REVIEW ARTICLE

ADVERSE EFFECTS OF ELECTRONIC CIGARETTE VAPOR CONDENSATION ON ORAL CELLS: A SCOPING REVIEW

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Highlights: (1) Damage to deoxyribonucleic acid (DNA), cytotoxicity, and genotoxicity may be present in oral cells when exposed to electronic cigarette (EC) vapor for up to 72 hours. (2) High alteration of apoptotic cells positive for terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), delaying their migration. (3) Xenobiotic metabolism, response to oxidative stress, and processes related to inflammation are influenced by EC vapor in oral cells.

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ABSTRACT

Electronic cigarettes (ECs), when internally heated, generate aerosol through e-liquid, with part of it being absorbed into the bloodstream. Consequently, little is known about the potential adverse events of this vapor on oral cells, which may contribute to alterations in their functionality. The present study aims to organize data from the literature on the adverse effects of EC vapor condensation on oral cavity cells. The analysis was conducted following the methodological approach of PRISMA-ScR and the Joanna Briggs Institute (JBI). Thus, two researchers from the team independently searched the PubMed/MEDLINE, Scopus, Web Of Science, and LILACS databases using combinations of descriptors through "and/or," tabulating studies published in English over a 10-year period (January 1, 2013, to October 13, 2023), with the assistance of the EndNote reference manager. With the search, a total of 803 studies were located, of which 15 in vitro studies were included in the final analysis. Among the qualitative results, exposure to EC vapor for up to 72 hours caused damage to deoxyribonucleic acid (DNA), oxidative stress, double-strand DNA breaks, apoptosis, cytotoxicity, and genotoxicity in human gingival fibroblasts (FGH), gingival mesenchymal stem cells (CTMG), primary human gingival epithelial cells (CEGHP), normal human oral keratinocytes (QOHN), and clustered human gingival epithelial progenitors (HGEPp). The evaluated cell cultures also showed a high percentage of apoptotic cells positive for terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), delaying their migration. Thus, xenobiotic metabolism, oxidative stress response, and processes related to inflammation are influenced by EC vapor in oral cells.

Keywords: Electronic cigarette. Cellular form. Immune cytotoxicity. Apoptosis induction factor.

ADVERSE EFFECTS OF ELECTRONIC CIGARETTE VAPOR CONDENSATION ON ORAL CELLS: A SCOPING REVIEW

EFEITOS ADVERSOS DA CONDENSAÇÃO DO VAPOR DO CIGARRO ELETRÔNICO NAS CÉLULAS ORAIS: UMA REVISÃO DE ESCOPO

RESUMO

Os cigarros eletrônicos (CEs) quando aquecidos internamente geram o aerossol por meio do *e-liquido*, sendo parte dele absorvido pela corrente sanguínea. Com isso, pouco se sabe sobre o potencial de eventos adversos desse vapor em células orais, o que poderá contribuir para alterações em sua funcionalidade. O presente estudo tem como objetivo organizar dados da literatura sobre os efeitos adversos da condensação do vapor de CE nas células da cavidade oral. A análise foi conduzida seguindo a abordagem metodológica do PRISMA-ScR e Joanna Briggs Institute (JBI). Assim, dois pesquisadores da equipe realizaram uma busca independente nas bases de dados da PubMed/MEDLINE, Scopus, Web Of Science e LILACS, utilizando combinações de descritores através de "*and/or"*, tabulando estudos publicados na língua inglesa em um intervalo de 10 anos (01 de janeiro de 2013 a 13 de outubro de 2023), com auxílio do gerenciador de referências EndNote. Com a busca, um total de 803 estudos foram localizados, sendo que desses, 15 pesquisas *in vitro* foram incluídas ao final. Dentre os resultados qualitativos, a exposição ao vapor dos CEs por até 72 horas gerou danos ao ácido desoxirribonucleico (DNA), estresse oxidativo, ruptura de fitas duplas do DNA, apoptose, citotoxicidade e genotoxicidade em fibroblastos gengivais humanos (FGH), células tronco mesenquimais gengivais (CTMG), células epiteliais gengivais humanas primárias (CEGHP), queratinócitos orais humanos normais (QOHN) e progenitores do epitélio gengival humano agrupados (HGEPp). As culturas de células avaliadas apresentaram ainda elevada alteração de células apoptóticas positivas para *o terminal deoxynucleotidyl transferase dUTP nick end labeling* (TUNEL), atrasando sua migração. Desse modo, o metabolismo xenobiótico, a resposta ao estresse oxidativo e os processos relacionados à inflamação são influenciados pelo vapor dos CEs em células orais.

