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In Vitro Anti-tumor Effects of Photodynamic Therapy on Oral Squamous Cell Carcinoma: A Review

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Abstract

Introduction: Due to the increasing prevalence and high mortality rate of oral squamous cell carcinoma (OSCC) and problems with its routine treatments, more recent modalities like photodynamic therapy (PDT) have been developed. PDT effectively destroys tumor cells with minimum side effects. Research on *in vitro* effects of PDT may be helpful in determining the molecular mechanisms responsible for its effectiveness and can lead to the development of more efficient techniques. The aim of this study was to review the use of PDT in OSCC among *in vitro* studies.

Methods: A literature search for English articles on PDT in OSCC was performed in PubMed, Scopus, Google Scholar, and Web of Science. Data were extracted based on the inclusion/exclusion criteria, which were detailed using the PICO framework: all eligible *in vitro* studies evaluating the effects of PDT on the viability of OSCC compared to controls without PDT were included.

Results: Forty-one out of 567 studies were selected. The tongue was the most common OSCC site, 5-aminolevulinic acid was the most used photosensitizer (PS), cell viability/toxicity and apoptosis were the most evaluated outcomes, and lasers with wavelengths of 600-700 nm were the most common light sources and wavelengths respectively.

Conclusion: PDT showed promising effects on reducing the viability of OSCC cells. Cell lines from various sources or even those originating from the same location sometimes responded differently to the same protocol. Considering the favorable results obtained from natural PSs and regarding their additional health-promoting properties, their use in future investigations with different cell lines and light specifications is recommended.

Keywords: Photodynamic therapy, Photosensitizing agents, Oral cancer, Mouth neoplasms

Introduction

Globally, about 650 000 new cases of head and neck cancer are diagnosed each year, and the annual number of deaths from this disease is about 350 000.[1] Oral and pharyngeal cancers are the sixth most common cancers worldwide[2] and more than 90% are squamous cell carcinomas (SCCs).[3] The 5-year survival rate of oral cancer is 40%, which is even lower in underdeveloped countries, and if diagnosed at an early stage, it may increase to 80%.[4] However, prognosis worsens as the disease progresses and is poor when there is limited access to the tumor site. Therefore, early detection can lead to better survival rates and fewer complications.[5] Treatment depends on the stage at diagnosis, the location of the lesion, and the extent of access to the area.[5] Due to their proximity to vital structures, oral cancers are difficult to treat, and functional consequences such as speech impairment, breathing, eating, and aesthetic issues may occur as a result of the tumor itself or the administered treatments.[6] Oral cancer management mainly include surgery, radiotherapy, and chemotherapy. Additionally, depending on the patient's specific requirements, further treatments involving dental, nutritional and speech issues, audiometry, occupational and physical therapies, and psychosocial therapies may also be required.[5]

Photodynamic therapy (PDT) is a promising therapeutic modality for cancer treatment.[7] It involves the use of a photosensitizer (PS), which, after excitation with a specific wavelength of light, produces cytotoxic oxygen free radicals that are capable of destroying cells via the induction of apoptosis or necrosis. PS uptake is lower in normal tissues compared to tumors since it is more readily absorbed by cells with a high proliferation rate like cancer cells; also, PS must adhere to the wall of blood vessels,

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and the nature of the different sizes and characteristics of blood vessels in tumor and normal tissues, as well as the physiological types of vessels in different organs, determine where PS will most likely localize.[8] Therefore, when the PS is activated during PDT, it has the ability to destroy the neoplasm without destroying the surrounding normal tissues. In general, PDT compared to other conventional treatments is a local, minimally invasive, and well-tolerated therapeutic approach. While selectively destroying malignant cells and tissues, it is not affected by drug resistance and does not have the systemic side effects of other routine treatment methods like chemotherapy.[9,10] Cancer tissue destruction by PDT can be a result of direct cytotoxicity, vascular injury or a local inflammatory response that subsequently leads to a systemic anti-tumor immunological effect.[11-13]

The concept of PDT was initially introduced by Oscar Raab in 1898, who found that paramecia incubated with a fluorescent dye were killed after being exposed to light.[14] In 1960, Lipson and Schwartz used this concept and uncovered the diagnostic features and therapeutic effects of a hematoporphyrin derivative (HpD) on cancer. This substance was used by Kelly and Snell in 1976 to study the effect of PDT on human bladder cancer for the first time. Photofrin, a purified form of HpD received its first approval to be applied in the PDT treatment of bladder cancer by a Canadian health agency in 1993 and was the first PS approved by the US Food and Drug Administration (FDA) for cancer treatment in 1995.[15,16] It has gained approval by the FDA to treat esophageal cancer (1995) and non-small cell lung cancer (1998).[17]

PDT can be used alone or in combination with chemotherapy or other modalities like surgery, especially in larger lesions.[18] Generally, it has shown successful results in early head and neck cancers and dysplasia.[19-23] PDT has been more successful in the treatment of superficial lesions because PS activation occurs by irradiation at a depth of 2 to 10 mm. This is due to a combination of the tissue characteristic and the physical properties of the applied light wavelength. Neoplasms situated at a > 10 mm depth can benefit from interstitial PDT, in which laser fibers are placed deep in the tissue so that they can be used as light sources.[12] One of the advantages of this method is that collagen and sub-epithelial elastin remain intact, which accelerates tissue repair and maintains esthetics with minimal scar formation.[24]

Multiple studies on PDT using various light-sensitive materials and light sources on different oral cancer cells have been performed. A number of reviews, which have mainly evaluated clinical results, have been conducted on PDT. We found only one review in 2019 on laboratory investigations, which mainly focused on PSs and *in vitro* models.[25-28] In addition to being a major prerequisite of clinical studies, *in vitro* research provides valuable data on the cellular and molecular mechanisms involved in the efficacy of PDT and enables the development of novel methods to improve the effectiveness of this treatment modality. Therefore, updated information on *in vitro* findings is essential to increase available knowledge about how oral cancer cells react to the most recent and ever-increasing materials and irradiation specifications used in PDT.

In the current investigation, we reviewed the latest evidence on the effect of PDT on oral cancer cells and tried to analyze different aspects of these studies and provide a comparison of findings regarding various cell lines, PSs, and radiation details and how they may impact treatment outcomes.

Methods

The focus question for the current review was defined as: "does PDT affect the viability of OSCC in *in vitro* experiments?"

The PICO(S) framework was employed to define the concepts of the study. All eligible *in vitro* studies (Study type, S) evaluating the effects of PDT (Intervention, I) on the viability (Outcome, O) of oral squamous cell carcinoma (Population, P) compared to no PDT (Comparator, C) were considered for inclusion.

