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Review

Unravelling the role of stem cell-derived exosomes in oral cancer treatment: A review

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ABSTRACT

Introduction: Oral cancer is the sixteenth most prevalent cancer globally, with Asian countries accounting for two-thirds of cases. Despite advancements in surgery, chemotherapy, and radiotherapy, late diagnosis, the absence of specific biomarkers, and the high cost of treatment result in poor outcomes. Tumor recurrence remains a significant challenge, highlighting the need for innovative therapeutic strategies. One promising avenue is the study of exosomes, which carry biomolecules like proteins, lipids, DNA, RNA, and microRNA, playing a key role in intercellular communication and the tumor microenvironment. Stem-cell-derived exosomes could revolutionize cancer therapy by targeting tumors and modulating immune responses. MicroRNAs within these exosomes are crucial in cancer progression, metastasis, and aggressiveness, contributing to high recurrence rates in oral cancer. **Methods**: This review followed PRISMA-ScR guidelines to explore the therapeutic potential of stem cell-derived exosomes in oral cancer. A literature search in PubMed and Web of Science used terms related to "exosomes," "stem cells," and "oral cancer," including studies in English published before March 1, 2024. Original research, clinical trials, *in vitro*, and *in vivo* studies were selected; reviews and conference abstracts were excluded. Two reviewers independently screened and reviewed studies. Data extraction included study characteristics such as exosome origin, cargo, target cells, animal species, sample size, pathways, and primary outcomes. **Results**: This review included nine studies, all conducted *in vitro*, with six also encompassing *in vivo* experiments. Notably, four of these studies were conducted in China. Findings suggest that stem cell-derived exosomes are promising candidates for oral cancer therapy, playing key roles in reducing pro-inflammatory cytokines, inducing apoptosis, enhancing cytotoxicity, inhibiting angiogenesis, and reducing oral cancer cell proliferation. The studies examined various types of exosomes derived from different stem cell sources, including umbilical cord mesenchymal stem cells, cancer stem cells, and other relevant tumor-related cells. **Conclusions**: This review unravels the therapeutic potential of stem cell-derived exosomes as promising tools for oral cancer therapy. Exosomes derived from UC-MSCs, SHED, MenSCs, and hBMSCs reduce inflammation, induce apoptosis, and modulate angiogenesis and metastasis. Offering advantages over conventional treatments, such as low immunogenicity and targeted delivery, further research and clinical trials are essential to validate their safety, efficacy, and mechanisms.

Key words: stem cells, exosomes, oral cancer, therapeutics, immunomodulation

INTRODUCTION

Malignant diseases pose a significant challenge to modern medical science[1]. Despite continuous efforts to develop novel treatment modalities, malignant diseases persist as a significant challenge for researchers owing to their multifaceted nature, genetic heterogeneity, and ability to adapt[2]. According to GLOBOCAN 2022 statistics, around 9.7 million cancer-related deaths were reported in 2022 alone, emphasizing the ongoing battle against this formidable clinical adversary[3].

Malignant tumors of the mouth that affect the lip and oral cavity are known as oral cancers[4]. They can originate from salivary glands or lymphoid tissues, and the most common subtype arises from squamous cells in the oral mucosa[5]. The diverse etiology of this genetic and epigenomic disorder includes tobacco smoking, alcohol consumption, human papillomavirus (HPV) infection, nutritional deficiency, radiation exposure, hereditary predisposition, and the presence of premalignant oral lesions[6,7]. Notably, the consumption of alcohol and tobacco stands out as major risk factors for oral cancer[8]. Oral carcinogenesis is characterized by heterogeneity, which is essential in forming the tumor microenvironment (TME), impacting interactions between tumor and non-tumor cells, and providing resistance to conventional therapies[9]. According to GLOBOCAN 2022, oral cancer ranked as

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the 16th most prevalent form of cancer globally, with a recorded incidence of approximately 389,495 new cases and 188,230 deaths in the year 2022. The incidence rates for lip and oral cavity cancer among males in South and Southeast Asia were highest in Taiwan, followed by Sri Lanka, India, and Pakistan [10]. The incidence and mortality rates of oral cavity cancer in this region are among the highest globally, contributing nearly two-thirds (66%) of all newly reported cases worldwide [3]. This significant incidence rate, especially in this region, underscores an urgent need for innovative therapeutic approaches beyond the current limitations of conventional treatments.

While surgical interventions, chemotherapy, and radiotherapy continue to serve as primary modalities for managing malignant diseases, the persistence of tumor recurrence remains a major challenge, further heightened by the adverse effects associated with therapeutic interventions [11,12]. Hence, there is a paramount interest in identifying novel, reliable therapeutic options capable of early detection of neoplastic events. These therapeutic options will offer significant advantages in combating this life-threatening malignancy and ultimately enhance individual health outcomes and survival [13].

One promising avenue is the study of exosomes, which play a crucial role in intercellular communication and shaping the TME. Exosomes have recently received considerable attention as a novel nanoplatform for drug delivery [14]. Their established function as carriers of various cargoes, including proteins, lipids, DNA, messenger RNA, non-coding RNA, and microRNA (miRNA), serves as a crucial mechanism for intercellular exchange of information and signal transduction [15]. Due to their intrinsic ability to interact with the TME, exosomes present a unique solution to overcoming resistance and recurrence in oral cancer, bridging gaps in current therapeutic approaches [16]. This phenomenon significantly impacts the TME, profoundly affecting immune system evasion, metastasis, angiogenesis, tumor development, and treatment resistance [17]. Consequently, exosomes hold promise as prognostic and diagnostic biomarkers, as well as therapeutic agents. By enabling targeted drug delivery, exosomes could provide a pathway to overcome current treatment resistance and recurrence challenges, especially in oral cancer treatment [18].