Palavras-Chave: Cigarro eletrônico. Forma celular. Citotoxicidade imunológica. Fator de indução de apoptose.

ADVERSE EFFECTS OF ELECTRONIC CIGARETTE VAPOR CONDENSATION ON ORAL CELLS: A SCOPING REVIEW

INTRODUCTION

Electronic cigarettes (ECs), defined by the United States Food and Drug Administration (FDA) as electronic nicotine delivery systems, are designed to heat a liquid mixture of nicotine and flavorings to produce vapor[1]. These devices utilize an internal liquid, known as e-liquid, which is aerosolized through heating, allowing the user to inhale the vapor[2]. A portion of this vapor is absorbed into the bloodstream, while the remainder is expelled into the atmosphere[3].

Beyond nicotine, ECs contain various chemical constituents that may contribute to toxic effects, potentially through synergistic interactions. Key components include solvents such as propylene glycol and vegetable glycerin, which, when heated, can release irritants or carcinogenic compounds like formaldehyde and acrolein[4]. Additionally, e-liquid formulations often incorporate flavorings and additives, whose toxicological effects remain not fully understood but are suspected to amplify cellular damage[5].

Contextually, since 2003, this device has undergone significant evolution, with intense promotion on social networks, contributing to its widespread use, especially among young people[6]. Currently, there are more than 10,000 combinations of e-liquids available, but they typically contain nicotine, a base, and various flavors in their formulation[7]. In this regard, literature authors highlight that the exposure of oral cells to liquid nicotine triggers a phenotype migration, activating the epidermal growth factor receptor (EGFR) signaling through a significant increase in fatty acid synthase expression[8,9], characteristic of a common pro-oncogenic event, relevant to oral carcinogenesis[10].

Studies also present evidence of vaping nicotine and its role in the signaling of fatty acid synthase/EGFR expression, along with an increase in the migration of pre-malignant cells through EGFR signaling[11,3]. Based on this, hypotheses can be raised regarding the safety of ECs, especially for ex-smokers with clinically unknown oral pre-malignant lesions, in which nicotine may trigger associated oncogenic signals[12].

When exposed to these vapors, cells from various sources exhibit a significant reduction in viability and colony-forming capacity, a phenomenon known as decreased clonogenic survival[5]. This term refers to the ability of surviving cells to proliferate and form colonies, a critical indicator of cellular functionality and integrity after exposure[10].

Furthermore, these effects are often associated with high rates of apoptosis and necrosis, as demonstrated in in vitro studies. Such cellular alterations occur independently of the nicotine content in the vapor, suggesting that other chemical components of e-cigarettes also play a significant role in the observed damage[11,13].

It is also observed that the cytotoxicity of e-liquids, containing nicotine or not, was investigated in the extracellular matrix of human gingival fibroblasts (FGH), assessing the safety of these new electronic devices in the oral environment, with oxidative stress induced by an increase in pro-apoptotic protein expression, leading to the induction of early and late apoptosis[14,15]. Aspects like these were more prevalent in liquid samples containing nicotine, as the substance contributes to intracellular oxidative stress, despite also triggering apoptosis in the samples[4]. Thus, it is of great importance that dental professionals be prepared to address issues related to ECs in clinical practice, as data in the scientific literature highlight similar problems to conventional cigarettes, especially in the periodontal tissue[5].

These findings underscore the importance of monitoring the state of different tissues and organs in individuals using ECs, posing a relevant concern for both adolescents and young adults. Therefore, the research demonstrates its significance in the field of stomatology, enabling the assessment of the potential impact of EC use on oral cells and the subsequent development of malignancy, influencing the proper physiology of the oral cavity. In this context, the present study aims to organize data from the literature on the adverse effects of EC vapor condensation on oral cavity cells.

