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Autor correspondente:
Aline Barbosa dos Santos
Graduate Program in Dentistry and Health, Federal University of Bahia, School of Dentistry, Salvador, Bahia, Brazil E-mail: alineebarbosaa@hotmail.com

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EFFECTS OF ELECTRONIC NICOTINE DELIVERY SYSTEMS AND NICOTINE POUCHES ON THE ORAL CAVITY: AN INTEGRATIVE REVIEW

Aline Barbosa dos Santos Xavier[a], Paloma Pereira Silva[a], Raissa Stephane Teles da Silva[a], Ludmilla Macedo Bacelar[a], Viviane Almeida Sarmento[a]

[a]Graduate Program in Dentistry and Health, Federal University of Bahia, School of Dentistry, Salvador, Bahia, Brazil

ABSTRACT

Aim: Investigate the clinical, toxicological, and epidemiological effects of ENDS on the oral cavity. **Methods:** This is an integrative literature review conducted in the PubMed, SciELO, Virtual Health Library (VHL), LILACS, and Cochrane Library databases, using controlled descriptors linked by Boolean operators, as well as their English equivalents. Articles published in the last ten years were included, provided they were available in full and without language restrictions. **Results:** Initially, 57 publications were identified, and after applying the eligibility criteria, 19 studies comprised the final sample. Scientific evidence demonstrates that users of ENDS and nicotine pouches exhibit hyperkeratotic lesions, edema, activation of inflammatory pathways, potential carcinogen activation, and other health impacts. **Conclusions:** The growing consensus regarding the harmful potential of these devices, as well as the need for longitudinal studies to deepen the understanding of their effects on the oral cavity.

Keywords: Electronic nicotine delivery systems. ENDS. Nicotine pouch. Oral mucosa. Nicotine.

INTRODUCTION

Nicotine addiction is a prevalent public health problem worldwide1. Despite advances in prevention policies, tobacco use remains one of the greatest global challenges. According to the World Health Organization (WHO), tobacco use is responsible for more than eight million preventable deaths per year, and it is estimated that about 20% of the world's adult population is affected by nicotine dependence2.

The use of electronic cigarettes, also known as electronic smoking devices or e-cigarettes, has seen significant growth on a global scale, exceeding

100 million users worldwide[2]. This increase is driven largely by marketing strategies that promote these devices as supposedly less harmful alternatives. In this context, electronic cigarettes pose a major public health challenge, especially in developing countries3. In Brazil, although the sale, import, and advertising of these devices are prohibited, there has been a steady increase in their use4,5.

Heat-not-burn tobacco products include electronic nicotine delivery systems (ENDS) and heated tobacco products (HTPs). These devices contain psychoactive agents, such as nicotine, as well as solvents and flavorings6. A new category has gained popularity in the European, American, and Japanese markets: oral nicotine pouches (ONPs). These pouches contain a sealed mixture of nicotine, flavorings, sweeteners, and fillers. They feature a discreet design and are placed between the gum and the lip, eliminating the need to swallow or spit7,8.

The use of nicotine delivery systems can affect oral and bronchial epithelial cells, trigger local and systemic toxicological responses, and cause gingival irritation and gastroesophageal reflux disorders1,9. Vaporized liquids have cytotoxic and genotoxic potential, capable of inducing DNA changes and triggering cell death, regardless of nicotine concentration10.

Given the rapid expansion in the use of electronic nicotine delivery systems and the emergence of new nicotine-containing products, there is growing concern regarding the potential impacts of these devices on overall health, particularly in the oral cavity, which is one of the first sites of contact with such substances. The widespread use of these devices, particularly among young people, underscores the relevance of this issue in the context of public health. In this context, this integrative review aims to compile and critically analyze the available evidence in the literature and investigate the effects of ENDS and nicotine pouches on the oral health of their users.

METODOLOGIA

This study is an integrative literature review that addressed the guiding question: "What are the clinical, toxicological, and epidemiological impacts of Electronic Nicotine Delivery Systems (ENDS) and nicotine pouches on the oral cavity?"

The search was conducted in the following major databases: Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed), SciELO, Virtual Health Library (VHL), Scopus, Lilacs, Cochrane Library, using controlled descriptors (MeSH and DeCS) and keywords related to electronic nicotine delivery systems, nicotine pouches, and oral mucosa, combined using Boolean operators (and and or) and their respective English terms: Electronic Nicotine Delivery Systems (ENDS), nicotine pouches, oral mucosa. Electronic Nicotine Delivery Systems OR Electronic Cigarette AND Oral mucosa.

