cells through ECE siRNA delivery depicts as a promising treatment for OSCC [113]. S-phase kinase-interacting protein 2 (Skp2) is essential for ubiquitination and consequent degradation of p27 protein and is overexpressed in OSCC. The transfection of Skp2 siRNA reduced Skp2 levels causing accumulation and stabilization of p27 in OSCC cells and causing inhibition of proliferation of cells both in vivo and in vitro [114]. Moreover, a similar investigation depicted that transfection of Skp2 siRNA into Tca8113 tongue squamous cell carcinoma (TSCC) cells inhibited growth in vitro and repressed in vivo tumor proliferation. Thus, Skp2 siRNA-based downregulation of Skp2 seems to be a promising therapeutic strategy to combat oral cancer [115].

A. type amino acid transporter 1 (LAT1) is crucial for Na+ -independent transport of neutral amino acids and is overexpressed in malignant tumours to aid tumor growth. The transfection of LAT1 siRNA into KB human OSCC cells inhibited the expression of LAT1 mRNA and LAT1 protein, the uptake of [116] L-leucine, and the growth of KB cells, showing potential as a therapeutic intervention for OSCC [117].

Oral cancer has an overabundance of the urokinase-type plasminogen activator receptor (uPAR), which is implicated in the progression and spread of the disease. According to Liang et al., uPAR siRNA transfection into highly malignant OSCC cells not only inhibited endogenous uPAR mRNA and protein expression but also lowered tumor growth, cell adhesion, migration, and invasion when compared to controls [118] A recent investigation highlighted a retroviral vector expressing uPAR siRNA was injected into OSCC xenografts of nude mice, resulting in inhibited endogenous uPAR expression, tumor growth, Ki-67 (a proliferation-related gene) expression, increased cell apoptosis and downregulation of MMP-9, MMP-2, VEGF-D, VEGF-C and VEGFR-3 (involved in metastasis and invasion). u-PAR siRNA also suppressed the expression of the MDR-1 gene, which is responsible for multi-drug resistance. u-PAR siRNA appears to be a promising treatment for stopping OSCC metastasis and progression [119].

A nuclear import carrier of Hsp70 namely heat-shock protein nuclear import factor (HIKESHI), is functional during heat stress. Tabuchi et al. silenced HIKESHI in HSC-3 OSCC cells by using siRNA for HIKESHI (siHIKE) causing downregulation of HIKESHI mRNA and protein in these cells. Cell viability of siHIKE-transfected cells was significantly decreased under mild hypothermia (MHT) conditions probably due to inhibition of cytoplasm-to-nucleus translocation of Hsp70. siHIKE-transfection to silence HIKESHI under MHT conditions appears to be a promising therapeutic approach for OSCC [120].

Nakagawa et al. found that BRCA2, a homologous recombination repair-related gene, repairs DNA double-strand breaks (DSBs) induced by 5-Fluorouracil (5-FU), a chemotherapeutic drug. The knockdown of BRCA2 in the human oral cancer cell lines, SAS and HSC3, using BRCA2 siRNA inhibited repair 5-FU-induced damage. BRCA2 siRNA-mediated downregulation of BRCA2 could be employed for enhancing the sensitivity of oral cancer cells to 5-FU chemotherapy [121].

Slug plays a role in cancer radioresistance and has an anti-apoptotic effect. The transfection of Slug siRNA into HSC3 and HSC6 OSCC cells, followed by radiotherapy in vitro caused decreased Slug expression, increased PUMA expression, reduced cellular survival, and proliferation accompanied by an elevated apoptosis rate and greater sensitivity to X-ray irradiation. The downregulation of Slug by Slug siRNA together with radiation upregulated PUMA expression causing increased radiosensitivity of OSCC cells in vitro, suggesting the therapeutic promise of Slug siRNA [122].

Survivin expression is upregulated in most cancer tissues and it promotes radioresistance in these tissues. Sun et al. demonstrated that survivin siRNA transfection to KB OSCC cells followed by X-ray irradiation significantly decreased cell proliferation, increased apoptosis, and decreased colony formation. While transfection of survivin siRNA alone increased apoptosis by knockdown of survivin, combinatorial therapy with radiation enhanced apoptosis further. Moreover, silencing of survivin in the KB xenograft murine model significantly enhanced tumor regression and apoptosis by irradiation. Thus, survivin siRNA appears to show promise as a therapeutic agent against OSCC [123].

