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Review

Electronic Cigarettes, Heated Tobacco Products, and Oral Health: A Systematic Review and Meta-Analysis

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Abstract: Smokers employing electronic nicotine delivery systems (ENDS) and heated tobacco products (HTP) are currently the most common types of smoking patients seen in the dental practice. Both types of smoking are currently viewed as less harmful than cigarette smoking. However, many studies already indicate that they could harm oral health. This systematic review and meta-analysis aimed to collect a comprehensive overview of the actual knowledge regarding ENDS and HTP from a clinical and a laboratory perspective. Publications available through PubMed, Embase, the Web of Science, Scopus, and Google Scholar were used to summarize the effects of ENDS and HTP on oral health. Six surveys on self-perceived gum disease (T2 = 9.47 I2 = 99.32%), three cross-sectional studies reporting the BOP score (T2 = 8.68 I2 = 99.13%), and four in vitro studies on apoptosis after vaping exposure in human oral fibroblasts (T 2 = 8.10 I2 = 91.50%) were separately analyzed. The risk of bias ranged from critical to low. Both ENDS and HTP seem to have detrimental effects on periodontal and peri-implant parameters, and laboratory tests confirmed the presence of carcinogenic and inflammatory biomarkers. flavored e-liquids may also be a caries risk factor. Comprehensive smoking counseling should be carried out with all types of smoking patients, investigating the type of habit in terms of duration, nicotine percentage, and additional flavorings. Additional research is necessary to assess the long-term effects of alternative tobacco products on oral health.

Keywords: electronic nicotine delivery systems; electronic cigarettes; E-Cig; oral health; heated tobacco products

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1. Introduction

Electronic cigarette smokers (ECS) are increasing all over the world [1,2], mainly because vaping electronic nicotine delivery system(s) (ENDS) are perceived to be safer than cigarette smoking and attracts young naïve subject, as well as adult smokers who want to quit or reduce tobacco consumption [3,4]. Nevertheless, the short- and long-term effects of ENDS within the oral cavity have been scarcely investigated and reported, considering the fact that ENDS entered the market between 2003 and 2004 [5,6].

ENDS consists of an LED battery-operated device that mimics the shape of a conventional cigarette; it comprises a metal heating element in a stainless-steel case, a cartridge

that holds the e-liquid, and an atomizer. The e-liquid solutions can have different nicotine percentages and are available in different flavors [7]. The cartridge and solution chemicals are mainly diethylene glycol, glycerin, nitrosamines, and potentially harmful contaminants, such as heavy metals, aldehydes, and carbonyls [8]. Today's available e-cigarettes are third-generation digitalized devices allowing for high consumer customization [9]. ENDS vaping is a "recreative style" of smoking that seems quite removed from conventional cigarettes and is common among teens and young adults for whom customization of any item is a popular marketing strategy [10]. Moreover, the way in which ENDS are switched on and off has changed "the smoking session"; ENDS can be turned off after one minute as well as after half an hour, while the cigarette, once lit, cannot be paused. Thus, vaping meets the needs of former cigarette smokers/quitters who are attracted to the possibility of controlling the nicotine concentration of the solution.

The effects of ENDS on general health are likely to be established with scientific evidence in the coming decades. Vaping side effects [11] have been related to:

- The respiratory system (cough, asthma and bronchitis);
- The cardiovascular system (heart rate and blood pressure increase);
- The oropharyngeal system (oral cavity and pharynx lesions);
- Skin and annexes (dermatitis);
- Second-hand smokers or passive smokers (increased cotinine levels);
- Other (headache, eye problems due to vapor and glycerol, burns and lacerations).

As alternative tobacco products, ENDS have not only been proposed on the market, but heated tobacco products (HTP) have also been developed. HTPs heat tobacco to a high enough temperature to release aerosol, without burning it or producing smoke. They differ from ENDS in that they heat a tobacco leaf/sheet and not a liquid [12]. As is the case for ENDS, HTPs have also been related to pulmonary [13] and cardiovascular diseases [14]. Moreover, it has been stated that they should not be recommended for smoking cessation [15]

Dental professionals are aware of the harmful effects of cigarette smoking, especially the increased risk of malignant lesions and the onset of periodontitis [16]. The onset and progression of periodontitis are directly related to the frequency of the habit. Smoking less than 9 cigarettes/per day is considered light smoking, while more than 31 cigarettes/per day is considered heavy smoking [17]. The use of electronic cigarettes has created doubts regarding the evaluation of the smoker/vaper profile, as a wide variety of ENDS and HTPs is available and dual smokers are quite frequent.

The design of the studies regarding the effects of ENDS and HTPs on the development and progression of periodontal and peri-implant diseases are mainly focused on comparisons between vapers, HTP smokers, cigarette smokers, and non-smokers. The clinical parameters evaluated are periodontal/peri-implant probing pocket depth (PPD), bleeding on probing (BOP), plaque index (PI), and clinical attachment loss (CAL). Along with the evaluation of these parameters, the collection of salivary and/or crevicular fluid samples was often performed, in which inflammatory biomarkers such as TNF-α, IL-1β, or IL-6 were measured. These inflammatory cytokines stimulate osteoclastic processes, increasing periodontal inflammation and bone loss [18]. Moreover, reactive aldehydes from ENDS aerosols may allow protein carbonylation that could lead to bone tissue injury in periodontitis [19]. These adverse effects require a systematic review employing a comprehensive overview of this topic, which poses a challenge for dentists who increasingly find themselves treating e-cigarette and HTP smokers.