We included articles published in the last 10 years that were available in full, with no language restrictions, encompassing original studies, systematic reviews, and experimental, observational, and toxicological studies conducted in humans or animal models, provided they addressed the impacts of ENDS on the oral cavity. Studies that did not address oral health, publications focused exclusively on conventional cigarettes, duplicate articles, and opinion pieces without scientific relevance were excluded.

The initial search yielded 57 publications, of which 28 were identified in PubMed, 1 in SciELO, 1 in Lilacs, 20 in BVS, and 7 in the Cochrane Library. After reviewing the titles and abstracts, removing duplicates, and applying the previously defined inclusion and exclusion criteria, 19 studies were selected to comprise the final sample for the review.

The selected studies were classified into three main categories: clinical, toxicological, and epidemiological impacts of electronic nicotine delivery systems on oral health. A predominance of narrative and systematic reviews was observed, in addition to experimental and observational studies, with a limited number of clinical trials that reflect the relatively recent introduction of ENDS to the market and the ethical limitations inherent in conducting long-term clinical studies (Table 1).

RESULTS

In the initial search, studies were identified; after applying filters and reviewing the titles, some were excluded because they were duplicates in the databases or met the exclusion criteria. Among the relevant articles, some were excluded after reviewing the abstracts because they did not contain content relevant to this review. Finally, articles were selected because they aligned with the research objective (Figure 1).

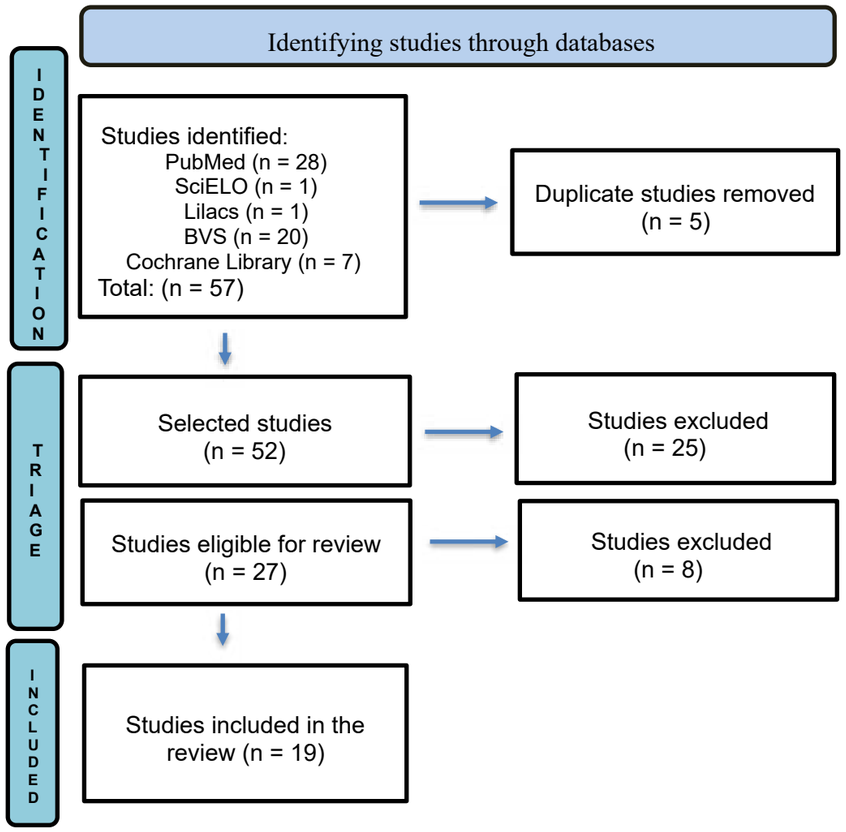


Table 1 - Overview of the articles included in the integrative review.

Authors	Year	Study Type	Study Objective	Main Findings
Pérez-Jardón A et al. [11]	2025	Case-control	To evaluate gene expression in e-cigarette users by exfoliative cytology.	Alterations were observed only in e-cigarette users. Use may induce early molecular and cytological changes in the oral mucosa, related to inflammation and immune response. Changes in the expression of p16 and TNF markers, associated with inflammatory processes, stand out.
Butler, et al. [12]	2025	Literature review	Synthesize clinical and molecular evidence of oral pathology associated with nicotine.	Evidence regarding the effectiveness of these interventions remains limited, highlighting the need for clinical and educational strategies to reduce health risks, including impacts on oral health.
Zou, H. et al. [13]	2025	Literature review	Synthesize clinical and molecular evidence of oral pathology associated with nicotine.	Nicotine pouches can cause localized pathological changes in the oral mucosa, manifested as hyperkeratotic white lesions at the site of contact. Histologically, hyperkeratosis, edema, and epithelial inflammation are observed, associated with oxidative stress and the activation of inflammatory pathways such as NF-κB and NLRP3.
Maan, M. et al. [14]	2025	Clinical trial	To evaluate the effects of e-cigarette aerosol on the oral mucosa.	Groups exposed to e-cigarettes containing nicotine and flavorings showed greater alpha diversity compared to controls. Metabolomics identified 13 elevated metabolites associated with the progression of oral cancer. These findings suggest alterations in the oral microbiome and potential impacts on oral health.