The transfection of IFITM1 siRNA (siIFITM1) into CAL27 and TSCC1

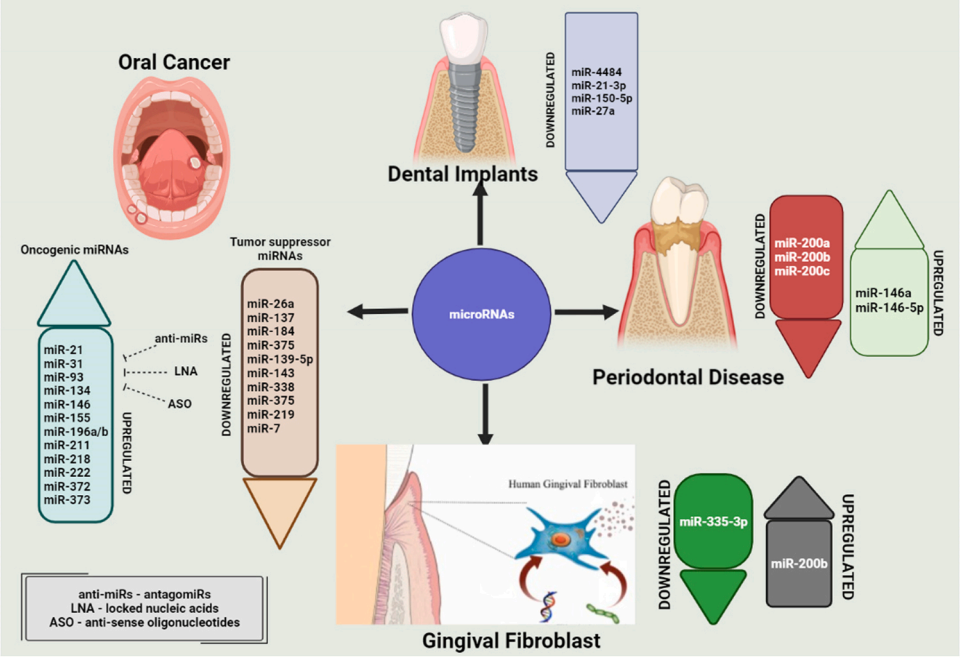

Fig. 10. Influence of miRNA as biomarker for diagnosis of dental diseases.

Table 1
Application of miRNA for the diagnosis of oral cancer.

miRNA	Disease	Tumor suppressor/ Oncogene	Type of preclinical study	Targets	Observation	References
miR-133a miR-133b	Oral cancer	Tumor suppressor hence downregulated	in vitro	a transcript of pyruvate kinase type 2 (PKM2)	Inverse relation between mir-133a and mir-133b with PKM2 indicates that overexpression of this oncogenic transcript has the potential to induce malignancy and inhibit apoptosis of the SCC cells	[94]
miR-138	Oral cancer	Tumor suppressor hence downregulated	in vitro	Targets RhoC and ROCK2	inverse relation is validated upon enhanced levels of Rho and ROCK1 induced by the knockdown of miR-138 using anti-miR-138 PNA	[95]
miR-98	Oral cancer	Tumor suppressor hence downregulated	in vitro	Insulin-like growth factor 1 receptor (IGF1R)	prevents colony formation, migration, proliferation, and invasion of OSCC cells, thereby serving as a significant therapeutic target against tumorigenicity and carcinogenic growth of OSCC cells	[96]
miR-211	Oral cancer	Oncogene hence upregulated	in vitro	mRNA LacZ gene associated with β-galactosidase activity	in-vitro study exhibited alleviated levels of miR-211 expression in comparison to NHOKs whereas SAS cells reported 45% reduction in β-galactosidase activity which validated the inverse relation with LacZ gene	[97]
miR-222	Oral cancer	Oncogenic hence upregulated	in vitro	Targets MMP1 and SOD2	Contributes to tumor initiation, metastasis, cell invasion, and proliferation of oral tongue squamous cell carcinoma(OTSCC)	[15]`
miR-125b	Oral cancer	Tumor suppressor hence downregulated	in vitro	Targets NHOK cells	in vitro transfection of miR-125b downregulated KLF13 gene and up-regulated CXCL11 and FOXA1	[98]
miR-223	Oral cancer	Tumor suppressor hence downregulated	in vitro *& in vivo*	Targets TCF7L2 gene	Reduces invasion, migration, and metastasis ability of OSCC via the Wnt/β-catenin signaling pathway both in vitro and in vivo.	[36]
miR-137	Oral cancer	Tumor suppressor hence downregulated	in vitro	Targets Cdk6 or E2F factor 6 genes	Downregulated in OSCC cells and induced aberrant DNA methylation and also downregulated for reduced cell growth	[22]
miR-7	Oral cancer	Tumor suppressor hence downregulated	in vitro	Targets insulin-like growth factor 1 (IGF1R)	Induces activation of Akt (protein kinase B) for suppressed cell proliferation and cell-cycle arrest in oral cancer cells in-vitro	[99]
miR-21	Oral cancer	Oncogenic hence upregulated	in vitro	Targets TPM1 and PTEN	exhibits the overexpression of the oncogenic miRNA-21 `in oral squamous cell carcinoma (OSCC) with suppressed levels of tropomyosin (TPM1) and phosphatase tensin homolog PTEN inhibiting apoptosis in the cancer cells	[100]
miR-203	Oral cancer	Oncogenic hence upregulated	in vitro	Targets Yes 1 gene	Overexpression of miR-203 induced downregulation of Yes 1 gene and augmented nuclear condensation and apoptotic population of KB cells.	[101]
miR-143	Oral cancer	Tumor suppressor hence downregulated	in vitro	Targets Tca8113 cells	frequently associated with augmented cell growth, proliferation, invasion, and glucose metabolism in OSCC by downregulation in Tca8113 cells while analyzing in vitro expression in 15 human normal oral health tissues and 15 oral cancer tissues.	[18]
miR-338	Oral cancer	Tumor suppressor hence downregulated	in vitro	Targets Neuropilin 1 (NRP1)	elicited anti-proliferative activity and inhibited metastasis, colony formation, invasion, and migration in OSCC through downregulation of the inversely correlated target, Neuropilin 1 (NRP1)	[24]
miR-219	Oral cancer	Tumor suppressor hence downregulated	in vitro	Targets SCC-15 and CAL-27 cells	Suppresses carcinogenesis in TSCC by protein kinase CI (PRKCI) which inherits the potential to induce tumorigenesis against the tumor-suppressive effects of miR-219 in SCC-15 and CAL-27 cells. Overexpression of miR-219, inversely related with the expression of the oncogenic target PRKCI, alleviated cell proliferation, invasion, migration, and colony formation of TSCC cells	[102]
miR-375	Oral cancer	Tumor suppressor hence downregulated	in vitro	Targets CIP2A gene	under expression in oral cancer cells causes uncontrolled CIP2A expression and subsequently extended stability of MYC, for promotion of cancerous phenotypes	[68]
miR-148a	Oral cancer	Tumor suppressor hence downregulated	in vitro	Targets WNT10B	significant downregulation of miR-148a in cancer-associated fibroblasts (CAFs) relative to normal fibroblasts (NFs) led to the restoration of miR-148a in CAFs for decreased migration and invasion of oral cancer cells (SCC-25) by directly targeting WNT10B	[80]
miR-31–5p	Oral cancer	Oncogenic hence upregulated	in vitro	Targets ACOX1	miR-31–5p-ACOX1 Axis enhances Tumorigenic Fitness in Oral Squamous Cell Carcinoma via the promigratory Prostaglandin E2.	[44]
miR-27a	Dental implants	Oncogenic hence upregulated	in vitro	Targets DKK2 and SFRP1	enhanced osteogenic and angiogenic activity by directly targeting Dickkopf2 (DKK2) and secreted frizzled-related protein 1 (SFRP1)	[103]
miR-455–5p	Oral submucous fibrosis	Oncogenic hence upregulated	in vitro	Targets protein tyrosine phosphatase receptor type sigma (PTPRS)	Plays an important role in the molecular pathway in OSF, in the modulation of OSCC cell growth and proliferation.	[104]
miR-1246	Oral cancer	Oncogenic hence upregulated	in vitro	_	Cancer relapse and metastasis in OSCC	[55]