Search Strategy and Study Selection

PubMed/Medline (National Library of Medicine, Bethesda, Maryland), Scopus, Web of Science and Google Scholar (first 50 hits, as a grey literature source) were comprehensively searched up to July 2022 (no starting date limitation), using both MeSH terms and relevant free text words as follows: (Cancer OR neoplasm OR tumor OR carcinoma OR malignant) AND (oral OR oropharyngeal OR "head and neck") AND (PDT OR "photodynamic therapy"). In this study, we only focused on SCCs of the oral cavity and not of the head and neck. This was done to limit any possible site-specific-associated effects and to better interpret the results, especially considering that the head and neck include a wide range of subsites like the sinonasal tract, larynx, and tonsil. However, in order to avoid overlooking oral squamous cell carcinomas (OSCCs) reported in large studies in which OSCC cells are only one of the evaluated cell lines, we also included "head and neck" in our keywords and extracted all articles that had evaluated an OSCC cell line as part of a large group of SCCs in other head and neck locations and analyzed their findings. All records were imported into EndNote software (version 20), and duplicate records were removed, after which the retrieved records were screened separately by four authors (SSh, SS, NH, PR) to select potentially eligible studies. The same four authors independently evaluated the retrieved full texts according to the study concepts and hand-searched the reference lists of the extracted papers to identify any missed studies. Disagreement about eligibility and any controversies among the reviewers were resolved through

a discussion with the fifth and sixth reviewers (SE, MA) until a consensus was reached.

The following inclusion and exclusion criteria were considered:

Reviews, clinical trials, case reports, conference papers, non-English language publications, potentially malignant disorders, articles reporting findings on non-human OSCC and KB cells (due to contamination), cell types other than OSCC, and those applying PDT in combination with any other treatment modalities and medications were excluded. Studies using PDT with at least one PS and those with a minimum of one oral cancer cell line were included in this review.

Data Extraction

The following data were extracted and tabulated: cell line, PS and its concentration type of light source, wavelength, energy density (J/cm^2), type of evaluation, and main outcomes (Table S1, Supplementary file 1).[9,23,29-67]

Results

Study Selection

Studies extracted according to the inclusion/exclusion criteria amounted to a total of 567 articles after the removal of duplicates. Following Title/Abstract evaluation, 82 papers remained for further assessment. Of these, 40 studies required adjudication of the 5th/6th reviewers, and 41 studies were ultimately selected by complete consensus. Figure 1 demonstrates the search and selection process in a flow diagram.

Photosensitizer

In general, the PSs used in the studies are shown in Table S1. The most common PS was 5-ALA (5-aminolevulinic acid) which is a second-generation photosensitizing ag ent.[9,33,35,37,40,46,48,52,55,66,67] Other porphyrin platform PSs such as PAD-S31, HpD, Photofrin II, Photosan III, hydroxy purpurin, mTHPP, and Protoporphyrin IX (PpIX) were studied in some articles.[56-59,62] Chlorophyll platform PSs, including chlorin e6, NPe6, chlorin p6, mTHPC, pheophorbide a, and 9-hydroxy pheophorbide a were applied in other studies[29,31,38,39,41,43,49,54] One study used 15(1)-hydroxypurpurin-7-lactone ethyl methyl diester as a PS, which was isolated for the first time from an Araceae plant and referenced to Pha.[61] Natural PSs, like *Spirulina platensis*[64] and curcumin,[30] were among the used PSs. Phenothiazine dyes such as methylene blue were used in one study.[23] Moreover, phthalocyanine dyes, including liposome-incorporated 2-(morpholin-4-yl) ethoxy phthalocyanines, Pc4, Pc4 loaded nanoparticles, IRDye700DX, and AlPc-NE, were also applied in the reviewed studies.[32,50,60,63,65]

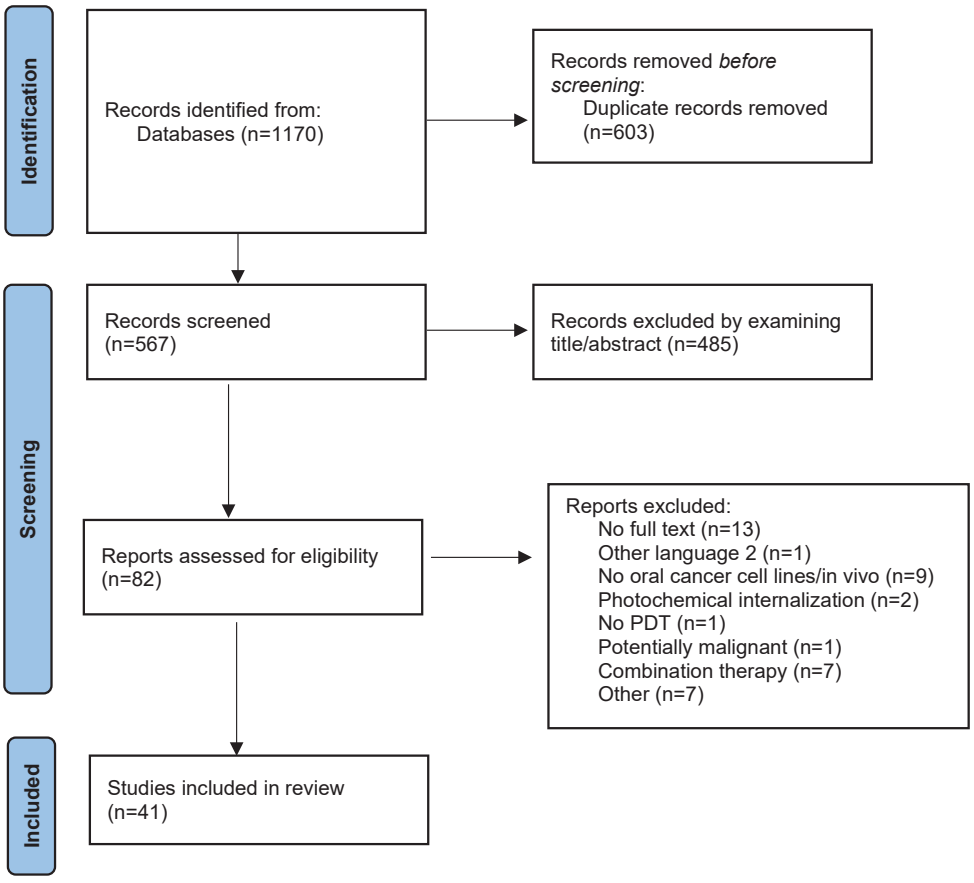

Figure 1. Flow diagram of the identification and selection process of the studies included in this review.

Other PSs such as Graphene quantum dots (GQDs) conjugated to polyethylene glycol (PEG),[53] new series of 1-benzothiazolylphenylbenzotriazoles,[47] porphyrazines,[44] palmatine hydrochloride (PaH),[45] HMnO2-IR780,[42] sulfur-doped carbon dots,[37] and erythrosine[36] were also used. Overall assessment showed slightly better results reported in the third generation and new PSs.