Hence, the present systematic review aimed to evaluate the effect of ENDS and HTP on oral health variables or on human cells/oral bacteria by comparing vaping, non-smoking, dual smoking, and cigarette smoking. This review analyzed observational, interventional, and laboratory studies on human cells.

2. Materials and Methods

2.1. Study Registration

The review protocol was registered in PROSPERO (CRD42021276707) and followed the PRISMA guidelines [20].

2.2. Reporting Format

The PRISMA recommendations were adopted throughout the process of the present systematic review [21].

2.3. Population (P), Exposure (E), Comparison (C), Outcomes (O), and Study Design

The research question was formulated according to the following PECOs: P (population): electronic cigarette and heated tobacco smokers or human cells/oral bacteria exposed to ENDS; E (exposure): the use of vaping electronic cigarettes or heated tobacco products and/or vapor from electronic cigarettes or heated tobacco products; C (comparison): non-smokers (NS), former smokers (FS), cigarettes smokers (CS), dual smokers (DS), other types of smokers, and cigarette-to-ENDS or HTP switchers; Os (outcomes): changes in oral health parameters due to electronic cigarettes or heated tobacco products, both clinically assessed and self-reported by users, or the expression of apoptotic/necrosis biomarkers in cells.

2.4. Inclusion Criteria

The following inclusion criteria were adopted:

- Interventional and observational studies on ENDS and HTP and their effects on oral health;
- Studies including subjects of any age or sex;
- Full and/or pilot studies reporting data;
- For the laboratory studies, articles considering human oral cells or oral bacteria;
- Studies in English, without time limits.

2.5. Exclusion Criteria

The following exclusion criteria were adopted:

- Systematic or narrative reviews and meta-analyses;
- Theses and dissertations;
- Case reports/series;
- Studies reporting insufficient/unclear information, or not allowing data extraction;
- Papers not published in English;
- Papers focused on different aspects of health other than oral health;
- Studies for which the authors did not respond to the email requesting data clarification.

2.6. Search Strategies

A detailed search strategy was developed for each database, considering differences in controlled vocabulary and syntax rules (NC). The search strategy for each database is given in the Supplementary File S1.

2.7. Electronic Search

The electronic search was conducted by one author (NC) across five databases: PubMed (National Library of Medicine), the Web of Science (Clarivate Analytics), Embase (Elsevier), Scopus (Elsevier), and Google Scholar.

The search was performed in February 2023 and updated in August of the same year. All retrieved references were uploaded onto Endnote 20® software to check for duplicates and for study selection.

2.8. Manual Search

The reference lists of the studies included were used to identify additional records that were hand searched (NC).

2.9. Study Selection

After the exclusion of duplicates, two independent authors (NC and MGC) screened the papers by title and abstract; when in doubt, consensus was reached after consultation with a third author (GC). Agreement between the two screeners was assessed using Cohen's Kappa score.

2.10. Data Extraction and Variable Analysis

Tables 1–3 display the summary of included articles divided by study type, such as observational studies in which the variables considered were age, sex, type of smoker, and type of records (clinical or from surveys). In the interventional studies, the variables considered were age, sex, type of smoker, and type of records (BOP, PD, and similar). In order to standardize the age of the samples of the included studies, the following classification was used: Early Adolescence (EA), for subjects aged 12 to 18 years; Young Adults (YA), for subjects aged 19 to 44 years; Middle Adults (MA), for subjects aged 45 to 65 years; and Older Adults (OA), for subjects aged 65 years and over [22].

Finally, in the laboratory studies, in addition to the type of smoker or cell, the type of exposure was also considered.

2.11. Risk of Bias

The quality of the randomized clinical trials (RCTs) was assessed using the ROB-2 tool [23]. For non-RCTs studies, the ROBIN-I (Risk Of Bias In Non-randomized Studies of Interventions) tool was used [24]. The biases evaluated for both tools were: confounding, selection of participants, classification of interventions, deviation from intended interventions, missing data, measurement of outcomes, and selection of reported results. The Risk-of-Bias Approach to Address Laboratory Studies [25] was used for articles with an exclusive ex vivo or in vitro design. Two reviewers (NC and TSC) conducted the assessments, and discussion resolved divergences. Details are reported in the Supplementary File S1.

2.12. Synthesis of the Results

Meta-analyses were conducted if at least three studies with similar comparisons reported the same outcomes. For dichotomous data (i.e., BOP), the primary measures of effect were risk ratios (RRs) and 95% confidence intervals (95% CI) [26]. The Stata 17.0 package® was used for the data analysis.

The estimate of variance between studies under the random-effects model requires better precision when the number of studies is very small. For this reason, the fixed-effect model and the inverse variance method were used to obtain pooled estimate rates. The I^2 statistics were calculated to describe the percentage of variation across studies due to heterogeneity rather than chance. The heterogeneity was categorized as follows: <30%, not significant; 30–50%, moderate; 51–75%, substantial, and 76–100%, considerable. Clinical and methodological heterogeneity was assessed by examining the characteristics of the studies, for example, the similarity between the characteristics of the participants, interventions, and outcomes as specified in the inclusion criteria.

2.13. Subgroup Analyses

If there were sufficient data, subgroup analysis was performed to explore the influence of study characteristics such as age, sex, type of cells, and smoking/vaping sessions/experimental conditions.

2.14. Sensitivity Analysis

An analysis was also conducted to assess whether the stratification of studies by design or risk of bias (i.e., overall low risk vs. high risk) yielded similar or different results.