Characteristics of stem cells include the ability to differentiate into several cell types, self-renewal, and pluripotency. They can be derived from a variety of vascularized tissues and organs, including the liver, adipose tissue, bone marrow, umbilical cord, cancer cells, and dental tissues, exhibiting migratory and regenerative potentials. Utilizing stem cell-derived exosomes as a targeted medication delivery system presents the promising potential for enhancing drug absorption and distribution within tumor sites [19]. This novel approach could significantly advance anticancer therapy, particularly in resistant forms of oral cancer. This review aims to unravel the therapeutic potential of stem cell-derived exosomes, introducing novel concepts for clinical management and therapeutic options for oral cancer.

METHODS

The review was carried out following the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement for Scoping Reviews (PRISMA-ScR) [20].

Search Strategy

A comprehensive literature search was performed using PubMed and Web of Science databases to identify pertinent studies. The search strategy employed a combination of terms related to "exosomes", "stem cells", and "oral cancer". An English language restriction was applied, and articles published before 1 March 2024 were included in the search.

Study Selection

The search aimed to identify pertinent research that explores the therapeutic potential of stem cell-derived exosomes in oral cancer.

Inclusion and Exclusion Criteria

This review included original research articles, clinical trials, *in vitro* studies, and animal model studies that investigated stem cell-derived exosomes as a potential therapeutic approach for oral cancer. Only studies published in English were included.

Studies were excluded if they did not focus specifically on oral cancer. Additionally, studies that did not involve stem cell-derived exosomes or focused on non-exosomal approaches were excluded. Reviews, meta-analyses, and conference abstracts were excluded due to a lack of original data.

The EndNote citation software was utilised to conduct a three-phase examination process on the articles acquired from the databases. Duplicate files were removed in Phase I. Phase II involved analysing the titles and abstracts. Phase III involved a thorough examination of articles from the selected abstracts. Two

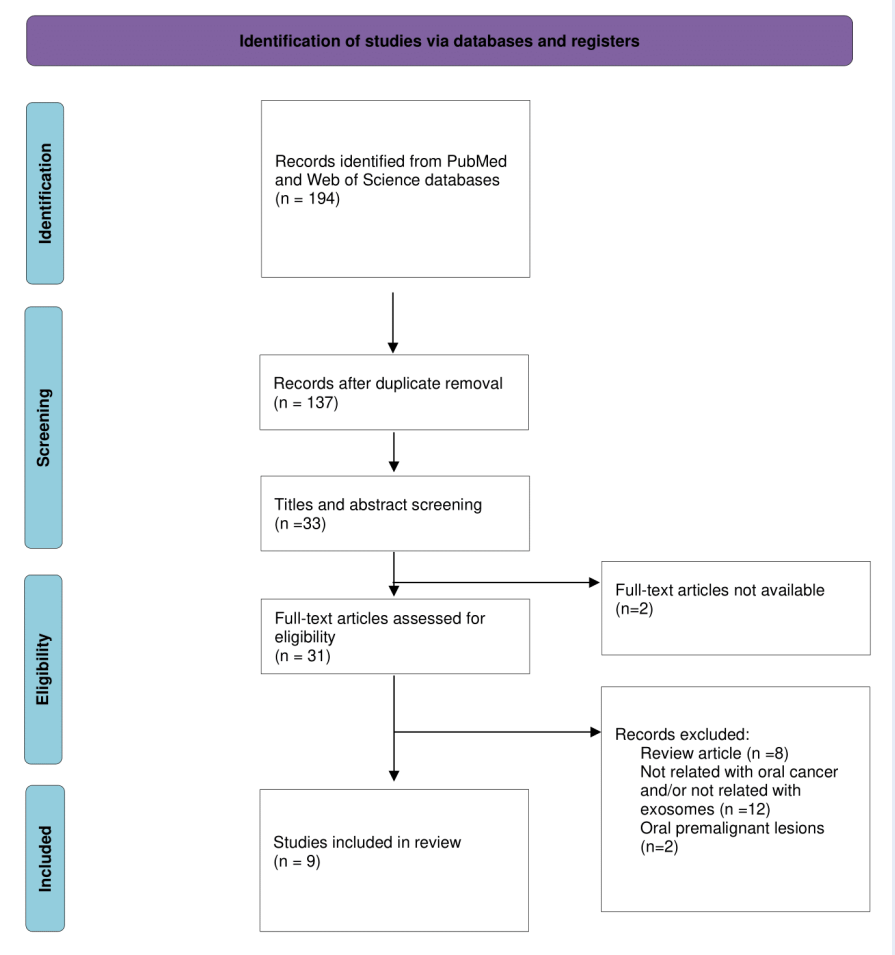

Figure 1: **Study selection flowchart through literature search.**

reviewers, MAM and WNS, conducted separate evaluations of the titles and abstracts of all identified studies. To ensure consistency and minimise bias, the reviewers adhered to a predefined process for article selection and data extraction, which included detailed discussions to resolve any discrepancies. Any disagreements were resolved through consultation with a third reviewer (RM).

Data Extraction and Analysis

For each study included, we utilised a structured data extraction process to gather relevant information, including the location, publication year, exosome origin, exosomal cargo, target cell (for *in vitro* studies), and animal species and sample size (for *in vivo* studies), pathway involved, and primary outcome. The re-viewers jointly reviewed the extracted data to ensure accuracy and consistency in interpretation, thereby reducing variability. This review presents its find-ings through a narrative synthesis methodology ad-hering to the PRISMA-ScR guidelines[20]. Addition-ally, no quality assessment was performed, as scoping reviews aim to inclusively identify all accessible evi-dence and underscore their primary attributes, irre-spective of their quality. **Figure 1** illustrates the liter-ature search process.