METHODOLOGY

Study design and protocol

This is a scoping review conducted in accordance with the methodology outlined by the Joanna Briggs Institute (JBI)[16]. The established criteria were guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR)[17]. The research protocol was registered on the Open Science Framework (https://osf.io/gqp8m/).

Search information and search strategy

For the conceptualization of the study, the following guiding question was formulated: "What are the main histopathological alterations in oral cells related to exposure to EC vapor?" This topic was developed using the PCC (Population, Concept, and Context) strategy, as recommended by the JBI protocol, as detailed below: Population (P): samples exposed to EC liquid, vapor, and/or nicotine in test cells; Concept (C): EC compared to non-users or test cells compared to control cells; Context (C): Frequency of clinical and laboratory aspects.

Subsequently, appropriate truncations and combinations of words were selected and adapted for each database search using the boolean operators "and" and/or "or" (Table 1). All references were managed in a reference management program (EndNote, Thomson Reuters, Philadelphia, PA, USA), and duplicate reports identified in the search were removed.

Eligibility criteria

Inclusion criteria

Peer-reviewed in vitro or in vivo studies on the adverse effects of exposure to EC in oral cells, published within a 10-year timeframe (January 1, 2013, to September 9, 2023) on the topic, and written in English. The research should include, in at least one of the evaluative groups, one of the following cells under assessment: 1) Human periodontal ligament fibroblasts, 2) Human gingival fibroblasts; 3) Oral epithelial cells; 4) Oral pharyngeal cells; 5) Oral keratinocytes. All samples in the tabulated studies should be collected from systemically and periodontally healthy non-smoking donors.

Exclusion criteria

Literature reviews (narrative, integrative), theses and/or master's or doctoral dissertations, editor's notes, pilot studies; duplicate studies, conference proceedings, data predating 2013, epidemiological studies, studies unavailable in full, cohort studies, cross-sectional studies, case reports, case series, opinion articles, and studies not written in the Latin (Roman) alphabet were excluded.

Samples obtained from isolated pre-malignant or malignant leukoplakic lesions without a healthy control group were disregarded. Additionally, research focusing on other cells in the body, studies with less than 24 hours of incubation/exposure, articles on ECs emphasizing smoking cessation assistance, perceptions and attitudes regarding EC use, and endothelial function studies alone were also removed from the final sample.

Sources of information

To identify studies to be included in this review, an electronic search was conducted on PubMed/MEDLINE, SciVerse Scopus, Web of Science, and Latin American and Caribbean Health Sciences Literature (LILACS). The search was conducted between May 20 and August 31, 2023, and updated on October 13, 2023.

Table 1 - Specific search terms for each database and truncations

Data base	Search strategy	Total
Medline - PubMed	("E-Cigarette Vapor" OR "Electronic Nicotine Delivery Systems" OR "Vaping OR Nicotine") AND ("Mouth Mucosa" OR "Gingiva" OR "Tongue" OR "Saliva" OR "Mouth Floor" OR "Periodontium" OR "Cells" OR "Fibroblastos" OR "Tongue") AND ("DNA Damage" OR "DNA Adducts" OR "Cytotoxicity", "Immunologic" OR "Cell Death" OR "Genotoxicity" OR "Oxidative Stress")	358
SciVerse Scopus	(TITLE-ABS-KEY (("Electronic Nicotine Delivery Systems" OR Vaping OR Nicotine))) AND TITLE-ABS-KEY (("Gingiva" OR Tongue OR Saliva OR Mouth Floor OR Periodontium OR "Cells" OR Fibroblastos OR Tongue))) AND AND TITLE-ABS-KEY (("DNA Damage" OR DNA Adducts OR Cytotoxicity, Immunologic OR Cell Death OR Genotoxicity OR Oxidative Stress)))	144
Web of Science	("E-Cigarette Vapor" OR "Electronic Nicotine Delivery Systems" OR "Vaping OR Nicotine") AND ("Mouth Mucosa" OR "Gingiva" OR "Tongue" OR "Saliva" OR "Mouth Floor" OR "Periodontium" OR "Cells" OR "Fibroblastos" OR "Tongue") AND ("DNA Damage" OR "DNA Adducts" OR "Cytotoxicity", "Immunologic" OR "Cell Death" OR "Genotoxicity" OR "Oxidative Stress")	209
LILACS	(tw: (("Electronic Nicotine Delivery Systems" OR Vaping OR Nicotine))) AND (tw: (("Gingiva" OR Tongue OR Saliva OR Mouth Floor OR Periodontium OR "Cells" OR Fibroblastos OR Tongue))) AND (tw: (("DNA Damage" OR DNA Adducts OR Cytotoxicity, Immunologic OR Cell Death OR Genotoxicity OR Oxidative Stress)))	72

Source: authors, 2023.