2.15. Unit-of-Analysis Issues

If some of the included studies possessed data from repeated or paired observations on participants, which could lead to unit-of-analysis errors, the advice given in Section 9.3.4 of the Cochrane Handbook for Systematic Reviews of Interventions was followed [27].

Table 1. Characteristics of the observational studies.

Authors, Year (Country) Study Design	Total N of Participants (% male); N of Participants in Each Group Age (Years)	Outcome	Aim	Conclusion
Part A—Studies with Clinical Examination				
Al Aali et al., 2018 (Saudi Arabia) [28] Cross-sectional with clinical examination	92 (100) EC: 47, NS: 45 YA	BOP, PPD, biomarkers, X-rays	Compare clinical and X-rays peri-implant parameters and levels of TNF-a and IL-1b levels among ECS and NS	Clinical, microbiological, and radiographic peri-implant parameters are compromised among ECS.
Alazmi et al., 2021 (Saudi Arabia) [29] Cross-sectional with clinical examination	127 (72); ECS 63, NS 64 YA	Peri-implant CBL, PD, PI, BOP, X-rays, and self-reported OH status and practice	Assess peri-implant parameters at 8 years follow-up	Implants of ECS and NS exhibited clinical and radiographical status when at home OH practice was good.
Ali et al., 2022 (Kuwait) [30] Cross-sectional with clinical examination	75 (21); ECS 18, CS 19, NS 38 MA	PPD, PI, GI, CAL, MBL, IL, whole saliva	Compare the periodontal status and saliva, IL-15, and -18 levels among CS, ECS, NS	Clinically, CS and NS demonstrate similar periodontal statuses; IL and salivary parameters are more elevated in smokers.
AlQahtani et al., 2018 (Saudi Arabia) [31] Cross-sectional with clinical examination	160 (100); ECS: Age: 42 YA	BOP, PI, PPD, biomarkers	Compare clinical and radiographic peri-implant parameters and proinflammatory cytokine profile in	ECS and OS (waterpipe) users may be at risk of poor peri-implant health. Tobacco smoking is associated with poor peri-implant health.

			the peri-implant sulcular fluid among the groups	
AlQahtani et al., 2019 (Saudi Arabia) [32] Cross-sectional with clinical examination	137 (100); ECS: 34, CS: 35, OS: 33, NS: 35 YA	Cotinine levels at peri-implant BOP, PI, PD, biomarkers	Compare cotinine levels in the peri-implant sulcular fluid among the groups	Cotinine levels in the peri-implant sulcular fluid of cigarette and OS (waterpipe) smokers and electronic-cigarette users are comparable.
Alqahtani et al., 2022 (Saudi Arabia) [33] Cross-sectional with clinical examination	150 (12); ECS 50, CS 50, NS 50 YA	Community periodontal index treatment need	Evaluate the periodontal treatment needs among CS, ECS, and NS	CS require more complicated periodontal treatment compared to ECS.
ArRejaie et al., 2019 (Saudi Arabia) [34] Cross-sectional with clinical examination	95 (100); ECS: 31, CS: 32, NS: 32 YA	BOP, PI, PPD, CAL, MBL, biomarkers (MMP, IL), X-rays	Compare clinical and radiographic peri-implant parameters and biomarkers among CS, ECS, and NS	Peri-implant health was compromised among CS than ECS and NS. Increased levels of proinflammatory citokines were found in CS and ECS.
Bardellini et al., 2018 (Italy) [35] Prospective case-control	90 (71); FS: 45, EC: 45 MA	Oral mucosal lesions	To evaluate the prevalence and characteristics of OMLs in FS compared to ECS	No statistically significant differences regarding total prevalence of OMLs between FS and ECS. Nicotine stomatitis, hairy tongue, and angular cheilitis were significantly more common among ECS.
Binshabaib et al., 2019 (USA) [36] Cross-sectional with clinical examination	135 (92); CS: 46, ECS: 44, NS: 45 YA	BOP, PI, PPD, X-rays, biomarkers	Compare the clinical periodontal status and gingival crevicular fluid (GCF) cytokine profile among CS, ECS, and NS.	Periodontal status is poorer and GCF levels of proinflammatory cytokines are higher in CS compared with ECS and NS.

Dalrmyple et al., 2022 (Germany) [37] Pilot study—cross-sectional	33 (45); ECS 11, CS 11, NS 11	Breath odor	Determine differences in breath odor between ECS, CS, and NS	ECS breath has a reduced smoke odor and more pleasant aroma than CS, and is comparable to NS.
Ghazali et al., 2019 (Malasya) [38] Cross-sectional with clinical examination	135 (99); CS: 45, ECS: 45, NS: 45 EA, YA, MA	DMFT	Evaluate caries experience among CS, ECS, and NS	CS and ECS have potential detrimental effect on caries development.
Herndon et al., 2022 (USA) [39] Cross-sectional questionnaire with clinical examination	4544 (48); current ECS: 260 , no current ECS: 4284 EA, YA, MA, OA	Self-reported OH	Recall of ECS for HPV test	E-cigarette use increases the persistence of HPV infection.
Ibraheem et al., 2020 (Saudi Arabia) [40] Cross-sectional with clinical examination	120 (100); ECS: 30, CS:30, NS: 30, OS: 30 MA	BOP, PI, PPD, X-rays, NF-kappa B ligand	Compare the levels of receptor activator of NF-kappa B ligand (RANKL) and osteoprotegerin (OPG) in the GCF of the groups	CS and OS (waterpipe) and ECS usage is associated with an increased expression of RANKL and OPG in the GCF.
Javed et al., 2017 (USA) [41] Cross-sectional questionnaire and clinical examination	94 (100); ECS: 31, CS: 33, NS: 30 YA	Self-reported OH status PI, GI, PPD, CAL, biomarkers	Assess periodontal parameters and self-perceived OH	Periodontal inflammation and self-perceived OH are exacerbated in CSS compared with ECS and NS.
Jeong et al., 2020 (South Korea) [42]	13,551 (58); ECS: 222, NS: 8342, CS: 2330, FS: 2667 EA, YA, MA, OA	Self-reported OH status	Self-report periodontal status, community periodontal index	The results of the current study could motivate both ECS and CS to quit by highlighting the association of conventional cigarette smoking and