Table 2
Therapeutic application of siRNA for the management of dental diseases.

Disease	Type of preclinical study	siRNA delivery system	Targeted gene/ Cell lines	Results	References
Oral cancer	-	peptide 599 possesses two combinatorial therapeutic derivatives, an endosome fusogenic peptide sequence, and residues of cationic cell-penetrating Nona D-arginine.	CIP2A	This approach had successfully delivered 18-fold higher levels of siRNA effectively silencing the target gene and resulting in reduced cell invasion and anchorage-dependent growth thereby offering a new therapeutic technique against oral cancer	[8]
Oral cancer	*In vivo*	EGFR –binding peptide	CIP2A	Prevents invasion and tumor growth	[127]
Oral cancer	*In vivo*	lipid-calcium-phosphate (LCP) nanoparticle-based delivery	HIF1α	Decreases HIF1α expression, increases cell death, and inhibits cell growth	[109]
Oral cancer	-	polyethylene glycol-polyethyleneimine-chlorin e6 (PEG-PEI-Ce6) nanoparticles	PDT-subjected KB OSCC cells	It mired Wnt/β-catenin signaling and vimentin expression, essential for epithelial to mesenchymal transition (EMT) causing inhibition of cell growth and greater cell death, which parades the promise of such a siRNA-mediated therapeutic strategy for OSCC	[110]
Oral cancer	-	Adeno associated viral vector	MDR 1 and MDR2	Regulation of MDR	[128]
Oral cancer	*In vivo*	mesoporous silica nanoparticles-polymer polyethyleneimine (MSNP-PEI)	MDR 1	It causes downregulation in MDR1 gene expression and induction of apoptosis in KBV cells post-delivery	[111]

oral cancer cells post-radiotherapy promoted the damage of DNA and apoptosis of cells, decreased the viability of cells, and suppressed cell proliferation. IFITM1 silencing post-irradiation led to upregulation of pSTAT1/2/p21 and downregulation of pSTAT3/p-p21 in vitro. *In vivo,* oral neoplasm tumorigenesis was significantly inhibited by IFITM1 silencing alone, but more so by a combination of IFITM1 silencing and radiation therapy which may serve as a potential therapeutic modality for oral cancer [124].

HuR protects AU-rich element-comprising mRNA from rapid degradation by binding to them. Kakuguchi et al. knocked down HuR in HSC-3 and Ca9.22 OSCC cells using HuR siRNA, causing decreased cytoplasmic expression and shorter half-lives of COX-2, c-myc, and c-fos mRNAs compared to control cells. HuR knockdown also caused loss of anchorage-independent cell growth, decreased motility and invasiveness, and reduced expression of cell cycle-related proteins such as cyclin-dependent kinase 1, cyclin D1, cyclin B1, and cyclin A. Thus, HuR siRNA-mediated silencing of HuR shows promise as a therapeutic strategy in OSCC [125].

3. Dental implants

Dental implants are utilized to support crowns, bridge abutments, and removable dentures. The surgically placed dental implant constitutes titanium to form an immobile bond with bone (osseo-integration) and prosthetic fixtures attached to the implant [129]. While dental implants have been reported to be stable functionally and have long-term success rates, Osseo-integrated implants suffer from biological complications referred as peri-implant diseases, most often characterized by inflammation around the implant [130,131]. Peri-implant mucositis and peri-implantitis are the two categories of peri-implant illnesses. Soft tissues around the implant become inflamed without bone loss in peri-implant mucositis. It's reversible if caught and treated early enough, and it's thought to be the prelude to peri-implantitis [130]. Peri-implantitis is defined by the 7th European Workshop on Periodontology as "changes in the level of crestal bone, presence of bleeding on probing and/or suppuration; with or without concomitant deepening of peri-implant pockets" [132]. Different studies have estimated varying prevalence of peri-implantitis [130,131]; this has been attributed to the lack of a standard threshold for the extent of tissue changes/damage required for a diagnosis of peri-implantitis [131]. Mombelli et al. estimated that the incidence of peri-implantitis was in the order of 10% implants and 20% patients during 5–10 years after implant placement [133].