Study evaluation

The examiners were trained to apply the study selection criteria in two phases. Phase 1 involved the analysis of titles and abstracts of all articles obtained from the databases to select studies for full-text reading. Phase 2 included the complete reading of the articles chosen in Phase 1 to assess eligibility based on the established inclusion and exclusion criteria.

Two examiners (Z.S.S. and R.C.S.O) independently (blinded) participated in both phases. In Phase 2, an additional manual search in the references of the selected studies after full-text reading was conducted to find possible articles inadvertently omitted during the database searches. In case of any discrepancies in the two phases, the article would be discussed between the two authors and the third researcher (R.P.M) until consensus was reached.

Data items

A pre-established Excel™ matrix, version 2021, was created to facilitate data mapping with the following study variables of interest: author, publication year, research design, cell type, study parameters, research results, and conclusions were tabulated (Table 2). In order to summarize the essential elements of each tabulated study, a descriptive analytical structure was employed to examine the content of each article.

This involved a comprehensive assessment of all materials, allowing for the identification and creation of categories resulting from in-depth analysis of the publications, which helped illustrate the topics of interest. Adverse effects of ECs on oral cavity cells were the primary outcomes of this review.

RESULTS

Study selection

This study relied on published data and generated prevalence results that allowed an assessment of the clinical characteristics of EC exposures in oral cells. The initial search identified a total of 803 studies through various sources. Based on the analysis of titles and abstracts, applying all the pre-established eligibility criteria, it was possible to select 15 studies for inclusion in the final sample. To clearly illustrate the prolonged methodological process during the database search, figure 1 was developed.

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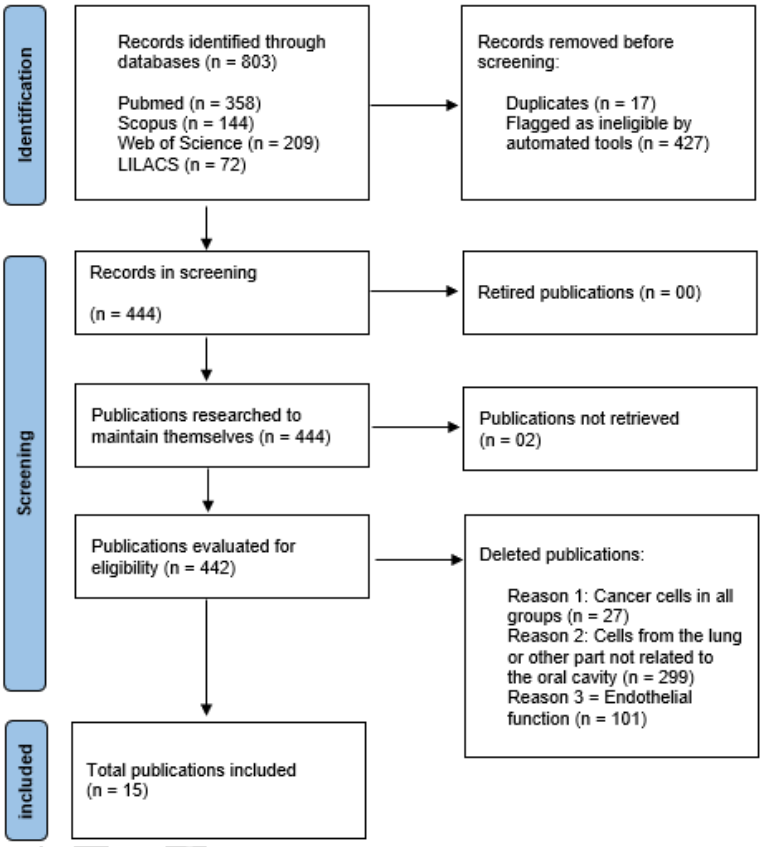
Figure 1 - Flow Diagram, adapted from PRISMA (2020), illustrating the study selection sequence and its inclusion in this scoping review.