Authors	Year	Study Type	Study Objective	Main Findings
Salih MM et al. [15]	2025	Cross-sectional	To evaluate the effects of electronic and traditional cigarettes on the oral mucosa.	E-cigarette users exhibited cytological changes in the oral mucosa, including alterations in epithelial cell morphology and signs of inflammation. Saliva analysis revealed biochemical changes and increased oxidative stress, indicating that vaping may alter the oral microenvironment, promote inflammation and compromise oral health.
CarvalhoBFC de et al. [16]	2024	Literature review	To investigate changes in the oral mucosa and saliva associated with the use of e-cigarettes.	E-cigarette users exhibited cytological changes in the oral mucosa, including alterations in epithelial cell morphology and signs of inflammation. Saliva analysis revealed biochemical changes and increased oxidative stress, indicating that vaping may alter the oral microenvironment, promote inflammation and compromise oral health.
Cichońska D et al. [17]	2024	Literature review	To review the literature on the impact of e-cigarette use on oral health.	The use of e-cigarettes can alter the oral microbiota, favoring bacteria associated with periodontal disease. This is linked to mucosal inflammation, oxidative stress, and impaired oral tissue integrity, increasing the risk of periodontal disease and changes in epithelial cells and fibroblasts.
Vámos O et al. [18]	2024	Case-control	To compare the acute effects of e-cigarettes and traditional cigarettes on palatal blood flow.	There were no significant differences in palatal blood flow between the e-cigarette and traditional cigarette groups. Acute use of these products has minimal impact on palatal blood flow, but further studies are needed to assess effects on the oral mucosa.
Gallagher KPD et al. [19]	2024	Systematic review	To review clinical evidence regarding e-cigarettes as a risk factor for potentially malignant lesions and oral cancer.	Vape users have been found to have carcinogenic compounds in their saliva, morphological changes, DNA damage, and activation of pathways associated with carcinogenesis. However, clinical evidence remains limited and inconclusive, requiring long-term clinical studies.
Rinaldi S et al. [20]	2023	In vitro study	To provide a basis for future studies on the toxicity mechanisms of nicotine pouches.	Nicotine pouches exhibited cytotoxic effects on gingival fibroblasts, with reduced cell viability and potential harmful effects on periodontal tissues.

Authors	Year	Study Type	Study Objective	Main Findings
Lima JM de et al. [21]	2023	In vitro study	To demonstrate that e-cigarettes morphologically alter oral keratinocytes and promote tumor progression.	E-cigarettes induce morphological and behavioral changes in normal oral keratinocytes and promote the progression of existing tumors, which increases the invasive capacity of oral squamous cell carcinoma.
Reeve GS et al. [22]	2022	In vitro study	To analyze the oral epithelial transcriptome in e-cigarette users.	Users exhibited changes in oral epithelial gene expression associated with inflammation and alterations in oral mucosal function.
Chapman F et al. [23]	2022	Randomized clinical trial	Comparing the pharmacokinetics, pharmacodynamics, and safety of two variants of nicotine pouches.	The pharmacokinetic profile of sublingual nicotine pouches suggests direct absorption, allowing nicotine to be absorbed through the oral mucosa. In the case of cigarettes, however, nicotine absorption occurs primarily through inhalation.
Guo J et al. [24]	2022	In vitro study	To investigate AP sites in human oral cells and in e-cigarette users.	Smokers exhibited an increased number of micronuclei (MN) in oral epithelial cells compared to non-smokers, suggesting the presence of cytological changes. The MN count can be used as an early indicator of susceptibility to oral mucosal changes and carcinogenesis.
Alanazi H & Rouabhia M [25]	2022	In vitro study	To evaluate the effect of exposure to e-cigarettes on the human oral mucosa and the secretion of pro-inflammatory cytokines.	E-cigarette aerosol disrupts tissue structure and increases the production of matrix metalloproteinases (MMPs), reduces the number of Ki67-positive epithelial cells and basement membrane proteins, and increases levels of pro-inflammatory cytokines.
pandara thodivil AK et al a M [25]	2021	Case-control	To evaluate the effect of exposure to e-cigarettes on the human oral mucosa and the secretion of pro-inflammatory cytokines.	E-cigarette aerosol disrupts tissue structure and increases the production of matrix metalloproteinases (MMPs), reduces the number of Ki67-positive epithelial cells and basement membrane proteins, and increases levels of pro-inflammatory cytokines.
Pop AM et al. [27]	2021	Case-control	To assess the frequency of micronuclei in oral epithelial cells of smokers.	Users of electronic cigarettes have a higher number of micronuclei in their oral epithelial cells. This marker may indicate early cytological changes and a risk of carcinogenesis.