Table 1: Characteristics of included *in vitro* studies

Study	Country	Origin of exosomes	Exosomal cargo	Target cells	Pathway involved	Outcome
Abdelwhab *et al.*, 2023 [21]	Egypt	UC-MSCs-exos	HOTAIR	Oral squamous cell carcinoma (OSCC) cell line (SCC-25)	UC-MSCs-exos down-regulated the expression of HOTAIR	UC-MSCs-exos exhibits therapeutic potential against OSCC *in vitro* by modulating inflammation, apoptosis, and HOTAIR expression.
Capik *et al.*, 2023 [22]	Turkey	hiTDEs	miR-1825	SCC-9 (human tongue squamous carcinoma) and FaDu (human hypopharyngeal carcinoma) cell lines	TSC2/mTOR pathway, which was deregulated by miR-1825	Promotes endothelial cell viability, migration, invasion, and angiogenesis.
Chen *et al.*, 2019 [23]	Taiwan	CSC_EVs	miR-21-5p	Human OSCC cell lines, SCC-15 and CAL27, and primary NGFs (PCS-201-018)	β-catenin, PI3K, STAT3, mTOR, and TGF-β1 pathways	CSC_EVs boost cisplatin resistance, clonogenicity, and tumorsphere formation in OSCC cells, while OSCC_EVs heighten metastasis, stemness, and chemoresistance, and worsen survival. OV treatment decreases EV cargo, hampers self-renewal, blocks NGF-CAF transformation, making CSCs sensitive to CDDP.
Liu *et al.*, 2022 [24]	China	SHED-Exo	miR-100-5p and miR-1246	HUVECs were the target cells used in the *in vitro* assays.	A tube formation assay involving endothelial cells	SHED-Exos show potential as a novel therapeutic approach for anti-angiogenic treatment, inhibiting angiogenesis.
Wu *et al.*, 2022 [25]	China	OSCC-CSC-sEVs	lncRNA UCA1, which acts as a ceRNA for miR-134.	The OSCC cell line Cal27 (CL-0265, human oral epithelial cells (HOEC, and HEK-293T cells.	The PI3K/AKT pathway was implicated in the mechanism by which lncRNA UCA1 modulates M2 macrophage polarization by targeting LAMC2.	*In vitro*: OSCC-CSC-sEV UCA1 transfer induces M2 macrophage polarization via LAMC2-mediated PI3K/AKT, aiding tumour progression and immunosuppression. *In vivo*: M2-TAMs enhance OSCC cell migration, invasion, and tumorigenicity by transferring exosomal UCA1 targeting LAMC2.

Continued on next page

Table 1 continued

Study	Country	Origin of exosomes	Exosomal cargo	Target cells	Pathway involved	Outcome
Rosenberger *et al.*, 2019 [26]	Chile	MenSC and UCMSC	*Unclear	HUVEC and human microvascular endothelial cell line	*Unclear	*In vitro*: Treatment of endothelial cells with exosomes leads to increased cytotoxicity, reduced VEGF secretion, and inhibited angiogenesis in a dose-dependent manner. *In vivo*: Intra-tumoral injection of exosomes results in a significant antitumor effect, associated with a loss of tumor vasculature.
Kase *et al.*, 2021 [27]	Japan	OSCC Exo and HSC-4-derived exosomes	*Unclear	HSC-2, -3, -4, and SAS	AKT and ERK signalling pathways	GFR inhibitors might inhibit OSCC cell malignancy by directly inhibiting EGFR downstream signalling and the cellular uptake of OSCC cell-derived exosomes via macropinocytosis.
Wang *et al.*, 2023 [28]	China	CAFs exo	miRNA (hsa-miR-139-5p) Proteins (ACTR2, EIF6) mRNAs (PIGR, CD81, UACA, PTTG1IP)	hOMF	mRNAs and miRNAs in CAFs-Exo with OSCC in immunomodulation	CAFs-Exo modulate tumor immune regulation via hsa-miR-139-5p, ACTR2, and EIF6, while PIGR, CD81, UACA, and PTTG1IP emerge as potential targets for OSCC treatment

Continued on next page

Table 1 continued

Study	Country	Origin of exosomes	Exosomal cargo	Target cells	Pathway involved	Outcome
Xie *et al*., 2019 [29]	China	hBMSCs	miRNA-101-3p	HEK-293T cells, human oral cancer cell lines (CAL27, TCA8113, SCC9, SCC25, HN4), and normal oral cell line (NOK	COL10A1 pathway	Exosomes derived from hBMSCs overexpressing miR-101-3p inhibit COL10A1 and inhibit progression, migration, proliferation and invasion in oral cancer cells *in vitro* and *in vivo*, suggesting a potential therapeutic strategy for oral cancer treatment.

Abbreviations: Umbilical cord mesenchymal stem cells exosomes (**UC-MSCs exo**); HOX transcript antisense intergenic RNA (**HOTAIR**); Oral squamous cell carcinoma (**OSCC**); human umbilical vein endothelial cells (**HUVECs**); Hypoxia-induced tumor exosomes (**hiTDEs**); Tuberous sclerosis complex 2 (**TSC2**); mammalian target of rapamycin (**mTOR**); Cancer stem cells secrete extracellular vesicles (**CSC_EVs**); Non-obese diabetic/severe combined immunodeficiency (**NOD/SCID**); Cisplatin, cis-diamminedichloroplatinum (**CDDP**); Phosphoinositide 3-kinase (**PI3K**); Signal transducer and activator of transcription 3 (**STAT3**); Transforming growth factor beta 1 (**TGF-β1**); Ovatodiolide (**OV**); normal gingival fibroblasts (**NGFs**); cancer-associated fibroblasts (**CAF**); Stem cells from human exfoliated deciduous teeth exosomes (**SHED Exo**); Chick Chorioallantoic Membrane (**CAM**); long non-coding RNA (**lncRNA**); urothelial carcinoma-associated 1 (**UCA1**); competing endogenous RNA (**ceRNA**); Tumor-associated macrophages (**TAMs**); Phosphatidylinositol 3-kinase/Protein kinase B (**PI3K/AKT**); Laminin subunit gamma 2 (**LAMC2**); Menstrual blood-derived stem cells (**MenSC**); Vascular endothelial growth factor (**VEGF**); Human squamous cell carcinoma (**HSC**); extracellular signal-regulated kinase (**ERK**); Growth factor receptor (**GFR**); Epidermal growth factor receptor (**EGFR**); human oral mucosal fibroblasts (**hOMF**); Actin-related protein 2 (**ACTR2**); Eukaryotic translation initiation factor 6 (**EIF6**); Polymeric immunoglobulin receptor (**PIGR**); Cluster of differentiation 81 (**CD81**); Uveal autoantigen with coiled-coil domains and ankyrin repeats (**UACA**); Pituitary tumor-transforming gene 1 protein interacting protein (**PTTG1IP**); human bone marrow mesenchymal stem cells (**hBMSCs**); Tongue squamous cell carcinoma cell line 8113 (**TCA8113**); Collagen type X alpha 1 chain (**COL10A1**).