Some studies used only one concentration,[33,38-40,43,45,47-49,51,55,56,58,59,66,67] while others evaluated the effect of different concentrations on their cell lines.[9,23,29-32,34,36,37,41,42,44,46,50,53,54,57,60-65,68] Most studies showed that the results were dependent on concentrations.[9,23,29-31,34,36,41,42,44,46,50,53,54,57,60-63,65,68] But in some studies, concentrations were not significant in the results.[32,37,64] The exact concentrations used for each of the specific PSs are stated in Table S1.

Light Source

The most frequent light source was the laser, used in 19 studies (Table S1).[9,23,29,34,37,38,41,42,45,46,49,52,54,58-60,62,64,66] Others included LEDs in 8,[32,40,50,51,57,63,65,69] a UV lamp[30,47,56] in three, and a Tungsten lamp[36,55] and a visible lamp,[30,48] each in two studies.

In general, the wavelengths ranged from ultraviolet to near infrared based on the applied PS. The most common range of wavelengths was 600-700 nm used in 26 studies.[9,23,29,31-35,38,40,41,43,44,46,48,49,52,54,57,60,63-67,69] Similarly, energy density had a wide range between 0.23 J/cm^2 and 122.58 J/cm^2. Details are demonstrated in Table S1.

Human Oral Squamous Cell Carcinoma Cell Lines

A total of 35 oral cancer cell lines treated with PDT were used in the 41 extracted studies. One of the most common was CAL-27, which is a tongue SCC cell line isolated from a 56-year-old male patient. It was used alone or in combination with other cells in 4 papers.[31,51,52,64] In general, the tongue was the most common source of cell isolation in the PDT studies with patients (as a cell line source) whose age ranged between 25 and 74, and their M/F ratio was 9.

The tongue was followed by the gingiva, which was used in six studies with two cell lines derived from patients with an age range of 43 to 67 and a male-to-female ratio of 1. The floor of the mouth was the origin of SCC cells in three studies with four cell lines (age range: 40 to 72, M/F:1/3). The buccal mucosa was the origin of SCC cells in two studies with two cell lines (age range: 53 to 56, M/F = 1/1).

Three studies[69-71] used KB cells, which were excluded because of the contamination of this cell line.

Applied Tests and Outcome of PDT

Viability/cytotoxicity and apoptosis were the most common outcomes examined in the included studies. Viability/cytotoxicity was mainly determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay,[9,23,29,32,38-40,43,45-47,50-52,54,58,61,64,66] although other tests including trypan blue exclusion assay,[29] CellTiter-Glo® luminescent cell viability assay,[31] WST-8 assay,[34] acridine orange-propidium iodide assay, cell counting Kit-8,[37,53] acridine orange/ethidium bromide assay,[32] live/dead cell assay,[46] modified alamarBlue assay,[50] and cytotoxicity lactate dehydrogenase release assay,[29,30,34] were also used.

A variety of methods were applied to assess apoptosis, which consisted of Annexin V-FITC- propidium iodide,[9,29,38-40,45,46,51,52,61] Hoechst/propidium iodide,[43,54] Western blot[29,33,37-40,45,51,54] with numerous proteins (phospho-ERK, ERK, phospho-p38, p38, phospho-JNK, JNK, Bax, Bim, Bcl-2, cytochrome C, caspase 7, caspase 3, caspase-8, caspase-9, caspase-12 and their cleaved forms, poly-adenosine diphosphate ribose polymerase and cleaved poly-adenosine diphosphate ribose polymerase, LC3B, Fas-associated death domain, phospho-Fas-associated death domain, RUNX3, cyclin E2, cdk2, p21), DNA content with propidium iodide using FACS sorter,[33] TUNEL,[33,34] cell death morphology analysis with scanning electron microscopy, and confocal laser scanning microscopy.[36]

DNA fragmentation and immunohistochemistry for cleaved caspase-3,[30] formation of apoptotic mono- and oligo-nucleosomal DNA fragments with ELISA,[33,34] caspase activity assay,[36] immunofluorescence for Bax, Bcl-2, caspase-3[37], NF-κB and p65,[33] polymerase chain reaction for RUNX3, Wnt-1-inducible signaling pathway protein 2,[38] RUNX3 knockdown,[38] and activity of caspase-3 using ApoAlert Caspase Colorimetric Assay kit[40] were used in different studies.

Measurement of intracellular reactive oxygen species (ROS) was also a common test among PDT studies[29,30,37-40,45,46,51,52,61]

Some papers investigated cell motility via scratch wound healing assay[32,45,47,66] and cell invasion assay,[47,66] and metastatic ability using RT-PCR and Western Blot for Syndecan, MMP, TIMP, Heparinase, EGFR, ERK,[66] MMP2, and MMP9.[52]

Other experiments included clone counting or clonogenic assay,[23] autophagy by detection of acidic vesicular organelles and monodansylcadaverine staining,[29] cell proliferation with BrdU[30] or immunocytochemistry with Ki67 or cell counting via Neubauer chamber,[32] calcium concentration (Ca^{2+}) detection,[37] mitochondrial membrane potential ($\Delta\Psi m$),[29,36,46] net O2 and net Ca + + flux measurement,[51] and cell cycle assay.[9,45,61]

The results indicated decreased viability/increased cytotoxicity following PDT application in virtually all the studies with most of them being dose- and time-de pendent[23,29-32,34,36-40,43-52,54,57-59,61,63-65]; however, only one study showed no changes in cell viability following PDT[62]. Increased apoptosis was reported in all the studies

that measured this parameter.[9,29-31,33,34,36-40,43,45,46,51-54, 61] Interestingly, one study showed a higher apoptosis rate in lower PS doses.[36] notably, there have been some studies that further reduced the cell viability or increased the apoptosis rate using some novel methods in addition to PDT.[31,37,42,46,61] Cell motility findings were mostly positive, showing inhibition or reduction of migration following PDT.[32,45-47,51,52] In studies evaluating reactive or singlet oxygen species generation, PDT groups were mostly found to have higher amounts[29,30,37-40,42,44,59,61,65] A number of studies have also focused on the cell cycle; A G0/G1 cell cycle arrest was observed in one of them,[45] while two others indicated a block in the G2/M phase.[55,61] Additionally, two studies determined self-renewal and CD44 positivity and found that PDT effectively eliminates these two factors.[35,67] Despite the results being concordant, the studies showed great variation in terms of PS type, methods used, and PDT features (Table S1).