Infection control, regeneration of lost tissues, detoxification of implant surfaces, and plaque-control regimens using mechanical debridement are some therapeutic interventions and modalities that are considered ideal for the administration of peri-implant diseases [130]. While peri-implant mucositis generally can be treated by oral hygiene instructions, scaling, and prophylaxis, peri-implantitis may be less responsive to non-surgical treatment, requiring the use of anti-microbial for site decontamination, and in more resistant cases, surgical intervention [134]. According to Menini et al. miRNAs may be valuable indicators of dental implant clinical outcomes, as well as possible prognostic and diagnostic biomarkers in peri-implant disorders[135].

Chaparro et al. quantified the expression of miRNA-26a-5p, miRNA-150–5p, and miRNA-21–3p in peri-implant crevicular fluid (PICF) of patient samples. miRNA-150–5p and miRNA-21–3p were downregulated significantly in patients with peri-implantitis relative to those with peri-implant mucositis. This downregulation was associated with peri-implantitis diagnosis. There was no discernible change in miR-26a expression between the two peri-implant disorders. As a result of these findings, it may be concluded that, while the results are intriguing, large-scale prospective studies are required to evaluate whether these miRNAs can be used as screening biomarkers for peri-implant health status [136].

miR-27a was found to be differently downregulated in samples from

a canine peri-implantitis model, and its ectopic overexpression in vitro improved osteogenesis–angiogenesis coupling by counteracting TNF-induced bone formation inhibition, according to Wu et al. Dickkopf2 (DKK2) and secreted frizzled-related protein 1 were specifically targeted by miR-27a, which increased osteogenic and angiogenic activity (SFRP1). When used to heal bone defects around implants in a canine peri-implantitis model, a miR-27a-enhanced delivery method might cure the defects and promote re-osseointegration. The therapeutic potential of miR-27a in the regenerative treatment of peri-implantitis seems promising [103].

according to Urvasizoglu et al. miR-4484 was found to be down-regulated in the saliva of peri-implantitis patients, Saliva samples taken 4–6 months after implant implantation had considerably lower levels of miR-4484 than samples collected before implant placement. Salivary miR-4484 has been proposed as a possible peri-implantitis early diagnostic biomarker [137].

The above findings strongly indicate the capability of several microRNAs in screening patients for dental implant diseases and their promise as treatment modalities in both peri-implantitis and peri-implant mucositis in the future. However, scientific articles investigating the diagnostic, prognostic, and therapeutic potential of miRNAs in peri-implant diseases are scarce. Since molecular biomarkers like miRNAs could facilitate early detection of peri-implant diseases, act as reliable indicators of peri-implant health, or aid in managing peri-implant diseases, more studies are necessary to determine suitable miRNAs that may fulfil these roles.

Titanium (Ti) implants were biofunctionalized with siRNA targeting casein kinase-2 interacting protein-1 (Ckip-1), a negative modulator of bone turnover promoting osteoporosis. The chitosan siRNA-targeting Ckip-1 (CS/siCkip-1) complex was physically adsorbed onto the Ti implant surface by thermal alkali (TA) treatment for enhanced delivery efficiency. TA-CS/siCkip-1 caused Ckip-1 gene silencing, in vitro osteogenic differentiation of bone marrow mesenchymal stem cells (MSCs), and in vivo osseo-integration in the osteoporotic rat model [138]. Huang et al. biofunctionalized a Ti implant with siRNA targeting MIR31HG (siMIR31HG) by loading CS/siMIR31HG on the TA-treated Ti surface. The siMIR31HG functionalized implant caused about 50% knockdown of MIR31HG which promoted osteogenic differentiation of bone marrow MSCs [139]. The biofunctionalization of titanium implant was reported in a similar investigation where the process was facilitated with chitosan/siRNA complex through loading-controllable and time-saving cathode electrodeposition (CED). Biofunctionalization of the Ti implant by CS/siCkip-1 improved osteogenic differentiation of rat MSCs by promoting collagen secretion, calcium deposition, and osteogenesis-related gene expression [140]. Thus, CS/siRNA biofunctionalization of Ti implants by TA treatment or CED could be a useful clinical approach to promote dental implant osseo-integration.

Moreover, titania nanotubes (NTs) fabricated by anodic oxidation were modified by CED with polyethylene glycol (PEG) and polyethyleneimine (PEI) dual-functionalized graphene oxide (GO) to deliver siRNA (NT-GPP/siRNA). NT-GPP/siCkip-1 delivery enhanced in vitro osteogenic differentiation in the mouse osteoblastic cell line MC3T3-E1 and probably improved in vivo osseo-integration [141]. Thus, implant biofunctionalization by NT-GPP/siRNA shows promise as a therapeutic strategy for improving dental implant osseo-integration.

Trigeminal nerve injury causes dental implant surgery and manifests as trigeminal neuropathic pain (TNP). For the major VEGF-A route in the development of TNP, downregulation of VEGF-A expression by VEGF-A164 siRNA caused considerable anti-allodynic effects [142]. In a similar investigation, a decrease in EphA4 expression by the use of EphA4 siRNA caused significantly long-lasting anti-allodynic effects, illustrating the role of EphA4 in promoting TNP [143]. Thus, VEGF-A164 siRNA delivery and EphA4 siRNA delivery could be used as a treatment approach for TNP resulting from dental implant surgery.

Only a handful of studies are currently available for the application of siRNAs in dental implant biofunctionalization and almost no reports on the application of siRNAs in therapeutic strategies in dental implant diseases like peri-implant mucositis and peri-implantitis. Hence, more studies in these directions are required to explore and firmly establish the potential of siRNAs in enhancing dental implant functionality and treating dental implant-related diseases.