Cross-sectional questionnaire and clinical examination				electronic cigarette vaping with periodontal disease.
Karaaslan et al.2020 (Turkey) [43] Cross-sectional with clinical examination	57 (68); ECS: 19, CS: 19, FS: 19 YA	PI, GI, PD, CAL, MBL, biomarkers	Effects of smoking on oxidative stress markers, proinflammatory cytokines levels, and periodontal clinical parameters in patients with periodontitis	Vaping ECS and CS had the same unfavorable effects on the markers of oxidative stress and inflammatory cytokines.
Mokeem et al., 2018 (Saudi Arabia) [44] Cross-sectional with clinical examination	154 (100); CS: 39, OS: 40, ECS: 37, NS: 38 YA	PPD, PI, BOP, CAL, X-rays	Compare periodontal index and biomarkers among smokers and NS	Clinical and radiographic parameters of periodontal inflammation were poorer in CS and OS (waterpipe) than ECS and NS.
Tatullo et al., 2016 (Italy) [45] Cross-sectional questionnaire and clinical examination	110 (81) ECS: 110 (all former CS) YA	Self-reported need to smoke PI, BI,PBI	Verify the clinical variations of periodontal health induced by EC and investigate the awareness of ECS about their health variations and need to turn back to CS	E-cigarette can be considered as a valuable alternative to tobacco cigarettes, with a positive impact on periodontal and general health status.
Vohra et al., 2019 (USA) [46] Cross-sectional questionnaire and clinical examination	105 (100); CS: 28, ECS: 51, NS: 26 YA	Self-reported OH BOP, PI, PPD, CAL	Compare self-rated oral symptoms with periodontal status	Pain in teeth and gums is more often perceived by CS than ECS and NS. CS is more associated with increased PI and PD than is ECS.

Part B—without Clinical Examination

Authors, Year (Country)	**Total N of Participants (% Male);**	**Outcome**	**Aim**	**Conclusion**

	N of Participants in Each Group			
Study Design	**Age (Erce)**			
Akinkugbe 2019 (USA) [47] Cross-sectional questionnaire	13,650 (50); current ECS 418, current CS 634, Other 12,598 EA	Self-reported OH status and OH practice—PATH	Epidemiology of dental status of CS and ECS among adolescents	Dual users are associated with poor oral health outcomes.
Alade et al., 2022 (Nigeria) [48] Cross-sectional questionnaire	2870 (51); CS 378, ECS 167, DS 401, NS 1916 MC, EA, YA	Self-reported oral lesions	Effects on OH for different smokers who had COVID-19 infection	ECS had 1.5 times higher odds of reporting oral lesions than NS. Those who had COVID-19 infection had higher odds of gingivitis.
Alhajj et al., 2022 (Yemen) [49] Cross-sectional questionnaire	5676 (40); ECS 255, CS 596, DS 261, NS 4565 YA, MA	Self-reported OH status and OH practice	Assess self-reported OH practices and events in ECS	ECS reported more oral health-related conditions, particularly xerostomia and black tongue, and heart palpitation.
Alqobaly et al., 2022 (UK) [50] Cross-sectional questionnaire	8129 (48); erce data not applicable MA	Self-reported periodontal status	Assess self-reported periodontal disease in ECS	ECS use is associated with self-reported periodontal disease.
Atuegwu et al., 2019 (USA) [51] Cross-sectional questionnaire	32,320 (46), in 3 waves of survey; NS: 9632, regular ECS: 329, non regular ECS: 8298	New cases of gum disease in 12 months	Assess the association between ECS and PD	ECS may be harmful to OH.

	EA, YA, MA, OA			
Ho Cho et al., 2017 (South Korea) [52] Cross-sectional questionnaire	65,528 (52); ECS: 1556, Former ECS: 3848, Never ECS: 60,124 EA	Oral symptoms (Gingival pain/bleeding, tongue or cheek pain, cracked or broken teeth)	Assess the relationship between EC use and OH	ECS among adolescents may be a risk factor for tongue and/or inside-cheek pain and cracked or broken teeth.
Huilgol et al., 2019 (USA) [53] Cross-sectional questionnaire	456,343 (43); ECS: 15,019, Non ECS: 441,324 EA, YA, MA, OA	Self-reported poor OH symptoms	Assess the ECS use on OH	Daily use, but not intemittent use, of ECS was independently associated with poor OH.
Irusa el al; 2022 (USA) [54] Cross-sectional questionnaire	13,080 (48); ECS 136, Other 12,944 EY, YA, MA, OA	Caries risk	CAMBRA tool (the caries management from risk assessment)	ECS had higher caries risk than non-ECS.
Abafalvi et al., 2018 (Hungary) [55] Cross-sectional questionnaire	930 (83) ECS: 767, DS: 163 EA, YA, MA, OA	Self-reported oral hygiene practice	Assess self-reported oral hygiene practice among ECS and DS	Both groups showed inadequate oral hygiene practices.
Vemulapalli et al., 2021 (USA) [56] Cross-sectional questionnaire	4618 (48); EC: 247, FS: 700, NS: 3671, DS:120, Former DS: 561 EA, YA, MA	Untreated caries	Examine the association between ECS and untreated caries	Both ECS and DS are associated with an increased occurrence of untreated caries.
Vora et al., 2019 (USA) [57] Cross-sectional questionnaire	TOT: 32,300 (48) ECS: 97, NS: 9076, CS: 4231, FS: 14,115, OS: 4748 EA, YA, MA	Self-reported OH status	Evaluate self-reported gum disease among ECS and other types of smokers	Numerous tobacco use patterns were associated with worse periodontal health compared to NS.