Discussion

Pre-clinical and *in vitro* studies are very important steps to observe the direct effect of experimentations on target cells and investigate the efficiency of treatment modalities. The current review explored the efficacy of PDT in various oral cancer cell lines. Different cell lines have different growth patterns[72]; therefore, it is important to evaluate a variety of cells when determining the impact of an intervention. The present review combines the data of a significant number of cell lines from different oral regions and provides a valuable summation that can be of great help in the design of clinical investigations.

Among the PDT protocols examined in the present review, 5-ALA, a naturally occurring PpIX precursor, was the most commonly used PS. When converted to PpIX in the mitochondria, it generates ROS. Activation by violet (405 nm) or orange-red light (635 nm) leads to the emission of red fluorescence (620–710 nm). These features in addition to its preferential accumulation in tumor tissues have been used to detect and/or obliterate cancer.[73] At present, neither the U.S. Food and Drug Administration nor the European Medicines Agency has approved the application of 5-ALA-PDT for cancer. However, the favorable published findings of its use as an anti-cancer approach may change these proceedings.[73-75]

5-ALA-PDT was used in a total of eleven studies,[9,33,35,37,40,46,48,52,55,66,67] of which eight reported a significant reduction in cell viability.[9,33,40,46,48,52,55,66] The induction of apoptosis, increased generation of intracellular ROS, and regulation of expression of different proteins involved in different signaling pathways related to invasion capacities were among the interesting outcomes of the included studies.

All the reviewed studies using natural substances as PSs reported a significant reduction in cell viability. The most recently introduced natural PS was *Spirulina platensis* that was used with a 635-nm diode laser at different energy densities from 2 to 24 J/cm^2, leading to decreased cell viability.[64] These PSs can be readily extracted from materials available in nature like plants and organisms, and their toxicity and side effects are minimal compared to chemical substances.[76,77] In addition to their availability, another advantage of natural PSs is that most of them possess additional valuable features like anti-oxidant and anti-inflammatory properties.[78] Considering the promising effect of natural PSs on OSCC observed in the current review, we recommend the use of these products in future in vitro and clinical studies.

Due to a significant variety of the applied PSs and a wide range of their concentrations, offering clinically relevant comparisons about concentration would be unfeasible. However, about 5-ALA in studies with different concentrations, higher concentrations were often associated with more apoptosis, but as the light doses are also different in ALA-mediated PDT protocols among the studies, making a definitive conclusion on the effective concentration is not possible.

Various light sources such as lasers, lamps, and LEDs are used in PDT treatment. The reviewed studies revealed that lasers with wavelengths corresponding to the maximum absorption of PSs were the most prevalently applied light source. Lasers are monochrome and possess distinctive characteristics like coherency, which make them an ideal light source for PDT.[79] Their monochromaticity translates to maximum light absorbance by the PS at a specific wavelength, reducing the risk of tissue temperature-increase by absorbing wavelengths outside the activation range of the PS. Coherence facilitates the concentration of light within optical fibers and therefore permits targeted transmission to tissues.[80]

The majority of the used PSs were activated by light sources with 600-700 nm wavelengths. Laser dosimetry was not fully and clearly reported in the retrieved papers, which is a limitation in rendering conclusive remarks about an ideal protocol. Energy density, as the most important parameter in PDT, varied widely between 0.2 and 122 J/cm^2. The predominant range in the evaluated articles was 1-10 J/cm^2. Some studies investigated several energy densities and reported differences in the results obtained from these energies.[64,34,36] In the 1-30 J/cm^2 range, 20 J/cm^2 showed the highest reduction of the survival rate in OSCC cell lines.[34] In a study on a tongue cancer cell line, PDT efficacy showed a dose-dependent manner with higher irradiation doses resulting in higher cell toxicity.[36] Conversely, recent reviews on the efficacy of PDT in the clinical treatment of OSCC found no significant difference between 0–50 J/cm^2, 50–100 J/cm^2, and 100–200 J/cm^2 energy densities.[81] This difference may be attributed to differences in the dosimetry principle between *in vitro* and clinical studies, as in clinics the light dose on the light source surface may be different from

that used on the target surface.

There was insufficient information on laser power and density in most of the extracted studies. A limited number of articles that provided this data reported powers to be less than 1 W and densities between 3 mW/cm^2 and 1000 mW/cm^2. Considering the role of oxygen in PDT, power density should be selected with care to prevent unwanted consequences like reduced efficiency due to accelerated oxygen consumption by high power densities. Values between 150 and 200 mW/cm^2 have been considered as the optimum range for PDT.[81]

To prove the efficacy of the PDT protocol, cell viability, apoptosis assays, ROS detection, and migration test were the most commonly applied tests respectively. Cell viability and migration ability are crucial in examining the active shifts in cell features undergoing PDT therapy.[82] ROS production measurement is important because these elements are central to PDT and have essential functions in cell signaling systems and homeostasis. The essence and continuous presence of ROS can impact the efficacy of PDT.[83] Moreover, cell proliferation-related proteins and those associated with invasion and apoptosis were the most significant measurements in the included studies that were used to explore the pathways involved in PDT. Osseous invasion and metastasis of OSCC are the debilitating sequelae of this cancer; therefore, knowledge of the mechanisms involved in its development is essential. Although poorly understood, invasion occurs through increased activity of osteoclasts at the invasion site, which has been suggested to result from an induction effect of tumor cells via promoting increases in the expression of various proteolytic enzymes like matrix metalloproteinases (MMPs) and cathepsins. Therefore, investigating the expression changes of these proteins could be valuable in PDT studies.[84] The current results of the retrieved studies revealed the down-regulation of MMP-2, 9 [47,49,52] and MMP-13,[49] suggesting the promoting effect of PDT on the suppression of molecular factors responsible for tumor invasion. According to our results, cell lines originating from the tongue were the most commonly applied cells[9,23,29,31,32,38-41,44-46,50-53,58,61,64] and demonstrated a general reduction in cell viability and increased apoptosis following PDT. Moreover, increased levels of intracellular ROS, migration inhibition, and down-regulations of the proteins responsible for tumor invasion were also reported. The findings related to cells from other oral sites were not consistent. For example, cell lines from the floor of the mouth were more resistant to PDT-induced cell death.[60,62] This information is valuable and with further future research and confirmation, it can be used to suggest modifications for PDT treatment of floor of mouth SCCs. Providing an explanation for the different response of the floor of the mouth SCC cells to PDT based on the limited current information would be speculative and requires further extensive research. However, a plausible justification is that this difference may be related to a variety of genomic specifications related to the different studied cell lines.[85] Also, numerous crucial differences have been reported between oral cancers originating from the floor of the mouth compared to other subsites, which can separately or collectively be responsible for this observation. Some of these differences are as follows: The floor of the mouth has significant anatomical complexity compared to other intraoral locations. Tobacco smoking and alcohol have a much higher impact on this subsite in comparison to others. Cancers in this location are more inclined towards the development of lymph node metastasis than those originating from the tongue, even when their thickness is similar. In addition, they are largely affected by field cancers and have a higher prevalence of multiple primary cancers compared to SCCs of the tongue, particularly in the anterior-subtypes compared to the posterior-subtypes. This anterior-posterior variation is interesting and implies that carcinogenesis might differ even among the different locations of the same subsite.[86]

Interestingly, studies that explored the efficacy of PDT in different cells from the same source stated that the results differed among the studied cell lines, which could be attributed to the features inherent in the cancer itself.[36,38,43,56] As an example, a comparison of two tongue SCC cell lines, SCC-9 and SCC-25, receiving the same PDT protocol, showed viability decreases of 70% and 30% respectively.[53] It is noteworthy that SCC-9 was derived from a 25-year-old male, while SCC-25 originated from a 70-year-old man. This validates the importance of personalized medicine when planning a treatment strategy.