4. Periodontal disease

Inflammation of the tooth-supporting tissues is one of the hallmarks of periodontal disease-causing the gradual loss of alveolar bone surrounding the teeth. When left untreated, it causes dental loosening and eventual tooth loss [116,144]. In recent years, the impact of periodontal disease over chronic degenerative disease was investigated which highlighted the need for early diagnosis and intervention of periodontal disease [145]. The modification of clinical manifestation of inflammation is influenced by epigenetic changes, including miRNAs and genetic polymorphisms. Individuals at high risk of periodontal disease are classified upon genetic and epigenetic factors [146]. miRNAs play a major role in the pathophysiology of periodontitis through dysregulation caused by bacterial components found in the oral biofilm. miRNAs lead the innate and adaptive immune systems to be ineffectual in combating microbial change or to generate an overactive catabolic response as a result of their actions. A miRNA expression using microarray analysis and qPCR validated transcript levels of inflammatory miRNAs [147]. Furthermore, miRNA pathways suggested a potential Toll-like receptor (TLRs) based regulation in periodontal inflammation.

A pilot study investigated the influence of miRNA on periodontal disease and obesity modulation [148,149]. Moreover, the comorbidities of obesity and periodontitis are linked to considerable regional over-expression of numerous miRNA types that have inflammatory and physiological mRNA targets in common. To validate the *in silico* predicted targets, whole-genome microarray analysis of the same specimens was used to look for miRNAs in healthy and diseased gingival tissues [150]. The four miRNAs were upregulated and seven down-regulated in gingival tissues when compared to controls and are thus used to diagnose periodontal disease. MiR-141 was shown to be one of the most frequently expressed microRNAs in human gingival keratinocytes [151] and thus could be utilized as a potential biomarker for its detections. Both miR-200a and miR-200c were shown to be lower in clinical samples of periodontitis compared to healthy gingiva [150] due to the downregulation of *Porphyromonas gingivalis* lipopolysaccharide (PgLPS) in gingival tissues and gingival epithelial cells [152,153] in murine models. However, miR-200b was considerably enhanced in the gingiva of obese periodontitis patients and chronic periodontitis [154]. During inflammatory situations, miR-200a, miR-200b, and miR-200c play various roles in chronic periodontitis lesions. The upregulation of miR-200c decreased LPS-tempted pro-inflammatory mediators in human gingival fibroblasts (HGFs) and localized intervention with miR-200c enhanced alveolar bone resorption in a rat model for improved periodontitis [155].

Nahid et al. investigated the miR-146a expression of cytokines causing inflammation through infection with heat dead and live periodontal pathogenic bacteria in THP-1 monocytes.In another investigation upregulation of miR-146a when THP-1 cells are stimulated with LPS through hindered TLR-NFB cascade from *P. gingivalis*, thus acting as a biomarker for diseases detection and correlating periodontitis with inflammation [156]. Moreover, the upregulation of miR-146b-5p and miR 146a in human gingival fibroblasts when stimulated via LPS in *P. gingivalis* wherein, miR-146 acts as a potent inhibitor of inflammation in periodontal disease [157]. Post-stimulating dental pulp, gingival, and periodontal fibroblasts with LPS from *Escherichia coli* resulted in differential expression of miR-155 and miR-146a. Gingival fibroblasts possess enhanced miR-146a expression, whereas gingival fibroblasts exhibited reduced miR-155 expression [158]. Thus, the expression titers of miRNA can be utilized for detection. Altered expressions of miR-146a in THP 1 macrophages in vitro post-stimulation with LPS from *Aggregatibacter*

actinomycetemcomitans, against *P. gingivalis*, from cigarette smoke extract. In human macrophages, various LPS generated both similar and distinct expressions of miRNAs. Furthermore, LPS from *P. gingivalis* cultured on cigarette smoke extract generated differential miRNA expression in human macrophages as compared to LPS from untreated *P. gingivalis.* Thus [159], these LPS-responsive miRNAs serve as a vital role in adjusting the host immune response to periodontal bacteria.

5. Gingival fibroblasts

Gingival fibroblasts (GF) are the most common type of cell in periodontal connective tissues, and they play different roles in periodontal tissue healing along with in inflammatory periodontal disorders [160]. Gingival overgrowth has been reported as a side effect of the immunosuppressive drug cyclosporine A (CsA) [161,162]. CsA's effect on the expression of microRNA-200b (miR-200b) in normal human gingival fibroblasts (HGFs) was examined, with CsA downregulating miR-200b in HGFs in a dose-dependent manner by immunomodulation of slug. The overexpression of miR 200b decreased CsA-induced cell proliferation and caused Slug upregulation. The findings revealed that miR-200b was an upstream regulator of CsA-induced EMT and could be utilized as a potential therapeutic target for gingival overgrowth [163]. Lina et al. carried out another investigation, wherein miR-200a regulates ZEB2 in a dose-dependent manner, in normal human gingival fibroblasts (HGFs) through upregulated levels of CsA. This caused HGFs regression by increased cell proliferation through miR-200a suppression was reversed by ZEB2 repression [164].

The nuclear receptor 4A1 (NR4A1) plays a pivotal role in fibrosis and the links between NR4A1 and drug-induced gingival overgrowth (DIGO) are yet unknown. Hatano et al. investigated the role of NR4A1 wherein CsA suppressed the up-regulation of Nr4a1 expression in gingival tissue caused by periodontal disease (PD) in the DIGO murine model but not Col1a1 or Pai1. TGF-induced rise of NR4A1 mRNA expression (hGF) in human gingival fibroblasts was suppressed by NFATc3 siRNA, and TGF-induced translocation of NFATc3 into the nucleus of hGF was inhibited by CsA. Moreover, NIF and PHT also inhibited NFATc3 translocation in hGF by lowering NR4A1 mRNA level. TGF β-upregulated NR4A1 expression was inhibited by CsA, NIF, and PHT, but CaCl2 promoted TGF- β upregulated NR4A1 expression [165].