Authors	Year	Study Type	Study Objective	Main Findings
Chopyk J et al. [28]	2021	Case-control	To determine whether exposure to e-cigarette aerosol induces persistent changes in the oral microbiome.	The oral mucosa showed a significant change in beta diversity between e-cigarette users and controls, with a significant increase in Veillonella and Haemophilus.
Schwarzmeier LA T et al. [29]	2021	Case-control	To investigate damage to the oral mucosa through micronucleus assessment.	E-cigarette users exhibited greater diversity and changes in the salivary microbiome compared to nonsmokers. There was an increase in Veillonella and Haemophilus and a tendency toward greater colonization by Staphylococcus aureus.

DISCUSSION

Literature has significant methodological limitations, and further studies are needed to elucidate, in greater depth, the mechanisms involved in the morphological changes and cytotoxic effects induced by nicotine on oral mucosal cells (Table 1).

ENDS have become appealing due to the wide variety of flavors available, the false perception of safety, and growing social acceptance6. However, the level of nicotine absorption depends on the brand and model, being comparable to or higher than that of conventional cigarettes11; even without combustion, they continue to expose users to various toxic substances and can cause dependence12,17.

The literature demonstrates an increase in the prevalence of oral manifestations and a greater predisposition to the development of dental caries, gingival bleeding, periodontal inflammation, changes in the oral epithelium—including xerostomia—, demineralization of tooth enamel, tooth discoloration, changes in the composition of the oral biofilm, halitosis, oxidative stress, dysbiosis, and carcinogenic effects1,2,11,22.

Pérez-Jardón et al. (2025)11, in a case-control study, identified early molecular and cytological changes in the oral mucosa associated with inflammatory and immunological processes. Similarly, Lima et al. (2023)21 and Guo et al. (2022)24 observed a significant increase in the frequency of micronuclei in oral epithelial cells, indicating genetic damage and genomic instability related to oral carcinogenesis. These findings demonstrate that subcellular alterations can occur even in the absence of visible clinical lesions, reinforcing the potential of micronuclei as early markers of susceptibility to oral cancer.

Regarding periodontal tissues, an in vitro experimental study demonstrated the cytotoxic effects of nicotine pouches on gingival fibroblasts, reduced cell viability, and possible periodontal damage20. In addition to causing hyperkeratotic lesions, functional changes, edema, epithelial inflammation, and activation of inflammatory pathways such as NF-κB (Nuclear Factor kappa B) and NLRP3 (NOD-like pyrin domain-containing protein 3), it alters gene expression in the oral epithelium13,21,27.

Regarding salivary parameters, ENDS may affect the antioxidant capacity of saliva and reduce pH, salivary flow, and viscosity compared to non-smokers16. Pandarathodiyil et al. (2021)26 assessed salivary LDH enzyme levels and found higher LDH activity in smokers, triggering cytotoxic effects on the oral mucosa. In an in vitro study, a significant increase ($p < 0.01$) in LDH levels was observed after tissue exposure to aerosols, along with a decrease in gingival epithelial proliferation25.

The primary route of nicotine absorption is through the oral mucosa23. In this regard, Salih et al. (2025)15 observed a strong association between smoking and cytomorphological changes, the severity of which was found to be related to the duration and intensity of exposure. Complementarily, in a clinical trial, Maan et al. (2025)14 found that there is greater alpha diversity in users exposed to nicotine and flavorings and a greater increase in metabolites related to the progression of carcinogenesis.

Chopyk et al. (2021)28 and Schwarzmeier et al. (2021)29 identified a significant increase in microorganisms associated with periodontal inflammation, such as Veillonella, and Haemophilus, as well as a tendency toward greater colonization by Staphylococcus aureus in e-cigarette users. These microorganisms can cause dysbiosis responsible for the progression of gingivitis, periodontitis, halitosis, and alterations in the local immune response.

CONCLUSION

Scientific evidence shows that the use of ENDS and nicotine pouches causes structural changes and intensifies tissue inflammation, negatively impacting oral and systemic health. However, it is noted that most of the available studies are cross-sectional in design and have methodological limitations, although there is a growing consensus regarding the cytotoxic, pro-inflammatory, and harmful potential of these devices. In this context, it is essential to develop prospective and longitudinal clinical studies that can elucidate, in a more comprehensive manner, the chronic effects associated with exposure to e-cigarettes and nicotine-derived products.

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