It has been shown that combinations of PDT with other treatment methods could be a promising approach against cancer, especially in cases where monotherapy has failed.[78] The present study excluded the articles that combined PDT with other treatment modalities like chemotherapy or gene therapy to provide a more focused analysis. However, this could be an interesting and important topic for further research.

Conclusion

The current review revealed the promising effects of PDT on different oral squamous cell carcinoma (OSCC) cell lines using different PDT protocols. A large body of evidence exists on tongue cancer cell lines, which may have a slightly superior response to PDT compared to SCC cells extracted from the floor of the mouth. These results need to be further validated by future studies. A significant reduction in cell viability and apoptosis induction were the most commonly reported outcomes. Among the various PDT protocols, 5 ALA using laser light of approximately 630 nm and energy density in a range of 4-10 J/cm^2 was on the top of the list of the

used PSs with a generally high success rate. Due to the promising results obtained from the use of natural PSs as well as their additional health-promoting properties, further investigation with different cell lines and light specifications on these materials is highly recommended.

Conflict of Interests
The authors declare no conflicts of interest.

Ethical Considerations
Not applicable.

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Supplementary Files
Supplementary file 1 contains Table S1.

References
1. Heroiu Cataloiu AD, Danciu CE, Popescu CR. Multiple cancers of the head and neck. Maedica (Bucur). 2013;8(1):80-5.
2. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009;45(4-5):309-16. doi: 10.1016/j.oraloncology.2008.06.002.
3. Lambert R, Sauvaget C, de Camargo Cancela M, Sankaranarayanan R. Epidemiology of cancer from the oral cavity and oropharynx. Eur J Gastroenterol Hepatol. 2011;23(8):633-41. doi: 10.1097/MEG.0b013e3283484795.
4. Warnakulasuriya S. Living with oral cancer: epidemiology with particular reference to prevalence and life-style changes that influence survival. Oral Oncol. 2010;46(6):407-10. doi: 10.1016/j.oraloncology.2010.02.015.
5. Chow LQM. Head and neck cancer. N Engl J Med. 2020;382(1):60-72. doi: 10.1056/NEJMra1715715.
6. Wong T, Wiesenfeld D. Oral cancer. Aust Dent J. 2018;63 Suppl 1:S91-S9. doi: 10.1111/adj.12594.
7. Yoo JO, Ha KS. New insights into the mechanisms for photodynamic therapy-induced cancer cell death. In: Jeon KW, ed. International Review of Cell and Molecular Biology. Vol 295. Academic Press; 2012. p. 139-74. doi: 10.1016/b978-0-12-394306-4.00010-1.
8. Castano AP, Demidova TN, Hamblin MR. Mechanisms in photodynamic therapy: part three-Photosensitizer pharmacokinetics, biodistribution, tumor localization and modes of tumor destruction. Photodiagnosis Photodyn Ther. 2005;2(2):91-106. doi: 10.1016/s1572-1000(05)00060-8.
9. Ma Y, Qu S, Xu L, Lu H, Li B. An in vitro study of the effect of 5-ALA-mediated photodynamic therapy on oral squamous cell carcinoma. BMC Oral Health. 2020;20(1):258. doi: 10.1186/s12903-020-01239-8.
10. Biel MA. Photodynamic therapy treatment of early oral and laryngeal cancers. Photochem Photobiol. 2007;83(5):1063-8. doi: 10.1111/j.1751-1097.2007.00153.x.
11. Allison RR, Sibata CH. Oncologic photodynamic therapy photosensitizers: a clinical review. Photodiagnosis Photodyn Ther. 2010;7(2):61-75. doi: 10.1016/j.pdpdt.2010.02.001.
12. Civantos FJ, Karakullukcu B, Biel M, Silver CE, Rinaldo A, Saba NF, et al. A review of photodynamic therapy for neoplasms of the head and neck. Adv Ther. 2018;35(3):324-40. doi: 10.1007/s12325-018-0659-3.
13. Allison RR, Moghissi K. Photodynamic therapy (PDT): PDT mechanisms. Clin Endosc. 2013;46(1):24-9. doi: 10.5946/ce.2013.46.1.24.
14. Abdel-Kader MH. The journey of PDT throughout history: PDT from Pharos to present. In: Kostron H, Hasan T, eds. Photodynamic Medicine: From Bench to Clinic. The Royal Society of Chemistry; 2016. p. 1-21.
15. Correia JH, Rodrigues JA, Pimenta S, Dong T, Yang Z. Photodynamic therapy review: principles, photosensitizers, applications, and future directions. Pharmaceutics. 2021;13(9):1332. doi: 10.3390/pharmaceutics13091332.
16. Usuda J, Kato H, Okunaka T, Furukawa K, Tsutsui H, Yamada K, et al. Photodynamic therapy (PDT) for lung cancers. J Thorac Oncol. 2006;1(5):489-93.
17. Gunaydin G, Gedik ME, Ayan S. Photodynamic therapy for the treatment and diagnosis of cancer-a review of the current clinical status. Front Chem. 2021;9:686303. doi: 10.3389/fchem.2021.686303.
18. Saini R, Lee NV, Liu KY, Poh CF. Prospects in the application of photodynamic therapy in oral cancer and premalignant lesions. Cancers (Basel). 2016;8(9):83. doi: 10.3390/cancers8090083.
19. Biel MA. Photodynamic therapy of head and neck cancers. Methods Mol Biol. 2010;635:281-93. doi: 10.1007/978-1-60761-697-9_18.
20. Jerjes W, Upile T, Hamdoon Z, Alexander Mosse C, Morcos M, Hopper C. Photodynamic therapy outcome for T1/T2 N0 oral squamous cell carcinoma. Lasers Surg Med. 2011;43(6):463-9. doi: 10.1002/lsm.21071.
21. Karakullukcu B, van Oudenaarde K, Copper MP, Klop WM, van Veen R, Wildeman M, et al. Photodynamic therapy of early stage oral cavity and oropharynx neoplasms: an outcome analysis of 170 patients. Eur Arch Otorhinolaryngol. 2011;268(2):281-8. doi: 10.1007/s00405-010-1361-5.
22. Rigual NR, Thankappan K, Cooper M, Sullivan MA, Dougherty T, Popat SR, et al. Photodynamic therapy for head and neck dysplasia and cancer. Arch Otolaryngol Head Neck Surg. 2009;135(8):784-8. doi: 10.1001/archoto.2009.98.
23. Kofler B, Romani A, Pritz C, Steinbichler TB, Schartinger VH, Riechelmann H, et al. Photodynamic effect of methylene blue and low level laser radiation in head and neck squamous cell carcinoma cell lines. Int J Mol Sci. 2018;19(4):1107. doi: 10.3390/ijms19041107.
24. Verrico AK, Haylett AK, Moore JV. In vivo expression of the collagen-related heat shock protein HSP47, following hyperthermia or photodynamic therapy. Lasers Med Sci. 2001;16(3):192-8. doi: 10.1007/pl00011354.
25. Olek M, Kasperski J, Skaba D, Wiench R, Cieślar G, Kawczyk-Krupka A. Photodynamic therapy for the treatment of oral squamous carcinoma-clinical implications resulting from in vitro research. Photodiagnosis Photodyn Ther. 2019;27:255-67. doi: 10.1016/j.pdpdt.2019.06.012.
26. Alkindi M. Therapeutic efficacy of photodynamic therapy in oral squamous cell carcinoma: a systematic review. Biosci Biotechnol Res Commun. 2020;13(1):187-94. doi: 10.21786/bbrc/13.1/33.
27. Binnal A, Tadakamadla J, Rajesh G, Tadakamadla SK. Photodynamic therapy for oral potentially malignant disorders: a systematic review and meta-analysis. Photodiagnosis Photodyn Ther. 2022;37:102713. doi: 10.1016/j.pdpdt.2022.102713.
28. Cerrati EW, Nguyen SA, Farrar JD, Lentsch EJ. The efficacy of photodynamic therapy in the treatment of oral squamous cell carcinoma: a meta-analysis. Ear Nose Throat J. 2015;94(2):72-9. doi: 10.1177/014556131509400208.
29. Ahn MY, Yoon HE, Kwon SM, Lee J, Min SK, Kim YC, et al. Synthesized pheophorbide a-mediated photodynamic therapy induced apoptosis and autophagy in human oral squamous carcinoma cells. J Oral Pathol Med. 2013;42(1):17-25. doi: 10.1111/j.1600-0714.2012.01187.x.