Yoshioka et al., 2022 (Japan) [58] Cross-sectional questionnaire	TOT 10,439 (54) 1034 CS, 437 heated tobacco products, FS 1853, 1049 DS, NS 5796 EA, YA, MA, OA	Self-reported history of PDis	Compare self-reported periodontal disease among smokers and NS	All the smokers were significantly associated with a higher prevalence of periodontal diseases compared to NS.

EC: electronic cigarettes; ECS: electronic cigarettes smokers; CS: cigarettes smokers/cigarettes; DS: dual smokers; NS: non-smokers/never-smokers; FS: former smokers; OS: other type of smokers (waterpipe, cigars etc.); OH: oral health, PDis: periodontal disease; PPD: probing pocket depth; BOP: bleeding on probing; PI: plaque index; CAL: clinical attachment loss; GI: gingival index; SRP: scaling and root planning; GCF: gingival crevicular fluid; IL: inter leucine; CP: chronic periodontitis; NA: not available; FMUS: full-mouth ultrasonic scaling; PDT: photodynamic therapy; p-iM: implant mucositis; MD: mechanical debridement; MBL marginal bone loss; BI: bleeding index; PBI: papillary bleeding index; OMLs: oral mucosal lesions; MC = middle children; EA = early adolescents; YA = young adults; MA = middle adults; OA = older adults.

Table 2. Characteristics of interventional studies.

Authors, Year Country, Study Design	**Sample (%Male) Age Category**	**Outcome and Parameters**	**Aim**	**Conclusions**
Akram et al., 2021 (Australia) [59] Longitudinal, three observations: 3 m, 6 m	TOT: 60 (100) ECS: 30, CS: 30 YA, MA	PPD, BOP, CAL periodontal disease, biomarkers	Evaluate the periodontal parameters and MMP-8 and CTX in ECS and CS	CS showed an increased periodontal worsening compared to ECS.
Al Deeb et al., 2020 (Saudi Arabia) [60] Randomized controlled clinical trial 3 observations: BL, 2 w 12 w	TOT: 71 (100) ECS: 21, CS: 25, NS: 25 Age: YA	BOP, PPD, PI, biomarkers	Effectiveness of PDT AAOAN adjunctive therapeutic modality in the treatment of peri-implant mucositis for ECS and CS	PDT with adjunctive mechanical debridement reduced PI and PD, while increasing BOP, in addition to reducing pro-inflammatory biomarkers CS.
Al Hamoudi et al., 2020 (Saudi Arabia) [61] Longitudinal, two observations, BL, 3 m	TOT: 71 (88) ECS: 36 Age: 47 YA, MA	GI, PPD, CAL, X-rays, GCF, IL	Periodontal parameters pre-post SRP	Levels of GCF IL-4, IL-9, IL-10, and IL-13 increased following SRP in ECS and NS with CP; the anti-inflammatory effect of SRP was more profound in NS.

Al Harti. 2019 (Saudi Arabia) [62] Prospective	TOT: 89 (100) ECS: 28, CS: 30, NS: 31 Age: 34 YA	BOP, PI Percentage of CS and EC on periodontal tissues after FMUS		After FMUS, gingival inflammation is worse in CS compared with ECS and NS.
Alhumaidan et al., 2022 (Saudi Arabia) [63] Longitudinal, two observations BL, 3 m	TOT: 54 (67) ECS: 18, CS 18, NS 18 YA	CAL, Mt, PDis, PI, and MBL, percent vary cortisol	Evaluate salivary CL and IL-1β levels in light CS and ECS users before and after non-surgical periodontal therapy	In CS and ECS, users without Pdis, clinical periodontal parameters and whole-salivary CL and Il-1β levels remain unchanged after non-surgical periodontal therapy.
AlJasser et al., 2021 (Saudi Arabia) [64] Longitudinal, four observations BL, 3 m, 6 m, 12 m	TOT: 60 (52) ECS: 20, CS 20, NS 20 MA	BOP, PI, PD, IL	Compare changes in clinical periodontal parameters and changes in salivary IL between CS, ECS, NS after peri-implant treatment	Electronic cigarette smoking was found to be a mercentagelent risk indicator for peri-implantitis.
AlRifaiy et al., 2018 (Saudi Arabia) [65] Randomized controlled clinical trial 2 observations BL, 3 m	TOT: 38 (100) ECS with PDT: 20 ECS without PDT: 18 YA	BOP, PI, PrD, MBL	Effectiveness of antimicrobial therapy and PDT or erconly in ECS with p-iM	Antimicrobial PDT is more effective compared to MD alone in the treatment of p-iM in ECS.
Alshibani et al., 2022 (Saudi Arabia) [66] RCT	TOT: 23 ECS Age not reported	CAL, PI, BOP, PPD,	Assess the effect of non-surgical periodontal therapy with adjunct photodynamic treatment for the management of periodontal inflammation in ECS	Photodynamic treatment is as effective as non- surgical therapy for the management of periodontal inflammation in ECS.
Reuther et al., 2016 (UK) [67] Pilot clinical trial, two observations BL, 30 min	TOT: 10 volunteers who vaped EC specifically for the trial (70) YA	Blood flow in oral mucosa	Blood flow after vaping measured with Doppler laser	EC may have an effect on blood flow in the oral mucosa.