*The exact pathways and some exosomalcargo involved remain unclear, and further research is required to identify theunderlying mechanisms.

Pathway descriptions:

- **TSC2 (Tuberous Sclerosis Complex 2)**: A negative regulator of mTOR (mechanistic target of rapamycin), a key proteincomplex that controls cell proliferation, survival, and autophagy.
- **Endothelial Cell Tube Formation Assay**: Assesses angiogenesis by evaluating capillary-like structure formation.
- **lncRNA UCA1**: Promotes M2 macrophage polarisation by targeting LAMC2, a protein thatregulates cell adhesion and migration, and activating the PI3K/AKT pathway,which plays a role in immune response and tissue repair.
- **AKT Pathway**: Regulates cell survival and growth.
- **ERK Pathway**: Controls cell proliferation and stress response.
- **COL10A1 Pathway**: Regulates cartilage development, extracellular matrix remodelling, andfibrosis, influencing tumour progression and metastasis.

RESULTS

Through electronic search methods, a total of 194 articles of potential relevance were identified. After removing duplicates and assessing titles and abstracts, 33 articles were selected for full-text evaluation. Following a thorough analysis of the full-text articles, 9 met the predefined inclusion criteria and were consequently included in the review.

The included studies demonstrated diverse outcomes related to exosomes in oral cancer. One study investigating umbilical cord mesenchymal stem cell-derived exosomes (UC-MSCs-exos) found that they significantly reduced tumour necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) levels in a dose-dependent manner, with statistical analysis revealing significant differences between groups (TNF-alpha: $F = 36.98$, $p < 0.001$; IL-6: $F = 43.48$, $p < 0.001$)[21]. Another study involving hypoxia-induced tumour-derived exosomes (hiTDEs) showed that they transferred miR-1825 to human umbilical vein endothelial cells (HUVECs), enhancing angiogenesis[22]. Additionally, a study exploring ovatodiolide (OV) treatment (4 μM) found that it downregulated CAF markers and inhibited NGF-derived CAF transformation. At the same time, OV-treated CSC-derived exosomes suppressed TGF-β1 secretion (1.53-fold, $p < 0.05$) and reduced cancer-associated fibroblast (CAF) migration (1.71-fold, $p < 0.001$) and invasion (1.95-fold, $p < 0.001$)[23]. SHED-derived exosomes (SHED-Exos) significantly inhibited endothelial cell growth, with Ki67 expression reduced from 82.1 $\pm$ 2.9% (control) to 59.2 $\pm$ 4.2% (treated)[24]. Furthermore, stem cell-derived exosome treatment also increased apoptosis in endothelial cells from 19.5 $\pm$ 2.0% to 46.6 $\pm$ 2.0%[26]. Another study demonstrated that cancer-associated fibroblast exosomes (CAFs-Exo) promoted oral squamous cell carcinoma (OSCC) proliferation and immunosuppression by regulating specific genes associated with tumour progression and immune response[28]. Lastly, human bone marrow-derived mesenchymal stem cell (hBMSC)-derived exosomes overexpressing miR-101-3p inhibited OSCC progression, and OSCC-CSC-derived exosomal Urothelial Carcinoma-Associated 1 (UCA1) enhanced M2 macrophage polarisation ($p < 0.05$), inhibited T-cell proliferation, and promoted OSCC migration and tumorigenicity *in vivo* ($p < 0.001$)[25].

Table 1 and **Table 2** outline the characteristics of the nine studies incorporated in this review. Furthermore, all nine studies were conducted *in vitro*, with six studies encompassing both *in vivo* and *in vitro* aspects. Notably, four of the studies were conducted in China.

A total of 9 types of exosomes were utilized in the included studies, namely: umbilical cord UC-MSCs-exos, hiTDEs, cancer stem cell-derived extracellular vesicles (CSC_EVs), stem cells from human exfoliated deciduous teeth-derived exosomes (SHED-Exo), oral squamous cell carcinoma cancer stem cell-derived small extracellular vesicles (OSCC-CSC-sEVs), menstrual blood-derived mesenchymal stem cells (MenSC), HSC-4 cell line-derived exosomes (human squamous cell carcinoma 4-derived exosomes), CAFs exosomes, and hBMSCs.

DISCUSSION

Summary of Evidence

Our objective was to assess the therapeutic potential of stem cell-derived exosomes in the treatment of oral cancer through a comprehensive evaluation. The most significant findings were as follows: Exosomes derived from stem cells identified as potential therapeutic agents include UC-MSCs, hiTDEs, SHED-Exo, MenSCs, CAF exosomes, and hBMSCs. These exosomes demonstrate multifaceted effects, including the reduction of pro-inflammatory cytokines, which are known to fuel tumor growth and progression[30]. Furthermore, they play a crucial role in inducing apoptosis, a process vital for eliminating cancerous cells[22,24]. Moreover, stem cell-derived exosomes have been shown to down-regulate HOX transcript antisense intergenic RNA (HOTAIR), an oncogenic long non-coding RNA associated with aggressive tumor behavior in oral cancer[21]. On the other hand, CSC_EVs play a crucial role in reshaping the tumor microenvironment (TME) by potentially inducing the transformation of normal gingival fibroblasts (NGFs) into cancer-associated fibroblasts (CAFs), thereby promoting their metastatic potential. Simultaneously, cancer stem cells contribute significantly to the progression of oral cancer by altering the TME[23,31,32]. Through the secretion of CSC_EVs, these cells enhance self-renewal, metastasis, and resistance to cisplatin in cancer cells. Additionally, CSC_EVs actively stimulate endothelial cell survival, migration, and invasion, crucial processes for tumor development, sustenance, and angiogenesis[23,33]. However, the addition of specific treatments has been shown to inhibit angiogenesis by exosomes, which is essential for tumor growth and metastasis[23].