30. Beyer K, Nikfarjam F, Butting M, Meissner M, König A, Ramirez Bosca A, et al. Photodynamic treatment of oral squamous cell carcinoma cells with low curcumin concentrations. J Cancer. 2017;8(7):1271-83. doi: 10.7150/jca.17176.
31. Bhuvaneswari R, Ng QF, Thong PS, Soo KC. Nimotuzumab increases the anti-tumor effect of photodynamic therapy in an oral tumor model. Oncotarget. 2015;6(15):13487-505. doi: 10.18632/oncotarget.3622.
32. Cangussu LMB, de Souza LR, de Souza MG, Junior RSM, Muehlmann LA, de Souza PN, et al. Photodynamic therapy mediated by nanoparticles Aluminum Chloro Phthalocyanine in oral squamous carcinoma cells. Lasers Med Sci. 2022;37(5):2509-16. doi: 10.1007/s10103-022-03517-z.
33. Chen HM, Liu CM, Yang H, Chou HY, Chiang CP, Kuo MY. 5-aminolevulinic acid induce apoptosis via NF-κB/JNK pathway in human oral cancer Ca9-22 cells. J Oral Pathol Med. 2011;40(6):483-9. doi: 10.1111/j.1600-0714.2010.00973.x.
34. Date M, Sakata I, Fukuchi K, Ohura K, Azuma Y, Shinohara M, et al. Photodynamic therapy for human oral squamous cell carcinoma and xenografts using a new photosensitizer, PAD-S31. Lasers Surg Med. 2003;33(1):57-63. doi: 10.1002/lsm.10188.
35. Fang CY, Chen PY, Ho DC, Tsai LL, Hsieh PL, Lu MY, et al. miR-145 mediates the anti-cancer stemness effect of photodynamic therapy with 5-aminolevulinic acid (ALA) in oral cancer cells. J Formos Med Assoc. 2018;117(8):738-42. doi: 10.1016/j.jfma.2018.05.018.
36. Garg AD, Bose M, Ahmed MI, Bonass WA, Wood SR. In vitro studies on erythrosine-based photodynamic therapy of malignant and pre-malignant oral epithelial cells. PLoS One. 2012;7(4):e34475. doi: 10.1371/journal.pone.0034475.
37. Li Q, Zhou R, Xie Y, Li Y, Chen Y, Cai X. Sulphur-doped carbon dots as a highly efficient nano-photodynamic agent against oral squamous cell carcinoma. Cell Prolif. 2020;53(4):e12786. doi: 10.1111/cpr.12786.
38. Moon S, Bae JY, Lee DY, Park GJ, Yoo H, Ko HJ, et al. RUNX3 is a biomarker for determining sensitivity to pheophorbide a-photodynamic therapy in human oral squamous cell carcinoma. Cancer Res. 2013;73(8_Suppl):3549. doi: 10.1158/1538-7445.am2013-3549.
39. Moon S, Kim DK, Kim J. Apoptosis-related microRNA-145-5p enhances the effects of pheophorbide a-based photodynamic therapy in oral cancer. Oncotarget. 2017;8(21):35184-92. doi: 10.18632/oncotarget.17059.
40. Moon YH, Park JH, Kim SA, Lee JB, Ahn SG, Yoon JH. Anticancer effect of photodynamic therapy with hexenyl ester of 5-aminolevulinic acid in oral squamous cell carcinoma. Head Neck. 2010;32(9):1136-42. doi: 10.1002/hed.21301.
41. Nakagawa H, Matsumiya T, Sakaki H, Imaizumi T, Kubota K, Kusumi A, et al. Expression of vascular endothelial growth factor by photodynamic therapy with mono-L-aspartyl chlorin e6 (NPe6) in oral squamous cell carcinoma. Oral Oncol. 2007;43(6):544-50. doi: 10.1016/j.oraloncology.2006.03.020.
42. Pan W, He Y, He M, Wang F, Qiu L. IR780 loaded hollow MnO2 nanoparticles for dual-mode imaging and enhanced photodynamic therapy of oral squamous cell carcinoma. Biocell. 2022;46(4):1079-88. doi: 10.32604/biocell.2022.016934.
43. Parihar A, Dube A, Gupta PK. Conjugation of chlorin p(6) to histamine enhances its cellular uptake and phototoxicity in oral cancer cells. Cancer Chemother Pharmacol. 2011;68(2):359-69. doi: 10.1007/s00280-010-1492-9.
44. Piskorz J, Konopka K, Düzgüneş N, Gdaniec Z, Mielcarek J, Goslinski T. Diazepinoporphyrazines containing peripheral styryl substituents and their promising nanomolar photodynamic activity against oral cancer cells in liposomal formulations. ChemMedChem. 2014;9(8):1775-82. doi: 10.1002/cmdc.201402085.