Wadia et al., 2016 (UK) [68] Pilot longitudinal, two observations BL, 2 w	TOT: 20 switchers from CS to ECS EA,YA, MA, OA	BOP and GCF parameters	Compare the gingival health of a group of switcherercentagementage of sites with BOP increased statistically significantly 2 weeks after the switch.	
Xu et al., 2021 (China) [69] Longitudinal, two observations BL, 6 m	TOT: 101 (71) ECS: 32, CS: 31, NS: 38 YA	PPD, BOP, CAL, saliva sample	Evaluate the adverse effects of vaping on periodontal health	Periodontal severity status after 6 months was significantly worse in CS and ECS than NS.
Pouly et al., 2022 (Switzerland) [70] Randomized controlled clinical trial 3 observations BL, 3 m, 6 m	TOT: 172 (81) CS: 84, DS: 17, HTP: 70, Other: 1 YA, MA, OA	PPD, BOP, CAL, GI, PI	PD after scaling and root planingin smokers who switched or did not to HTP.	Scaling and root planing improves the course of PD similarly in CS and HTP. The treatment may mask favorables Pdis changes in the switchers.

EC: electronic cigarettes; ECS: Electronic cigarettes smokers; CS: Cigarettes smokers/cigarettes; DS: dual smokes; NS: non-smokers/never-smokers; FS: former smokers; OS: other type of smokers (waterpipe, cigars etc.); HTTP: hetated tobacco smokers, OH: oral health, PDis: Periodontal disease; PPD: probing pocket depth; BOP: bleeding on probing, PI: plaque index; CAL: clinical attachment loss; GI: gingival index; SRP: scaling and root planning; GCF: gingival crevicular fluid; IL: inter leucine; CP: Chronic periodontitis; NA: not available; FMUS: full mouth ultrasonic scaling, PDT: photodynamic therapy, p-iM: implant mucositis; MD: mechanical debridement, MBL marginal bone loss CL: cortisol, BL: baseline, M: months, W: weeks, EA = early adolescents, YA = young adults, MA = middle adults, OA= older adults. .

Table 3. Characteristics of laboratory studies.

Authors, Year Country, Sub-Section	Cell line/Strain/Teeth/Sample	Outcome	Aim and Exposure	Conclusion
Alanazi et al., 2019 Canada [71] Oral Candida	Gingival epithelial cells	*C. albicans* activity	Impact on *C. albicans* growth and expression of different virulent genes Exp: ECS	EC may interact with *C. albicans* to promote their pathogenesis, which may increase the risk of oral candidiasis in e-cigarette users.
Alanzi et al., 2018 Canada [72] Periodontology	HGF	HGF proliferation, migration, and apoptosis	Effects on HGF Exp: ECS ± nicotine and CS	Exposure to CS and EC negatively modulates gingival fibroblast activities.

Aldakheel et al., 2020 Saudi Arabia [73] Periodontology	Subgingival oral biofilm sample from CS, ECS, NS	Quantity of pathogenic bacteria	Compare and quantify pathogenic bacteria from ECS, CS, NS, with and without periodontitis	Counts of periodontopathogen bacteria in the subgingival oral-biofilm are comparable among CS and ECS.
Alzoubi et al., 2020 Giordania [74] Oral microbioma	Nasal and oral swabs from ECS, CS, NS	Microbial profile from ECS, CS, NS	To examine the oral and nasal microbial profile and antibiotics susceptibility in the ECS, CS, NS	ECS might be less harmful to microbiota compared to CS.
Catala-Valentin et al., 2022 USA [75] Oral microbioma	S. sanguinis, S. gordonii, S. mutans	Bacterial growth	The effect on the growth of S. mutans, S. sanguis, S. gordonii the formation of biofilm, Exp: ECS	ECS exposure hinders S. sanguis and S. gordonii growth while enhancing biofilm formation, hydrophobicity, and attachment for S. mutans.
Catala-Valentin et al., 2022 USA [76] Oral microbioma	S. aureus	Bacterial growth and oral epithelial cells deregulation	S. aureus attachment to oral epithelial cells and bacterial biofilm formation Exp: ECS	ECS promote S. aureus colonization and modulate the oral inflammatory response, possibly promoting oral periodontitis and preneoplasia.
Chopyk et al., 2021 USA [77] Oral microbioma	Saliva, oral mucosa cells	Oral microbiome changes	Comparative analysis of the microbial community profiles Exp: ECS, NS	There are notable differences in the oral bacterial community composition and diversity in EC users as compared to the controls.
Cicho'nska et al., 2019 Poland [78] Other	Salivary sample from ECS, CS, NS	Chemical property of saliva	Asses if ECS have an influence on selected antibacterial properties of saliva	Saliva of ECS showed changes in antibacterial properties in comparison to the NS and CS.
Cicho'nska et al., 2021 Poland [79] Other	Salivary sample from ECS, CS, NS	Antioxidant capacity and nucleotide metabolites in saliva	Assess if ECS influence the antioxidant capacity of saliva	ECS affects antioxidant capacity of saliva to the same extent as CS, when comparing smokers to NS.