Source: Research data, 2023.

Characterization of included studies

The tabulated studies were published between 2014 and 2022. Material collection in the analyses was conducted in healthy adults, with a minimum age of 18 years and a maximum of 54 years. Regarding prevalent techniques, 3-(4,5-dimethylthiazol-2yl)-2,5-di-phenyl tetrazolium bromide (MTT), polymerase chain reaction (PCR), and Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) were present, along with fluorescence optical microscopy. The condensation time for exposed cells ranged from 24 to 72 hours, with only 2 studies located with a longer time frame[18,24]. The studies were tabulated in descending order by the year of publication and characterized regarding their primary outcome, based on the research's variables of interest, as either positive (+) or negative (-).

Table 2 – Cellular effects due to the use of CE

Author/year	Sample	Exhibition	Genotoxicity	Cytotoxicity	Apoptosis	Oxidative stress	Outcome
El-Mouelhy *et al.*[18]	FG/ CTMG	2 weeks	+	+	-	+	Deregulation
Alanazi; Rouabhia[15]	CEGHP e FG	24 hours	+	+	+	-	Inflammation
Tellez *et al.*[19]	Epithelial lineages MOE1A, MOE1B e MSK-LEUK1	48 hours	+	-	-	+	Deregulation and severe damage to DNA
Ramenzoni *et al.*[20]	Cells HGEK-16 NA: N/E	24 hours	-	+	+	-	Inflammation
Urena et al.[21]	CCEOH e FG	24 hours	+	-	-	+	Deregulation
Vermehren *et al.*[22]	FG	72 hours	+	+	-	-	Deregulation
Alanazi *et al.*[23]	*FGH*	24 hours	+	+	+	-	Deregulation and severe damage to DNA
Rouabia *et al.*[7]	CEGHP	24 hours	+	+	+	+	Deregulation
Ganapathy *et al.*[24]	Human normal bronchial epithelial cells (Nuli1)	2 weeks	+	+	+	+	Deregulation and severe damage to DNA
Sancilio *et al.*[25]	FG	24 hours	+	+	+	+	Deregulation (Periodontitis)

Sundar *et al.*[26]	FG, HGEPp and gingival epithelium	24 hours	+	+	+	+	Deregulation (Periodontitis)
Welz *et al.*[27]	Oropharyngeal mucous tissue	24 hours	+	+	+	+	Deregulation and severe damage to DNA
Ji *et al.*[28]	QOHN	24 hours	+	+	+	+	Inflammation and Deregulation
Yu *et al.*[3]	*Bloodlines HaCaT, UMSCC10B and HN30*	48 hours	+	+	+	+	Deregulation and severe damage to DNA
Willershausen *et al.*[29]	*FG*	24 hours	+	+	+	+	Reduced migration

Caption: Sample number (NA); Not specified (NE); 3-(4,5-dimethylthiazol-2yl)-2,5-di-phenyl tetrazolium bromide (MTT); Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL); Human gingival fibroblasts (FG)/gingival mesenchymal stem cells (CTMG); Human oral squamous cell carcinoma cells (CCEOH); Primary human gingival epithelial cells (CEGHP); Normal human oral keratinocytes (QOHN); Clustered human gingival epithelial progenitors (HGEPp).

Source: Research data, 2023.

Cells tested, exposure time, and morphological changes

FGH cells are the most common in the connective tissue of the gum and play a fundamental role in maintaining gum structure and the extracellular matrix[30,31]. They play a crucial role in tissue repair and wound healing through their functions of adhesion, growth, and migration. However, exposure to electronic smoke can impair their proper functionality[14].