Therapeutic Potential of Stem Cell-Derived Exosomes in Oral Cancer

EVs are lipid bilayer vesicles that cells constantly release into the extracellular environment. EVs consist of three different types: exosomes, microvesicles,

Table 2: Characteristics of included *in vivo* studies

Study	Animal species	Sample size	Outcomes
Chen *et al.*, 2019[23]	Mice	NR	Ovatodiolide treatment suppresses oral squamous cell carcinoma tumorigenesis by reducing EV cargo and re-sensitizing cancer stem cells to cisplatin, effectively curbing tumour growth and metastasis.
Liu *et al.*, 2022[24]	Mice	25	Exosomes from stem cells of human deciduous exfoliated teeth show potential as a novel therapeutic approach for anti-angiogenic treatment, inhibiting angiogenesis.
Wu *et al.*, 2022[25]	Mice	18	M2-TAMs enhance oral squamous cell carcinoma cell migration, invasion, and tumorigenicity by transferring exosomal UCA1 targeting LAMC2.
Rosenberger *et al.*, 2019[26]	Hamsters	16	Intra-tumoral injection of exosomes results in a significant antitumor effect, associated with a loss of tumor vasculature.
Wang *et al.*, 2023[28]	Mice	15	Exosomes from cancer-associated fibroblasts promoted oral squamous cell carcinoma tumor growth and proliferation, with immunosuppressive effects. They regulated immune-related genes (*PIGR, CD81, UACA, PTTG1IP*) and facilitated tumorigenesis in nude mice.
Xie *et al.*, 2019[29]	Mice	54	Bome marrow mesenchymal stem cells-derived exosomes carrying miR-101-3p inhibited oral cancer cell proliferation, invasion, and migration by targeting COL10A1

Abbreviations: **EV**: extracellular vesicle, **M2-TAMs**: Tumor-associated macrophages M2

Table 3: Sources of stem cell-derived exosomes and their application in oral cancer

Source of stem-derived exosomes	Application
Umbilical cord mesenchymal stem cells derived exosomes	Reduction of pro-inflammatory cytokines, induction of apoptosis, increased cytotoxicity, and inhibition of angiogenesis
Hypoxia-induced tumour-derived exosomes	Promotion of endothelial cell viability, migration, invasion and angiogenesis.
Stem cells from human exfoliated deciduous teeth derived exosomes	Inhibit cell proliferation, and migration and induce apoptosis
Menstrual blood-derived mesenchymal stem cells exosomes	Increased cytotoxicity and inhibition of angiogenesis, accompanied by reduced VEGF secretion, contribute to the anti-tumour effects
Human bone marrow-derived mesenchymal stem cells exosomes	Inhibit cell proliferation, invasion, and migration of oral cancer cells

and apoptotic bodies[34,35]. The molecules carried by these EVs include RNAs, miRNAs, proteins, DNA fragments, and noncoding RNAs, which are commonly carried within EVs as cargo and could potentially function as therapeutic and diagnostic biomarkers for OSCC[36,37]. The biological effects of exosomes on recipient cells are influenced by their cell of origin, which also affects their composition and ability to target cells. MSCs generate exosomes that interact with different types of cells, affecting their biological properties and possibly controlling disease progression and maintaining physiological homeostasis, in contrast to exosomes produced from human epidermal carcinoma cells (A431-exo)[38]. MSC-derived exosomes exhibited greater tumor accumulation, penetration, and distribution within tumor tissues in an animal model of head and neck cancer[39]. These results imply that exosomes produced from MSCs may have greater potential for targeted tumor therapy.

The promising role of stem cell-derived exosomes in oral cancer therapy is underscored by their ability to down-regulate pro-inflammatory cytokines, in-

duce apoptosis, and inhibit oncogenic processes[40]. When compared to other emerging cancer therapies, such as targeted therapies (including immune checkpoint inhibitors, small-molecule inhibitors, monoclonal antibodies, and CAR-T cell therapy), exosome-based therapies offer several potential advantages[41]. While these conventional treatments are highly effective for specific cancers, including oral cancer, they can present challenges such as high costs, complex administration, and immune-related adverse events. In contrast, exosomes are naturally derived, with low immunogenicity and excellent biocompatibility, enabling them to deliver therapeutic molecules directly to tumor cells[42]. These distinct characteristics position exosomes as a promising treatment strategy with the potential to overcome some limitations of conventional therapies[43]. Furthermore, exosome-based therapies can modulate gene expression and cellular signaling without permanently altering DNA, providing a safer and more controlled intervention[16].

Exosomes released by stem cells demonstrate the ability to inhibit tumor growth, invasion, and migration, as well as trigger programmed cell death[44]. A study conducted by Abdelwhab *et al.* in 2023 demonstrated that treatment with UC-MSCs-exos exerted a suppressive effect on OSCC cell lines, indicating a potential therapeutic role. Notably, UC-MSCs-exos treatment led to a substantial decline in the levels of IL-6 and TNF-alpha, with the extent of reduction depending on the dosage[21]. IL-6 and TNF-alpha are recognized for their pivotal involvement in numerous tumorigenic mechanisms, including angiogenesis and sustaining proliferative signaling in solid cancers[45]. Dysregulation of IL-6 signaling has been implicated in promoting cancer cell proliferation and survival[46]. Furthermore, the role of HOTAIR has been recognized as a tumor suppressor in head and neck tumors through its function as a molecular sponge for miR-148a[47]. UC-MSCs-exos have an inhibitory effect on the expression of HOTAIR in OSCC cells, leading to the inhibition of cell proliferation and tumor development[21]. Another study conducted by Rosenberger *et al.* in 2019 demonstrated that treating endothelial cells with MenSCs and UC-MSCs resulted in increased cytotoxicity, decreased secretion of vascular endothelial growth factor (VEGF), and inhibited the formation of new blood vessels both *in vitro* and *in vivo*[26]. The included studies showcased the therapeutic potential of exosomes derived from various stem cells, as outlined in **Table 3**. The proposed model for the therapeutic utilization of exosomes derived from stem cells could be utilized to facilitate anti-proliferative effects in anticancer treatment, as depicted in **Figure 2**.