45. Qi F, Sun Y, Lv M, Qin F, Cao W, Bi L. Effects of palmatine hydrochloride mediated photodynamic therapy on oral squamous cell carcinoma. Photochem Photobiol Sci. 2019;18(6):1596-605. doi: 10.1039/c9pp00040b.
46. Qin J, Zhou C, Zhu M, Shi S, Zhang L, Zhao Y, et al. Iron chelation promotes 5-aminolaevulinic acid-based photodynamic therapy against oral tongue squamous cell carcinoma. Photodiagnosis Photodyn Ther. 2020;31:101907. doi: 10.1016/j.pdpdt.2020.101907.
47. Senadi GC, Liao CM, Kuo KK, Lin JC, Chang LS, Wang JJ, et al. Design, synthesis and antimetastatic evaluation of 1-benzothiazolylphenylbenzotriazoles for photodynamic therapy in oral cancer cells. MedChemComm. 2016;7(6):1151-8. doi: 10.1039/c6md00034g.
48. Sharma S, Jajoo A, Dube A. 5-aminolevulinic acid-induced protoporphyrin-IX accumulation and associated phototoxicity in macrophages and oral cancer cell lines. J Photochem Photobiol B. 2007;88(2-3):156-62. doi: 10.1016/j.jphotobiol.2007.07.005.
49. Sharwani A, Jerjes W, Hopper C, Lewis MP, El-Maaytah M, Khalil HS, et al. Photodynamic therapy down-regulates the invasion promoting factors in human oral cancer. Arch Oral Biol. 2006;51(12):1104-11. doi: 10.1016/j.archoralbio.2006.05.012.
50. Skupin-Mrugalska P, Szczolko W, Gierlich P, Konopka K, Goslinski T, Mielcarek J, et al. Physicochemical properties of liposome-incorporated 2-(morpholin-4-yl)ethoxy phthalocyanines and their photodynamic activity against oral cancer cells. J Photochem Photobiol A Chem. 2018;353:445-57. doi: 10.1016/j.jphotochem.2017.12.005.
51. Song L, Li C, Zou Y, Dai F, Luo X, Wang B, et al. O2 and Ca(2+) fluxes as indicators of apoptosis induced by rose bengal-mediated photodynamic therapy in human oral squamous carcinoma cells. Photomed Laser Surg. 2015;33(5):258-65. doi: 10.1089/pho.2014.3863.
52. Wang X, Jin J, Li W, Wang Q, Han Y, Liu H. Differential in vitro sensitivity of oral precancerous and squamous cell carcinoma cell lines to 5-aminolevulinic acid-mediated photodynamic therapy. Photodiagnosis Photodyn Ther. 2020;29:101554. doi: 10.1016/j.pdpdt.2019.08.036.
53. Zhang X, Li H, Yi C, Chen G, Li Y, Zhou Y, et al. Host immune response triggered by graphene quantum-dot-mediated photodynamic therapy for oral squamous cell carcinoma. Int J Nanomedicine. 2020;15:9627-38. doi: 10.2147/ijn.s276153.
54. Ahn JC. The apoptosis pathway of photodynamic therapy using 9-HpbD-a in AMC-HN3 human head and neck cancer cell line and in vivo. Gen Physiol Biophys. 2013;32(3):405-13. doi: 10.4149/gpb_2013040.
55. Allman R, Cowburn P, Mason M. Effect of photodynamic therapy in combination with ionizing radiation on human squamous cell carcinoma cell lines of the head and neck. Br J Cancer. 2000;83(5):655-61. doi: 10.1054/bjoc.2000.1328.
56. Boonkitticharoen V, Kulapaditharom B, Punnachaiya S, Kraiphibul P. Differences in in vitro photodynamic sensitivity among head and neck cancers. Lasers Med Sci. 1997;12(3):274-9. doi: 10.1007/bf02765109.
57. Chen WH, Lecaros RL, Tseng YC, Huang L, Hsu YC. Nanoparticle delivery of HIF1α siRNA combined with photodynamic therapy as a potential treatment strategy for head-and-neck cancer. Cancer Lett. 2015;359(1):65-74. doi: 10.1016/j.canlet.2014.12.052.
58. Cohen EM, Ding H, Kessinger CW, Khemtong C, Gao J, Sumer BD. Polymeric micelle nanoparticles for photodynamic