In this context, most studies conducted analyses with FGH (n=08), followed by CEGHP (n=04), QOHN (n=1), HGEPp (n=1), and CTMG (n=1). The presence of copper nanoparticles in the constituent material of CE has the ability to mediate genotoxicity and oxidative stress in cells, inducing pro-inflammatory responses in FGH. Moreover, cells treated with aerosol showed slight morphological changes compared to those exposed to tobacco smoke. Of the 15 studies analyzed, a total of 14 studies highlighted the presence of genotoxicity, while cytotoxicity was present in 13 studies. Apoptosis was observed in 11 studies, and oxidative stress was identified in 11 research papers.

The overview of differentially expressed genes and the biological interpretation of the data revealed that xenobiotic metabolism, response to oxidative stress, and processes related to inflammation are influenced by cigarette smoke and aerosols. At similar concentrations, tobacco smoke in some studies had a greater impact on gene expression related to the oxidative stress network than aerosol, causing a greater effect on oral samples in the collected data[3,28,29,32,33].

Oxidative damage to deoxyribonucleic acid (DNA) not only resulted from exposure to specific genotoxic agents but also depended on the cells' ability to respond to antioxidant detoxification and DNA repair processes. In this context, the results revealed that, similar to conventional tobacco smoke, prolonged exposure to CE aerosol leads to a significant increase in cellular reactive oxygen species (ROS) and a reduction in the total antioxidant capacity of cells.

Tabulated data further highlight that condensation of CE and its vapor with or without nicotine for 60 minutes once a day, between 24 to 72 hours, induces a morphological alteration in oral cells, reducing their proliferation rate. Exposed cell cultures show a high incidence of apoptotic cells positive for TUNEL, delaying migration and inducing apoptosis.

Meanwhile, morphological changes and cytoskeleton reorganization were present at the molecular level. Thus, the articles emphasized that high nicotine levels in CEs demonstrate antiproliferative effects that can subsequently cause toxic effects on osteoblasts and bone metabolism.

DISCUSSION

This scoping review identified a series of alterations in oral cavity cells due to exposure to EC vapor, demonstrating a significant role in inducing oral microbiome imbalance. Under appropriate and healthy conditions, the oral microbiota is considered commensal, as there is harmony between the host and the individual. However, under dysbiotic conditions, oral diseases such as periodontitis and the caries-promoting bacterium Streptococcus mutans become prevalent[6].

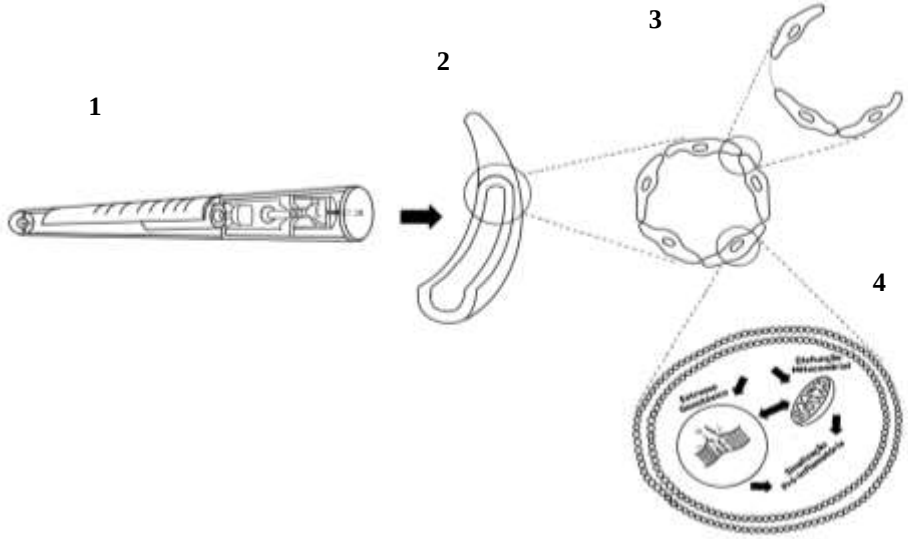
The oral mucosa acts as an initial protective layer against aerosols released by ECs. Due to the combination of high temperatures and the presence of chemicals, ECs have the

ability to cause damage to tissues in the oral cavity, including the gingival mucosa[2,34,35]. In this assessment, issues related to the proliferation, viability, apoptosis of cells exposed to EC vapor, and their relevance in DNA dysregulation were described, as highlighted below.