A significant challenge in oral cancer management is chemoresistance[48,49]. Cancer stem cells (CSCs), a small subpopulation of tumor cells distinguished by specific markers, are implicated in disease progression and treatment resistance in various cancers. CSC-derived small extracellular vesicles (sEVs) are particularly responsible for promoting tumor growth and therapy resistance[49,50]. These CSCs secrete sEVs that contribute to an immunosuppressive tumor microenvironment and facilitate M2 macrophage polarization, as observed in glioblastoma and colon cancer[51,52]. M2 tumor-associated macrophages (M2-TAMs) are among the most abundant immunosuppressive cell types in the tumor microenvironment[53]. Additionally, CSCs exhibit characteristics such as enhanced self-renewal, drug efflux, promotion of epithelial-mesenchymal transition (EMT), and secretion of oncogenic factors, remodeling the tumor microenvironment to promote cancer progression[54]. Therefore, targeting CSCs has become a priority in OSCC management.

A study conducted by Chen *et al.* in 2019 reported that CSC_EVs enhance the development of resistance to CDDP, the ability to form colonies, and the formation of tumor spheres in OSCC cells. The bioinformatics research indicated that EVs derived from OSCC_EVs contain a high concentration of microRNA (miR)-21-5p. This specific microRNA is linked to enhanced metastasis, stem cell-like properties, resistance to chemotherapy, and poor prognosis in patients[23]. Moreover, CSC_EVs induced a CAF phenotype in NGFs, which in turn enhanced the oncogenic properties of OSCC cells[55]. Treatment with OV, a bioactive compound from *Anisomeles indica*, successfully inhibited the development of OSCC and decreased the cargo content in CSC_EVs. This inhibition disrupted the interaction between EVs and the TME, leading to a reduction in self-renewal and transformation of normal fibroblasts into cancer-associated fibroblasts (NGF-CAF)[23]. The results provide compelling evidence that, despite CSCs promoting oral cancer progression and chemoresistance, treatment with OV decreased the oncogenic content of EV cargos in both OSCC cells and CSCs.

A study conducted by Wu *et al.* in 2022 highlighted the pivotal role of OSCC-CSC-derived exosomes in modulating the tumor microenvironment. These exosomes transfer UCA1, a long non-coding RNA, which targets LAMC2 to promote M2 macrophage polarization[25]. This polarization significantly contributes to immunosuppression by inhibiting $CD4^+$ T-cell

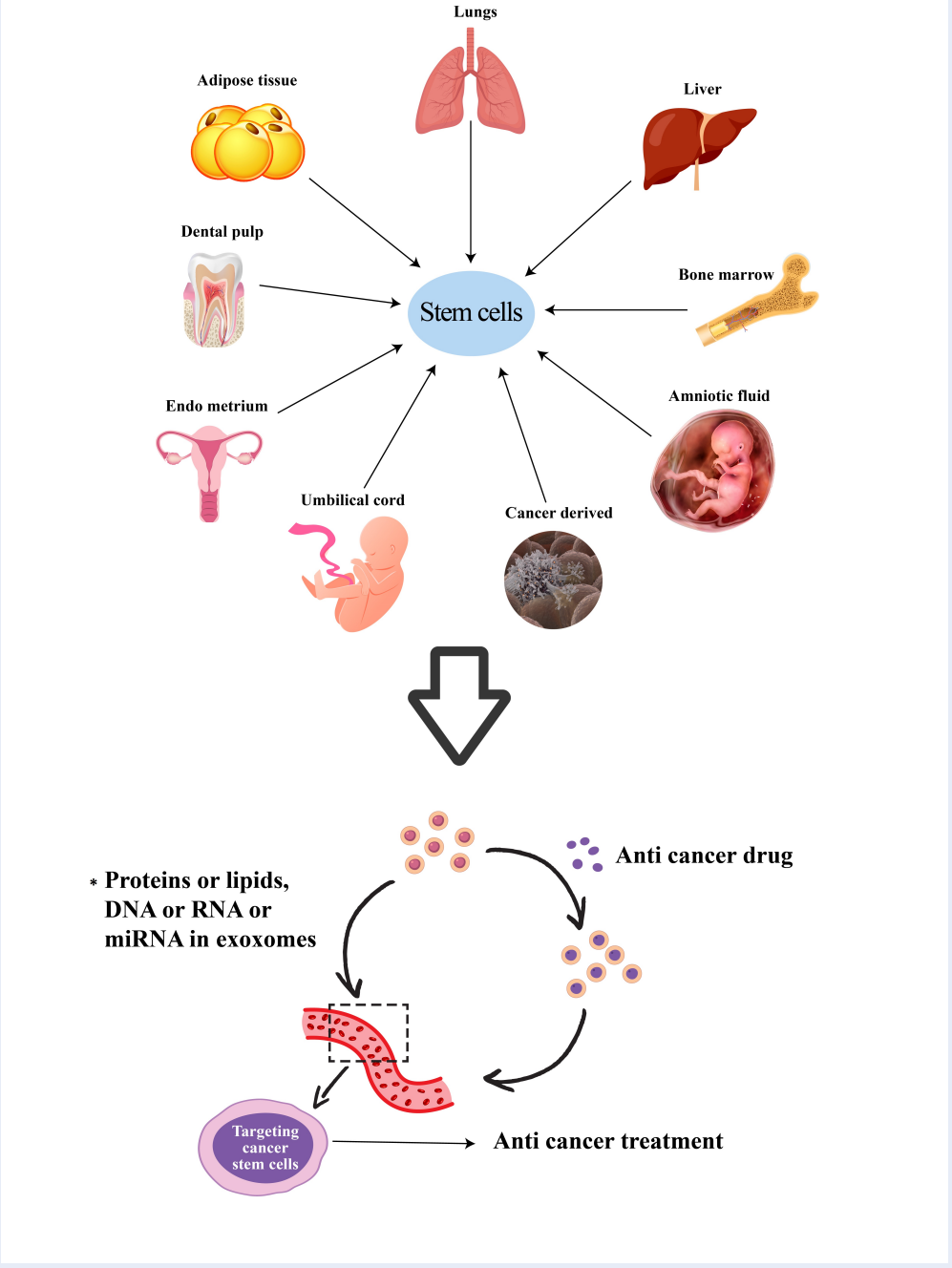

Figure 2: **The proposed model for the therapeutic utilisation of exosomes derived from stem cells could be utilised to facilitate anti-proliferative effects in anti-cancer treatment**. *These cargoes induce apoptosis, inhibit proliferation, and modulate the tumour microenvironment.