Hereditary gingival fibromatosis (HGF) is another form of genetically diverse GF with a high recurrence rate, and the present treatment options are restricted to surgical excision [166,167168]. A novel miRNA screening methodology targeted a functionally similar gene and identified miR-335–3p as a unique HGF therapy by suppressing key components in profibrotic networks and reducing the fibrogenic activity of HGF [169].

6. Oral submucous fibrosis

Oral submucous fibrosis (OSF) is a pre-malignant state of oral cancer with a complicated etiology [170] affecting patients between 20 and 40 and causing substantial mortality. According to WHO, there are more than 5 million OSF cases in the world affecting women primarily in Asian countries [171,172173]. Chewing areca nuts plays an important role in the formation of OSF via myofibroblast trans differentiation of BMFs induced by arecoline stimuli (an alkaloid extracted from areca nut). Increased ZEB1 in areca-nut-associated OSF may lead to pathogenesis by stimulating the -SMA promoter and increasing BMF myofibroblast activation, according to Chang et al. [174].

The expression levels of miR-1246 in OSF tissues and fibrotic buccal mucosal fibroblasts were investigated by Liu et al. (fBMFs). MiR-1246 is important not only for maintaining oral stemness but also for initiating myofibroblasts. Type I collagen is also linked to miR-1246, as it is a downstream regulator of miR-1246 and is responsible for the fibrosis effect on fBMFs [175]. Arecoline administration reduced miR-200b gene expression in BMFs in a dose-dependent manner, implying that miR-200b suppression plays a role in the pathogenesis of areca quid-associated OSF by modulating ZEB2 and myofibroblast markers [176]. Even though miR − 200c has recently been identified as a key regulator of carcinogenesis and tumor metastasis, its involvement in controlling OSF is unclear. Lu et al. explored the role of miR-200c in the activity of myofibroblastic differentiation and recognized it as a possible target through modulation of ZEB1 for OSF pathophysiology via areca nut-associated OSF[177].

Initial microarray analysis of the miRNA expression pattern screens out differently expressed miRNA in OSF, suggesting 11 distinct miRNAs. Hsa-miR-455–5p, hsa-miR-455–3p, and hsa-miR-623 were overexpressed miRNAs, while hsa-miR-1290, hsa-miR3180–3p, hsa-miR-4792, hsa-miR-509–3–5p, hsa-miR-5189, hsa-miR-610, hsa-miR-760 and hsa-miR-921 were downregulated. This research demonstrates that miRNA chips could be utilized for high-throughput miRNA screening. The most common roles of the predicted targets of these newly discovered miRNAs are metabolic, binding, metabolic, cellular, and molecular processes [60]. In another investigation, the expression of miR-21 in the blood samples with oral squamous cell carcinoma (OSCC), oral submucous fibrosis (OSMF), and healthy people. The results exhibited an up-regulation of circulating miR-21 in serum samples of OSCC patients compared to OSMF serum and miR-21 expression increased significantly in clinical stages I-IV of oral cancer. Moreover, miRNA 21 is upregulated in OSMF and chewing habit patients. However, the levels of expression were not shown to be related to the harshness of the disease condition [178]. In another investigation, the miR-29b expression was inhibited and there was a negative relationship between miR-29b and these fibrosis biomarkers showing that arecoline triggered H19 upregulation via TGF β-pathway.

7. Radiation-induced Oral mucositis

Radiation-induced oral mucositis (RIOM), which affects nearly everyone with head and neck cancer and causes terrible pain and ulceration, is one of the most common side effects of radiotherapy in cancer patients. The five stages of RIOM development include initiation, primary damage response, signal amplification, ulceration, and healing [179,180]. The essential regulators implicated in RIOM pathogenicity, are mainly unexplored. Tao et al. depicted a novel function for miR-200c family numbers (miR-200c, miR-200b, miR-200a, and miR-141) except miR-429 as a part of the miR-200 family in RIOM pathogenesis in the murine model. They exhibited that miR-200 knockdown accelerated DNA double-strand break repair post-irradiation. Moreover, decreasing miR-200c stops the production of pro-inflammatory cytokines (TGF-, TNF-, and IL-1) in NHKs exposed to IR through suppressing NF-B and Smad2 activation. Moreover, the inhibition of miR-200c boosted the expression of molecules effectors in a Snail, Vimentin, ZEB-1, and Bmi-1 dependent manner for epithelial to mesenchymal transition, and enhanced NHK migration. These findings not only reveal miR-200c as a critical player in the etiology of RIOM but also provide a new treatment target for the disease [181].