Cicho'nska et al., 2022 [80] Poland Other	Salivary sample from ECS, CS, NS	Physicochemical properties of saliva (pH, protein, calcium phosphates)	Assess the impact of ECS on selected physicochemical properties of saliva	Saliva of ECS presents changes in physicochemical composition in comparison to CS and NC; statistically significant differences were observed only in calcium concentration.
Cicho'nska et al., 2022 Poland [81] Oral microbioma	Buccal oral mucosa from ECS, CS, NS	Bacterial survival and growth	Observe if there were any changes in oral bacteria of ECS	ECS caused changes in oral bacteria compared to CS and NS, especially with respect to colonization of potentially pathogenic bacteria.
Cuadra et al., 2019 USA [82] Cariology	S. gordonii, S. intermedius, S. mitis, S. oralis	Bacterial survival and growth	Impact on survival and growth of OCS Exp: various ECs and CS aerosols	Flavorless EC aerosol (± nicotine) is less detrimental to the survival and growth of OCS than CS.
Fischman et al., 2020 USA [83] Cariology	S. gordonii, S. intermedius, S. mitis, S. oralis	Planktonic growth curves	Effect on the growth of OCS Exp: flavor and flavorless ECS	Flavored e-liquids are more detrimental to the growth of OCS than flavorless e-liquids.
Franco et al., 2016 Italy [84] Oral cancer	Cytologic exam from ECS, CS, NS	Oral cancer cytologic exam—scraping oral mucosa	Evaluate the safety of EC and to establish their role in the prevention of oral cancer	The use of ECS seems to be safe for oral cells and should be suggested as an aid to smoking cessation.
Ganesan et al., 2018 USA [85] Oral microbioma	Subgingival plaque	Biofilm architecture changes	Effects on the subgingival microbiome Exp: ECS	The study questions the safety of EC.
Guo et al., 2021 USA [86] Oral cancer	Buccal human cells	DNA damage	Evaluate the formation of apurinic/apyrimidinic (AP) sites EXP: ECS, CS, NS	Propylene glycol may inhibit bacteria in oral cells, resulting in reduced inflammation and related effects, and reduced AP site levels in ECS DNA.

Ji et al., 2019 USA [87] Other	Human oral keratinocytes	Gene changes	Impacts on the gene pathways of normal human oral keratinocytes Exp: ECS	EC aerosols upregulate the UPR pathway genes in human oral keratinocytes, as well as the induction of UPR response.
Kim et al., 2018 USA [88] Cariology	S. mutans	Microbial adhesion to enamel	Cariogenic potential Exp: EC aerosols with sweet flavors	Flavored EC products negatively affect teeth and pose a potential OH risk (similar properties of gelatinous sweets or acidic drinks).
Kamal et al., 2022 Egypt [89] Oral cancer	Saliva	IL, biomarkers	Evaluate the effect of vaping and cigarette smoking on IL and salivary growth factor compared to NS Exp: ECS, CS, NS	ECS have higher levels of inflammatory and cancer risk biomarkers than NS, but lower than CS.
Manyaga et al., 2021 USA [90] Oral cancer	Oral cancer cells	Cell viability	Effects on cisplatin resistance in head and neck cancer cells Exp: ECS	EC use might increase chemotherapy resistance.
Mokeem et al., 2018 Saudi Arabia [91] Oral Candida	Oral rinse from CS, ECS, waterpipe smokers, NS	Oral candida carriage from oral rinse culture	To compare oral Candida carriage among CS, ECS, waterpipe smokers, NS	Oral *C. albicans* carriage was significantly higher among smokers than NS.
Nelson et al., 2019 USA [92] Cariology	S. gordonii, S. mitis, S. oralis	Planktonic growth curves	Impact on growth of OCS Exp: ECS and CS	CS is more detrimental to the growth and biofilm formation of OCS than the use of flavorless EC aerosols or liquid ± nicotine.
Park et al., 2023 USA [93] Oral Microbioma	Sub-gengival plaque and saliva	Bacterial composition/diversity	Evaluate the microbiome and gingival inflammation Exp: ECS, NS	ECS can increase microbial dysbiosis that may lead to periodontal disease.
Rouabhia et al., 2020 Canada [94] Cariology	S. mutans	Bacterial growth and expression virulence genes	The effect on the growth of S. mutans, the formation of biofilm, and the expression of virulence genes	EC increased the growth of S. mutans and the expression of virulent genes and

			Exp: ECS	promoted the adhesion and formation of biofilms on teeth surfaces.
Rouabhia et al., 2016 Canada [95] Periodontology	Human gingival ephitelial cells	Cell modification and apoptotic activity	Effects on human gingival epithelial cells Exp: ECS	Exposure to e-cigarette vapor induced cell shape modification and increased LDH activity and mediated cell activity by promoting apoptosis (caspase-3).
Sancilio et al., 2016 Italy [96] Periodontology	HGF	HGF and ROS production	Effects on HGF Exp: ECS	There is a role for EC fluids in the pathogenesis of oral diseases, such as periodontitis.
Sancilio et al., 2017 Italy [97] Periodontology	HGF	HGF citotoxicity markers	Effects on HGF Exp: EC liquids (with and without nicotine)	EC liquids (with and without nicotine) trigger molecular and morphologic responses in oral fibroblasts.
Schwarzmeier et al., 2021 Brasil [98] Other	Exfoliative cytology of the tongue and the mouth from ECS, CS, NS, FS	Oral cells anomalies	To investigate cytogenetic and cytotoxic damage through the evaluation of micronuclei in the oral mucosa of ECS	The use of ECS and alcohol by former smokers can cause more damage to the cells of the oral mucosa compared to those who have not used ECS.
Shaikh et al., 2019 UK [99] Periodontology	Human gengival mucosa	Cell morphology alterations, healing process	Effects on the proliferation of normal and cancerous monolayer of human oral mucosa and oral wound healing Exp: EC liquid after short-term and medium-term exposure	Medium-term exposure to high concentrations of the EC liquid had cytotoxic effects on normal human oral fibroblasts and keratinocytes. The exposure prolonged the wound healing of NOF and OKF6 oral mucosa cells.
Sundar et al., 2016 USA [100] Periodontology	Human periodontal fibroblast	ROS presence	Mechanism of gingival epithelial inflammation and pro-senescence in human oral epithelial cells and periodontal ligament fibroblasts Exp: EC aerosols with flavorings	There is a pathologic role of EC aerosol and its flavoring to cells and tissues of the oral cavity.