proliferation and IFN-γ production *in vitro* and *in vivo*. Moreover, M2-TAMs influenced by exosomal UCA1 enhance OSCC cell migration, invasion, and tumorigenicity[25,56]. LAMC2, a laminin gamma 2 chain, is known to drive aggressive cancer behavior through interactions with microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) and has been associated with macrophage infiltration in lung cancer[57,58]. It also mediates chemotherapy sensitivity in ovarian cancer via exosomal miR-146a and the PI3K/AKT pathway[59]. These findings reveal that LAMC2 facilitates the effects of OSCC-CSC-derived exosomal UCA1, promoting M2 macrophage polarization through the PI3K/AKT pathway and further emphasizing its central role in OSCC progression.

Therapeutic agents like proteins, RNAs, miRNAs, small interfering RNAs (siRNAs), and targeted drugs have been integrated with exosomes to improve bioactivity and facilitate targeted drug delivery[60]. This integration is achieved through methods such as electroporation, ultrasonication, parental cell alteration, or direct incubation[61]. Following the integration of therapeutic agents into exosomes, they are able to penetrate the targeted recipient cell, facilitating the subsequent release of the intended cargo. The most common cargo is miRNAs, which are of great interest owing to their essential role in post-transcriptional gene regulation[62]. A recent study by Liu *et al.* (2022) demonstrated that SHED-Exos are enriched with miR-100-5p and miR-1246, which are transferred to endothelial cells, leading to a reduction in tube formation through the downregulation of vascular endothelial growth factor A (VEGFA) expression. VEGFA plays a critical role in tumor angiogenesis, growth, and metastasis, highlighting the potential of SHED-Exos as a novel therapeutic strategy for anti-angiogenic treatment, as evidenced by their ability to inhibit angiogenesis both *in vitro* and *in vivo*[24]. In contrast, a more recent study observed that SHED-Exo aggregates promoted angiogenesis, which contrasts with the findings of Liu *et al.* (2022). The study showed that OSCC-released miR-1825 was efficiently transferred to endothelial cells via exosomes, contributing to angiogenesis[22]. Moreover, miR-1825 in endothelial cells was found to promote angiogenesis by disrupting the TSC2/mTOR axis, which is known to be involved in angiogenic processes[63]. The TSC/mTOR axis in endothelial cells is essential for vasculature and embryogenesis, with cancer-related kinases modulating mTOR activity by inactivating the TSC complex[63,64]. TSC2, an upstream negative regulator of mTOR, plays a key role in regulating processes such as cell proliferation and angiogenesis and is often dysregulated in various cancers[65]. Additionally, mTOR is involved in the early response to hypoxia, inducing endothelial cell proliferation primarily through Akt signaling[22]. These contrasting findings underscore the paradoxical role of exosomes in angiogenesis, where they can either suppress or promote angiogenesis depending on the tumor microenvironment. In addition to those highlighted in this review, additional miRNAs such as miR-1825, miR-21-5p, miR-100-5p, miR-1246, and miR-101-3p may hold substantial implications in oral cancer. The precise functions and contributions of these miRNAs might be elucidated in forthcoming studies.

Limitations of Included Studies

Cell lines used *in vitro* for oral cancer research are essential for discovering potential therapeutic targets; however, their responses may differ from those of cells within an organism[66]. While *in vitro* studies provide valuable insights into the underlying mechanisms, methodological differences such as variations in exosomal molecular cargo, donor cell types, and cell culture conditions may limit the generalizability of the results. Out of the nine studies reviewed, six included *in vivo* components, which are more reflective of real-world scenarios, but these *in vivo* studies also exhibited varying animal species and small sample sizes, with one study failing to report its sample size[23]. Furthermore, none of the studies provided long-term follow-up data, and none specified the histological grade of oral cancer, both of which may have influenced the outcomes. Regarding the role of MSC-derived exosomes in angiogenesis, one study reported that MSC-derived exosomes enhance angiogenesis[22], while other studies suggested that they inhibit blood vessel formation[24,26]. To validate the specificity of these exosomes, well-controlled studies with standardized methodologies and longer follow-up periods are needed to confirm the findings, as this would significantly enhance the clinical applications of stem cell-derived exosomes in oral cancer treatment.

Limitations of This Study

Some potentially pertinent studies may have been overlooked owing to their absence from the indexed databases utilized in the search process. The quality of the studies was not assessed in this review, in accordance with the fundamental characteristics of reviews.

Future Perspectives

Advanced studies on exosomes in oral cancer are crucial for elucidating their roles in chemotherapy re-

sistance, tumor phenotypic alteration, immunological control, angiogenesis, and metastasis. Despite progress, several questions remain unanswered and warrant further exploration. Exosomes represent a promising frontier in drug delivery owing to their low immunogenicity and superior biocompatibility, offering potential applications in diagnosis and prognosis[67]. As indicated by our included studies, stem cell-derived exosomes unravel the therapeutic potential for oral cancer.

To advance this research, it will be essential to explore the molecular mechanisms that govern exosome-mediated communication between cancer cells and the tumor microenvironment. This can include investigating the role of exosome cargo, such as specific proteins, DNAs, RNAs, miRNAs, and lipids, in promoting or inhibiting tumor progression[68]. Additionally, future studies should investigate the modulation of exosome release in response to different environmental stimuli, such as hypoxia or drug treatment, to better understand how these factors influence their therapeutic potential.