8. Dental pulp

The dental pulp is a particular layer of connective tissue that is intensively perfused and is encircled in rigorous surroundings composed of 3 mineralized tissues: dentin, enamel, and cementum, that offer tactile care and strength counter to the oral cavity's microbiota [182]. The pulp inflammation is a defensive physiological response that tries to remove damaging stimuli, followed by the commencement of the pulp tissue's recovery process [183]. Pulp inflammation is characterized primarily by capillary dilatation, migration, and deposition of inflammatory cells in the pulp tissue [184]. The proliferation of dental pulp stem cells (DPSCs) is important for tooth growth and injury healing, as well as tissue engineering treatment. miR-584 acts as a crucial regulator in the development of DPSCs by modulating TAZ expression through the

AKT signalling pathway and is a potentially useful biomarker for the diagnosis of pulp disease [185]. Nara et al. found that miR-121 was highly expressed in dental pulp cells (hDPC) induced with LPS and that it was capable of suppressing the production of pro-inflammatory cytokines such as IL-1, IL-1, IL-6, and TNF- through the conquest of TNF receptor-associated factor (TRAF)− 6 and programmed cell death (PDCD)− 4 mRNAs [186]. Thus, miR-21 possesses a protective function in the progress of pulpitis. miR-766 was considerably elevated in inflamed pulps when compared to normal pulps, suggesting that its likely target gene is a heat-shock factor (HSF)− 1, a heat-shock transcription factor rapidly activated following extremes of temperature [187,188]. Hence, miR-766 may act as a potential biomarker to diagnose Pulp disease.

9. Oral lichenoid disease

Oral lichenoid disease (OLD) is a chronic inflammatory disease with an immunological basis that affects around 2% of the population and primarily women [189–191]. This condition is classified as an oral potential malignant condition with a low rate of malignant transformation, ranging from 0.4% to 6.5% [190]. Oral lichen planus (OLP) is an inflammatory oral epithelial condition characterized by keratinocyte death whose pathogenesis is still a mystery. When comparing OLP patients to healthy controls, miR-26a/b levels were significantly lower in oral mucosal biopsies, blood, and saliva suggesting that vitamin D/VDR-triggered miR-26a/b protects OLP by reducing apoptosis and limiting the inflammatory reaction in oral keratinocytes [192].

Setién-Olarra et al. used the expression profile of mature OLD samples to validate 13 best-positioned microRNAs for OLD (microRNA-629, microRNA-625, microRNA-152, microRNA-1247, microRNA-339, microRNA-223, microRNA-7, microRNA-342, microRNA-146b, microRNA140, microRNA-146a, microRNA-142, microRNA-150) and highlight their role in disease progression [193]. In another similar investigation, the microRNA expression pattern was compared in seven patients having oral lichen planus (OLP) and seven healthy controls, suggesting dysregulated microRNAs and transcribed mRNAs, the majority of which are functionally linked to inflammatory or premalignant processes. Thus, microRNAs influence disease-related pathways and could be utilized as a biomarker for disease detection [194]. Moreover, the expression of microRNA 146a in CD4 + cells in peripheral blood of clinical patients diagnosed with OLP was compared with healthy control for validating the upregulation of miR-146a in OLP. Thus, indicating that miR-146a plays a significant role in the malignancy of erosive OLP, albeit more research is needed [195]. miR-21, miR-125b, and miR-203 were correlated with p53, DNp63, and TGF via gene analysis to determine the downregulation in lichen planus samples [196]. Thus, suggesting the role of miRNA in the theragnostic of OLP. Dang et al. looked studied epigenetic changes in the microRNA-137 promoter in OLP tissue samples, OSCC tissue samples, and controls. Both microRNA-137 and the p16 protein were discovered to be methylated in OLP patients, however to a lesser level than in OSCC patients. Furthermore, a link between this methylation and the epithelium in OLP patients revealed that the epithelium, rather than the connective tissue, is the beginning of the first malignant process [197]. Nylander et al., used serum to examine the aberrant microRNA pattern in patients with multifocal lichen planus and compared it with healthy controls. The overexpressed miR-143, miR-21, and miR-123 possess a link to OSCC and potentially lead to tumor progression so that it can be applied for disease detection [198].

10. Current challenges and expert opinion

Existing literature evinces miRNAs, particularly miR-34a, are linked to bone remodelling, tooth growth, and dental stem cell differentiation [199]. In addition, a number of miRNAs have been linked to oral malignancies as well as an increased chance of premalignant lesions in the mouth developing into cancer [200,201]. Oral cancer risk factors have been linked to changes in the expression of various miRNAs, such as increased miR-31 and miR-138 expression and decreased expression of miR-10b, miR-92a, miR-200b, miR-372, miR-375, miR-378a, and miR-145 with use of smokeless tobacco [202]. According to present records, till date only twenty or fewer miR therapies have started clinical studies, but none have advanced to phase III trials. In comparison, there are over 60 siRNA medicines approved and in clinical studies. A larger frequency of terminated/suspended clinical studies (50% vs. 35%) and none in phase III clinical trials (0% vs. 12%) suggest inexplicable barriers in the development of miR therapies when compared directly to siRNA therapeutics [203]. Validation is required for candidate miRNAs with differential expression found in pilot investigations. The majority of earlier research employing tissues used samples from few people without matching for potential confounding variables including age and gender, which are known to affect periodontitis susceptibility [204]. Additional validation research with sizable, well-characterized cohorts is necessary [205]. Even though recent developments in molecular biology and high-throughput screening methods have made it possible for researchers to characterise miRNA patterns in body fluids like serum, plasma, and saliva on a large scale, this is still constrained by the lack of appropriate endogenous controls for normalising salivary miRNAs. [206]. Deregulated miRNAs are also being investigated for their potential use as biomarkers for clinic-pathological indicators, precision therapy, and the creation of expression profiles for oral cancer [207]. In order to use miRNA datasets in the future, endogenous salivary miRNA controls are necessary. Standardized techniques for sample collection should be taken into consideration because saliva samples taken from the same person can exhibit significant variation depending on the technique utilised for collection. The investiture of appropriate treatments and preventative measures for patients who test positive for these biomarkers is also necessary, even though the discovery of biomarkers is of utmost importance. To benefit from early diagnosis, highly sensitive individuals require effective, targeted therapies, without which a certain cost-benefit advantage cannot be attained [208]. The occurrence of many targets of miRNAs provides a significant difficulty in the development of miRNA therapies. Although this is a natural property of miRNAs, it can be mitigated by targeted delivery and chemical changes to the molecules that increase their binding to the target genes. Furthermore, miRNAs produced from plants that influence a pathogen-specific gene but do not target host genes might be used to build miRNA therapies [209]. Although miRNAs have certain benefits over siRNA molecules in terms of efficacy, many of the constraints in miRNA delivery are comparable to those experienced by siRNAs and DNAs, such as inadequate or improper biodistribution, poor in vivo stability, and undesirable side effects, with some exceptions. Novel and advanced methods of tissue regeneration, combining cutting-edge technologies for controlled delivery of stem/progenitor cells with the use of bioengineered scaffolds and selected miRNAs, will pave the way for more promising regenerative medicine and targeted therapies in patients soon [210].