Proliferation, viability, and apoptosis of cellular samples exposed to electronic cigarette vapor

The condensate of electronic vapor with a high concentration of nicotine demonstrated a significant influence on the morphology of oral cells, affecting proliferation and migration/closure capacity in the tabulated studies, as illustrated in figure 2.

Figure 2 - Mechanism of action of electronic cigarette vapor on oral cells



Caption: 1) Illustration of an electronic cigarette (CE) condensing vapor into a blood vessel; 2) Macroscopic view of a blood vessel; 3) Cellular epithelial view of a blood vessel; 4) Condensation of electronic cigarette vapor causing dysplasia, oxidative stress, and cytotoxicity in tissues and epithelial cells.
Source: Adapted from Mohammadi et al.[13].

Regarding this, El-Mouelhy et al.[18] highlighted that EC aerosol showed a significantly lower impact on cell proliferation and viability compared to conventional cigarettes and cannabis, but with alterations in its morphology. In this study, a lower expression of the ataxia-telangiectasia mutated (ATM) gene was also observed in the EC group, suggesting

the absence of DNA damage and a reduction in reactive oxygen species (ROS) production, similar to the study by Vermehren et al.[22].

On the other hand, Sancilio et al.[25] described that both nicotine and non-nicotine fluids resulted in an increase in ROS production after 24 hours, accompanied by an increase in Bax expression and followed by the induction of apoptosis after 48 hours of exposure, suggesting a role of EC fluids in the pathogenesis of oral diseases such as periodontitis.

Thus, the structural changes observed in the epithelium suggest the possibility of adverse effects caused by EC aerosol on the gingival tissue structure[2]. Exposure of the oral mucosal epithelium to EC aerosol over four days, with a total of eight exposures, resulted in significant changes in the deposition of collagen type IV in the basement membrane in the study by Alanazi; Rouabhia.[15]. For the authors, this indicates that EC aerosol had a negative impact on the presence of collagen type IV, which, in turn, may affect the interaction between epithelial cells and fibroblasts through the structure of the basement membrane.

Thus, it is observed that the ability to induce cytotoxicity and genotoxicity may be related to the chemical components present in e-liquids and the production of toxic substances such as formaldehyde, acetaldehyde, and acrolein. Based on this, some studies assessed whether the presence or absence of nicotine in EC would influence the cytotoxicity observed in the material. In this perspective, in the study by Tellez et al.[19], the presence or absence of nicotine did not seem to play a significant role in the level of cytotoxicity in oral epithelial cells. However, notably, in the case of flavorless e-liquid containing nicotine, no cytotoxic effects were observed in any of the analyzed cell lines.

Programmed cell death was also evaluated by some tabulated studies. Ramenzoni et al.[20] emphasized the toxic adverse effects caused by EC aerosols on normal cells, highlighting an apoptotic morphology. The authors observed that a single exposure to EC aerosol resulted in increased cell mortality, and this increase showed a positive correlation with aerosol concentration. The study's conclusion indicates that ECs affect oral cavity epithelial cells, increasing cellular toxicity, also highlighted by Urena et al.[21], promoting the release of inflammatory mediators.

In this regard, Alanazi et al.[23] pointed out that exposure to both conventional cigarette smoke and electronic vapor condensate had an adverse impact on gingival fibroblast

activities. It was observed that the damage was more pronounced in the presence of conventional cigarette smoke condensate compared to electronic vapor condensate, even when the latter was rich in nicotine.

In the study by Yu et al.[3], cells subjected to EC exposure showed a notable reduction in cell viability and clonogenic survival capacity. Additionally, there was a substantial increase in apoptosis and necrosis rates, regardless of the presence of nicotine in EC vapor. Willershausen et al.[29] observed that certain additives present in ECs can result in significant damage to cell proliferation.

Thus, within this context, gingival fibroblasts (FGH/CTM) play a key role in periodontal repair and regeneration. For EC users, this increased pro-inflammatory response may promote oral infections, periodontal diseases, and cavities[19].