treatment of head and neck cancer cells. Otolaryngol Head Neck Surg. 2010;143(1):109-15. doi: 10.1016/j.otohns.2010.03.032.
59. Ding H, Mora R, Gao J, Sumer BD. Characterization and optimization of mTHPP nanoparticles for photodynamic therapy of head and neck cancer. Otolaryngol Head Neck Surg. 2011;145(4):612-7. doi: 10.1177/0194599811412449.
60. Hung HI, Schwartz JM, Maldonado EN, Lemasters JJ, Nieminen AL. Mitoferrin-2-dependent mitochondrial iron uptake sensitizes human head and neck squamous carcinoma cells to photodynamic therapy. J Biol Chem. 2013;288(1):677-86. doi: 10.1074/jbc.M112.422667.
61. Lim SH, Lee HB, Ho AS. A new naturally derived photosensitizer and its phototoxicity on head and neck cancer cells. Photochem Photobiol. 2011;87(5):1152-8. doi: 10.1111/j.1751-1097.2011.00939.x.
62. Lippert BM, Teymoortash A, Külkens C, Folz BJ, Werner JA. Photodynamic effects of anthracyclin derivatives on squamous cell carcinoma cell lines of the head and neck. Lasers Surg Med. 2004;34(5):391-7. doi: 10.1002/lsm.20040.
63. Master A, Malamas A, Solanki R, Clausen DM, Eiseman JL, Sen Gupta A. A cell-targeted photodynamic nanomedicine strategy for head and neck cancers. Mol Pharm. 2013;10(5):1988-97. doi: 10.1021/mp400007k.
64. Saberi S, Khoobi M, Alaeddini M, Etemad-Moghadam S, Jamshidloo R, Mohammadpour H, et al. The effect of photodynamic therapy on head and neck squamous cell carcinoma cell lines using spirulina platensis with different laser energy densities. Photodiagnosis Photodyn Ther. 2022;37:102688. doi: 10.1016/j.pdpdt.2021.102688.
65. van Driel P, Boonstra MC, Slooter MD, Heukers R, Stammes MA, Snoeks TJA, et al. EGFR targeted nanobody-photosensitizer conjugates for photodynamic therapy in a pre-clinical model of head and neck cancer. J Control Release. 2016;229:93-105. doi: 10.1016/j.jconrel.2016.03.014.
66. Yang TH, Chen CT, Wang CP, Lou PJ. Photodynamic therapy suppresses the migration and invasion of head and neck cancer cells in vitro. Oral Oncol. 2007;43(4):358-65. doi: 10.1016/j.oraloncology.2006.04.007.
67. Yu CH, Yu CC. Photodynamic therapy with 5-aminolevulinic acid (ALA) impairs tumor initiating and chemo-resistance property in head and neck cancer-derived cancer stem cells. PLoS One. 2014;9(1):e87129. doi: 10.1371/journal.pone.0087129.
68. Wang X, Jin J, Li W, Wang Q, Han Y, Liu H. Differential in vitro sensitivity of oral precancerous and squamous cell carcinoma cell lines to 5-aminolevulinic acid-mediated photodynamic therapy. Photodiagnosis Photodyn Ther. 2020;29:101554. doi: 10.1016/j.pdpdt.2019.08.036.
69. Kim J, Jung H, Lim W, Kim S, Ko Y, Karna S, et al. Down-regulation of heat-shock protein 27-induced resistance to photodynamic therapy in oral cancer cells. J Oral Pathol Med. 2013;42(1):9-16. doi: 10.1111/j.1600-0714.2012.01155.x.
70. Lim HJ, Oh CH. Indocyanine green-based photodynamic therapy with 785nm light emitting diode for oral squamous cancer cells. Photodiagnosis Photodyn Ther. 2011;8(4):337-42. doi: 10.1016/j.pdpdt.2011.06.002.
71. Liu YQ, Meng PS, Zhang HC, Liu X, Wang MX, Cao WW, et al. Inhibitory effect of aloe emodin mediated photodynamic therapy on human oral mucosa carcinoma in vitro and in vivo. Biomed Pharmacother. 2018;97:697-707. doi: 10.1016/j.biopha.2017.10.080.
72. Jiang L, Ji N, Zhou Y, Li J, Liu X, Wang Z, et al. CAL 27 is an oral adenosquamous carcinoma cell line. Oral Oncol. 2009;45(11):e204-7. doi: 10.1016/j.oraloncology.2009.06.001.
73. Shinoda Y, Kato D, Ando R, Endo H, Takahashi T, Tsuneoka Y, et al. Systematic review and meta-analysis of in vitro anti-human cancer experiments investigating the use of 5-aminolevulinic acid (5-ALA) for photodynamic therapy. Pharmaceuticals (Basel). 2021;14(3):229. doi: 10.3390/ph14030229.
74. Wang X, Li S, Liu H. Co-delivery of chitosan nanoparticles of 5-aminolevulinic acid and shGBAS for improving photodynamic therapy efficacy in oral squamous cell carcinomas. Photodiagnosis Photodyn Ther. 2021;34:102218. doi: 10.1016/j.pdpdt.2021.102218.
75. Alekseeva PM, Efendiev KT, Shiryaev AA, Rusakov MA, Simonova MS, Samoylova SI, et al. Sublingual administration of 5-aminolevulinic acid for laser-induced photodiagnostics and photodynamic therapy of oral cavity and larynx cancers. Photodiagnosis Photodyn Ther. 2021;34:102289. doi: 10.1016/j.pdpdt.2021.102289.
76. Kubrak TP, Kołodziej P, Sawicki J, Mazur A, Koziorowska K, Aebisher D. Some natural photosensitizers and their medicinal properties for use in photodynamic therapy. Molecules. 2022;27(4):1192. doi: 10.3390/molecules27041192.
77. Muniyandi K, George B, Parimelazhagan T, Abrahamse H. Role of photoactive phytocompounds in photodynamic therapy of cancer. Molecules. 2020;25(18):4102. doi: 10.3390/molecules25184102.
78. Mansoori B, Mohammadi A, Doustvandi MA, Mohammadnejad F, Kamari F, Gjerstorff MF, et al. Photodynamic therapy for cancer: role of natural products. Photodiagnosis Photodyn Ther. 2019;26:395-404. doi: 10.1016/j.pdpdt.2019.04.033.
79. Mostafa D, Tarakji B. Photodynamic therapy in treatment of oral lichen planus. J Clin Med Res. 2015;7(6):393-9. doi: 10.14740/jocmr2147w.
80. Kalka K, Merk H, Mukhtar H. Photodynamic therapy in dermatology. J Am Acad Dermatol. 2000;42(3):389-413. doi: 10.1016/s0190-9622(00)90209-3.
81. Lin J, Ni G, Ding T, Lei S, Zhong L, Liu N, et al. Photodynamic therapy for oral squamous cell carcinoma: a systematic review and meta-analysis. Int J Photoenergy. 2021;2021:6641358. doi: 10.1155/2021/6641358.
82. Roshan Moniri M, Young A, Reinheimer K, Rayat J, Dai LJ, Warnock GL. Dynamic assessment of cell viability, proliferation and migration using real time cell analyzer system (RTCA). Cytotechnology. 2015;67(2):379-86. doi: 10.1007/s10616-014-9692-5.
83. Dąbrowski JM. Reactive oxygen species in photodynamic therapy: mechanisms of their generation and potentiation. In: van Eldik R, Hubbard CD, eds. Advances in Inorganic Chemistry. Vol 70. Academic Press; 2017. p. 343-94. doi: 10.1016/bs.adioch.2017.03.002.
84. Erdem NF, Carlson ER, Gerard DA, Ichiki AT. Characterization of 3 oral squamous cell carcinoma cell lines with different invasion and/or metastatic potentials. J Oral Maxillofac Surg. 2007;65(9):1725-33. doi: 10.1016/j.joms.2006.11.034.
85. Ludwig ML, Kulkarni A, Birkeland AC, Michmerhuizen NL, Foltin SK, Mann JE, et al. The genomic landscape of UM-SCC oral cavity squamous cell carcinoma cell lines. Oral Oncol. 2018;87:144-51. doi: 10.1016/j.oraloncology.2018.10.031.
86. Oikawa Y, Tanaka K, Ohsako T, Kugimoto T, Kuroshima T, Hirai H, et al. Comparison of clinicopathological characteristics between the anterior and posterior type of squamous cell carcinoma of the floor of the mouth: the anterior type is a risk factor for multiple primary cancer. Front Oncol. 2021;11:682428. doi: 10.3389/fonc.2021.682428.