11. Future prospects of the application of miRNA in clinical translation

The advancement of siRNA medicines in clinical trials has been troubled with difficulties. These drawbacks include the siRNA therapeutics' ineffectiveness due to transitory expression, insufficient efficacy, increasing resistance to the siRNA, and off-target TLR activation. Controlling the specificity of the siRNA and avoiding potential off target effects associated to the sequencing of both dsRNA strands are two other important hurdles for RNAi-based therapies. siRNAs are known to start off-target gene silencing by acting similarly to microRNAs (miRNAs) [211]. MiRNAs provide prospects for greater emphasis on early identification and less on late therapy of oral malignancies. Significant research is required to determine if one or more miRNAs must be targeted for long-term tumour regression and whether such a method may

be utilised as a monotherapy or as an adjuvant treatment approach. Furthermore, the duration of miRNA therapy must be decided, since either a short or extended treatment might result in tumour recurrence or major adverse effects. Future research on early detection biomarkers such as miRNA, which could represent the onset of malignant neoplastic event, would provide the professional with useful information about the course of further treatment [212]. When new genetic testing technologies like RNA sequencing are made available, it will be possible to get around current technical constraints and improve test accuracy when working with extremely small samples. The discovery of connections between diverse diseases will be aided by fundamental study into the mechanisms underlying the regulation and activity of miRNAs. Additionally, improved bioinformatic pipelines and more effective computational prediction models will provide the best use of miRNA datasets [213]. The use of saliva collection in conjunction with novel diagnostic tests will enable large-scale and follow-up studies to be carried out at a cheaper cost than when utilising conventional blood or tissue samples [214]. With the advent of new and improved procedures, more people who are predisposed to periodontal disease and have bleak prognoses for other disorders will be identified early, enabling therapeutic therapies that are patient-focused. The foundation for the future development of genetically-based personalised dentistry will be set by this initial step [215].

12. Conclusion

In summary, the review article discussed the role of miRNA and siRNA in oral biome. In particular, the application of miRNA and siRNA as a biomarker against oral cancer has been discussed. The role of various miRNAs as oncogenes or tumour suppressors has been discussed along with their targets. The therapeutic application of siRNA for the management of dental diseases and their target genes have also been explored in details. miRNAs may be valuable indicators of dental implant clinical outcomes, as well as possible prognostic and diagnostic biomarkers in peri-implant disorders. miRNAs could facilitate early detection of peri-implant diseases, act as reliable indicators of peri-implant health, or aid in managing peri-implant diseases. Titanium (Ti) implants were biofunctionalized with siRNA targeting casein kinase-2 interacting protein-1 (Ckip-1). miRNAs play a major role in the pathophysiology of periodontitis through dysregulation caused by bacterial components found in the oral biofilm. miRNAs lead the innate and adaptive immune systems to be ineffectual in combating microbial change or to generate an overactive catabolic response as a result of their actions. miRNA expression using microarray analysis and qPCR validated transcript levels of inflammatory miRNAs. Furthermore, miRNA pathways suggested a potential Toll-like receptor (TLRs) based regulation in periodontal inflammation. They also play a role in gingival fibroblasts and oral submucous fibrosis. miRNAs like miR-200c act as critical players in the etiology of RIOM (radiation-induced oral mucositis) and also provide a new treatment target for the disease. dental pulp, and oral lichenoid disease. Some miRNAs possess a protective function in the progress of pulpitis and can be used as potential biomarkers to diagnose pulp disease. The overexpressed miR-143, miR-21, and miR-123 possess a link to OSCC and potentially lead to tumor progression so that it can be applied for disease detection. We have also discussed the impact of miRNA and siRNA over the various pathways and molecular effectors pertaining the same. The influence of upregulation and downregulation of molecular effector post-treatment with miRNA and siRNA have also been elucidated and their impact on clinical setting has been discussed. Further research is required to understand the role of various miRNAs and siRNAs in dentistry.

CRediT authorship contribution statement

Adrija Sinha: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, **Rahul Bhattacharjee:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, **Basudha Bhattacharya:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, **Aditya Nandi:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft. **Ramya Shekhar:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, **Ankit Jana:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, **Koustav Saha:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, **Lamha Kumar:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, **Swadheena Patro:** Methodology, Formal analysis, Investigation, Resources, Writing – review & editing, **Nagendra Kumar Kaushik:** Methodology, Formal analysis, Investigation, Resources, Writing – review & editing, **Pritam Kumar Panda:** Methodology, Investigation, Formal analysis, Software, Validation **Mrutyunjay Suar:** Conceptualization, Methodology, Software, Validation, Resources, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Suresh K. Verma:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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