Furthermore, our findings provide a foundation for future research using *in vivo*, *in vitro*, and preclinical trials to evaluate the effectiveness of treatments for oral cancer. In forthcoming research, it will be imperative to evaluate the efficacy of exosomes in a metastatic disease model. To achieve this, it is crucial for exosomes to specifically target tumor sites in the body after being administered systemically. Previous research has demonstrated that exosomes released by different types of cells are capable of reaching tumors. Nonetheless, different exosome subtypes may exhibit distinct innate homing capabilities *in vivo*. Hence, conducting focused studies on stem cell-derived exosomes is crucial for evaluating their biodistribution and tumor-homing characteristics[14]. In clinical applications, it will be critical to assess the safety and toxicity profile of exosome-based therapies. Well-designed phase I and II clinical trials that evaluate the pharmacokinetics, biodistribution, and immune response to exosomes will be essential in confirming their clinical feasibility. Long-term follow-up studies will be needed to assess the sustained efficacy and potential adverse effects of exosome-based treatments, particularly in patients with advanced-stage or metastatic oral cancer.

Finally, investigating the potential for combination therapies, where exosomes are used alongside conventional chemotherapy, immunotherapy, or targeted therapies, could provide synergistic benefits. This approach could enhance the overall treatment response, reduce resistance, and improve patient outcomes. By incorporating these research directions into future studies, we can better define the clinical applications of stem cell-derived exosomes in oral cancer treatment and significantly enhance their therapeutic potential.

CONCLUSIONS

This review unravels the therapeutic potential of stem cell-derived exosomes, which represent promising therapeutic tools for oral cancer owing to their ability to modulate tumor progression, inflammation, and chemoresistance. Exosomes from sources such as UC-MSCs, SHED, MenSCs, and hBMSCs offer promising strategies by reducing pro-inflammatory cytokines, inducing apoptosis, and modulating angiogenesis and metastasis. Exosome-based therapies have advantages over conventional treatments, including low immunogenicity, improved biocompatibility, and targeted drug delivery. However, further research is needed to explore their mechanisms, particularly in metastasis and chemotherapy resistance. Clinical trials assessing their safety and efficacy are essential for advancing their therapeutic use in oral cancer. Future studies will be critical in validating their effectiveness and integrating them into cancer treatment strategies.

ABBREVIATIONS

A431-exo: Exosomes derived from human epidermal carcinoma cells (A431), **Akt**: Protein Kinase B, **CAF**: Cancer-Associated Fibroblast, **CAFs-Exo**: Cancer-Associated Fibroblast Exosomes, **CAR-T**: Chimeric Antigen Receptor T-cell, **CDDP**: Cisplatin, **CSC**: Cancer Stem Cell, **CSC_EVs**: Cancer Stem Cell-Derived Extracellular Vesicles, **EMT**: Epithelial-Mesenchymal Transition, **EVs**: Extracellular Vesicles, **GLOBOCAN**: Global Cancer Observatory, **HOTAIR**: HOX Transcript Antisense Intergenic RNA, **HPV**: Human Papillomavirus, **HSC-4**: Human Squamous Cell Carcinoma 4, **HUVECs**: Human Umbilical Vein Endothelial Cells, **hBMSC**: Human Bone Marrow-Derived Mesenchymal Stem Cell, **hBMSCs**: Human Bone Marrow-Derived Mesenchymal Stem Cells, **hiT-DEs**: Hypoxia-Induced Tumor-Derived Exosomes, **IFN-γ**: Interferon-gamma, **IL-6**: Interleukin-6, **LAMC2**: Laminin Gamma 2 Chain, **MenSCs**: Menstrual Blood-Derived Mesenchymal Stem Cells, **miR-100-5p**: MicroRNA-100-5p, **miR-101-3p**: MicroRNA-101-3p, **miR-1246**: MicroRNA-1246, **miR-146a**: MicroRNA-146a, **miR-1825**: MicroRNA-1825, **miR-21-5p**: MicroRNA-21-5p, **miRNA**: MicroRNA, **MSCs**: Mesenchymal Stem Cells,

M2-TAMs: M2 Tumor-Associated Macrophages, **mTOR**: Mechanistic Target of Rapamycin, **NGF-CAF**: Normal Gingival Fibroblasts transformed into Cancer-Associated Fibroblasts, **NGFs**: Normal Gingival Fibroblasts, **OSCC**: Oral Squamous Cell Carcinoma, **OSCC-CSC-sEVs**: Oral Squamous Cell Carcinoma Cancer Stem Cell-Derived Small Extracellular Vesicles, **OV**: Ovatodiolide, **PI3K/AKT**: Phosphoinositide 3-Kinase/Protein Kinase B, **PRISMA-ScR**: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement for Scoping Reviews, **SHED**: Stem Cells from Human Exfoliated Deciduous Teeth, **SHED-Exo**: Stem Cells from Human Exfoliated Deciduous Teeth-Derived Exosomes, **siRNA**: Small Interfering RNA**TME**: Tumor Microenvironment, **TNF-alpha**: Tumor Necrosis Factor-alpha, **TSC2**: Tuberous Sclerosis Complex 2, **TSC2/mTOR**: Tuberous Sclerosis Complex 2/Mechanistic Target of Rapamycin, **UC-MSCs**: Umbilical Cord Mesenchymal Stem Cells, **UCA1**: Urothelial Carcinoma-Associated 1, **VEGF**: Vascular Endothelial Growth Factor, **VEGFA**: Vascular Endothelial Growth Factor A

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AUTHOR'S CONTRIBUTIONS

(I) Conception, data curation, data analysis, methodology and writing-original draft: MAM; (II) Administrative support, review and editing: WNS, TPK, SM, KMFM, NM; (III) Data curation and formal analysis: MAM, RM, WNS; (IV) Collection and assembly of data: MAM, RM, WNS; (V) Data analysis and interpretation: MAM, RM, WNS, TPK, SM, KMFM; (VI) Final approval of manuscript: All authors

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Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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