Condensation of EC and its relevance in the role of DNA deregulation

DNA damage was intrinsically investigated in all studies included in this review. According to Welz et al.[27], DNA fragmentation was assessed through alkaline microgel electrophoresis. In this research, a significant reduction in cell viability induced by all tested liquids was observed. Remarkably, flavored liquids showed even higher toxicity compared to flavorless ones.

Effectively, exposure to flavored liquids resulted in a significant increase in DNA fragmentation, while exposure to flavorless liquids did not cause significant DNA damage[36]. These results indicate that e-liquids exhibit cytotoxicity to oropharyngeal tissues, and some liquids may cause considerable DNA damage. Therefore, the authors suggest that the possibility of mutagenicity of the upper aerodigestive tract (UADT) mucosa and e-liquids being risk factors for head and neck cancer cannot be completely ruled out.

In this context, Ganapathy et al.[24] exposed epithelial cells to various doses of aerosol extract for 1 hour. As a result, exposure to EC aerosol extracts can lead to significant DNA damage, including the occurrence of elevated levels of 8-oxo-2'-deoxyguanosine (8-oxo-dG), which is a highly mutagenic oxidative lesion in epithelial cells. Sundar et al.[26] highlighted that exposure to EC aerosol triggers an increase in oxidative stress and the formation of

carbonyl products, inducing inflammatory responses and cellular senescence with persistent DNA damage.

These effects occur through RAGE-HDAC2-dependent mechanisms in gingival epithelium, being more pronounced when it comes to flavored ECs. The authors suggest that ECs may negatively affect the regenerative potential of human progenitor cells due to increased inflammatory responses and DNA damage.

Ganapathy et al.[24] emphasized that when investigating the underlying mechanisms influencing DNA damage, they identified an increase in ROS in cells, along with a reduction in total antioxidant capacity and a decrease in the expression of proteins essential for DNA repair. For the authors, these factors represent new mechanisms by which exposure to EC aerosol can cause DNA damage and potentially increase the risk of cancer.

Based on the above-mentioned data, EC aerosols demonstrate cytotoxicity to in vitro oral epithelial cells. Moreover, the underlying molecular mechanisms may be, at least in part, associated with oxidative stress induced by toxic substances, such as nanoparticles and chemicals present in EC aerosols[28]. These cells also showed a significant increase in comet assay tail length and higher formation of γ-H2AX foci, indicating an increase in DNA strand breaks[3].

Other in vitro study designs involved the use of human airway oral epithelial cells and in vivo experiments with mice, demonstrating that EC aerosol induces oxidative stress, contributing to glutathione depletion and positively regulating the production of inflammatory cytokines[11]. These findings are of utmost importance as they identify additional mechanisms, beyond the genotoxic content of EC aerosols, that may contribute to increased DNA damage resulting from exposure to electronic cigarette aerosol.

Contributions and limitations of the study

Significantly, this analysis integrated and provided relevant information for dentistry, conducting a thorough search across various databases to enhance the exploration of existing literature. A deeper understanding of the chronic effects of vaporization can equip dentists with greater insight into the molecular mechanisms that increase susceptibility to periodontitis. It can also help identify potential therapeutic targets and biomarkers for assessing

oral complications linked to the flavoring agents used in vaporization and their impact on oral cavity cells and tissues.

Thus, there is an urgent need to adopt modern, reliable, and validated analytical methods to quantify toxic metals and other chemicals inhaled by users of different generations of ECs. Understanding the long-term effects of exposure to these compounds is particularly crucial, as knowledge in this area remains incomplete.

FINAL CONSIDERATIONS

The mechanisms of action of chemicals present in electronic aerosols involve alterations at biochemical, cellular, and molecular levels. Exposure to aerosols generated by ECs has been shown to potentially exert deleterious effects on human oral health. These effects include dysbiosis, induction of inflammation, cytotoxicity, and genotoxicity, as well as cellular reduction and apoptosis, collectively contributing to DNA dysregulation and the pathogenesis of periodontal diseases. Nonetheless, further comprehensive research is imperative to elucidate the full extent of the impact of electronic aerosols on oral cavity tissues and to evaluate their long-term consequences.

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ADVERSE EFFECTS OF ELECTRONIC CIGARETTE VAPOR CONDENSATION ON ORAL CELLS: A SCOPING REVIEW

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