Thomas et al., 2022 USA [101] Oral Microbioma	Subgengival plaque	Bacterial composition/diversity	Evaluate the microbiome in subjects with mild periodontitis Exp: ECS, CS, NS	ECS have a unique microbiome that seems healthier than CS, but not compared with NS.
Tishchenko et al., 2022 Ukraine [102] Oral Microbioma	Plaque from cervical region	Bacterial growth	Evaluate the changes of dental microbiocenosis among adolescents who use devices for heating tobacco products and vaping	ECS promotes opportunistic transient streptococci, while hindering resident plaque microflora.
Tommasi et al., 2019 USA [103] Oral cancer	Oral ephitelium	Gene transcript deregulation	Regulation of genes and associated molecular pathways, genome-wide, in oral cells Exp: ECS, CS, NS	There is a deregulation of critically important genes and associated molecular pathways in the oral epithelium of vapers that bears both resemblances and differences with that of smokers.
Tsai et al., 2020 USA [104] Oral cancer	Gingival and tongue squamous cell	Cell invasion and gene expression	impact on gingival squamous cell carcinoma invasion, RAGE expression, and the elaboration of pro-inflammatory molecules. Exp: ECS with flavor and nicotine	Electronic cigarette flavoring and nicotine orchestrate the differential regulation of oral squamous cell carcinoma (OSCC) cell invasion and inflammatory effects.
Vermehren et al., 2020 Germany [105] Periodontology	HGF	Metabolic activity of HGF	Compare the effects on HGF in terms of proliferation, metabolic activity, cell death, and formation of ROS. Exp: ECS and CS	Exposure of HGF to ECS does not seem to be as harmful as traditional CS.
Willershausen et al., 2014 Germany [106] Periodontology	HF	HFs proliferation	Influence on the viability and proliferation of human periodontal ligament fibroblasts Exp: different EC liquids	The proliferation rates of the cells incubated with nicotine or the various flavored liquids were reduced in comparison to those of the untreated control cells (not all reductions were statistically significant).

Zhao et al., 2019 USA [107] Other	Human premolars	Tooth discoloration	Effects on the color of enamel, dentin, and composite resin restorations, as well as the effects of whitening treatments Exp: ECS, CS, red wine, coffee, and soy sauce	Tooth discoloration associated with EC aerosol is minimal.
Morishita et al., 2022 Japan [108] Oral cancer	Oral mucosal cells	Gene mutations	Regulation of genes and associated molecular pathways, genome-wide, in oral cells Exp: HTP, CS	Heated tobacco products and CS had similar cytotoxic effects.
Uehara et al., 2023 Japan [109] Oral cancer	Human gingival cells	Gene deregulation	Gene mutation in human cells Exp: heated tobacco products, non- heated tobacco products	Long-term HTP stimulation affected the epithelial differentiation and keratinization of gingival epithelial cells.
Pagano et al., 2021 Italy [110] Other	HGF and keratinocytes	Cells alterations/biological effects	Effect on cell viability, morphology, migration, apoptosis, and cell cycle Exp: heated tobacco products	HTP extracts increased both cell viability and migration. No morphological alterations were observed. HTP may have clinical effects on oral cell populations.
Marinucci et al., 2022 Italy [111] Other	HGF and keratinocytes	Cells alterations/biological effects	Effect on cell viability, morphology, migration, apoptosis, cell cycle, and epithelial–mesenchymal transition Exp: heated tobacco products, CS, and EC	CS induced significant damage, EC did not result in morphological and functional alterations in vitro, and HTP mainly modified oral cell function.

ECS: electronic cigarette smoker/electronic cigarette smoke; CS: cigarettes smokers/cigarettes smoke; NS: non smoke aerosol; OH: oral health; OCS: oral commensal streptococci; HGF: human gingival fibroblasts; HF: human fibroblasts; ROS: reactive species oxygen; LDH: cytotoxicity markers; NOF: normal oral fibroblasts; HTP: heated tobacco products.

3. Results

3.1. Search

A total of 1104 articles were retrieved. Five additional articles were found via cross-referencing. After the removal of duplicates (n = 420), 689 papers were screened by title and abstract; the agreement between the two screeners was 95.72%, with a Cohen's Kappa score of 0.65 (SE = 0.05; $p < 0.01$). Finally, 96 papers were obtained in the full-text format. After full-text reading, 12 articles were excluded, as the inclusion criteria were unmet (Figure 1). All the included studies were published between 2014 and 2023. Every effort was made to obtain original data from the authors, when needed.

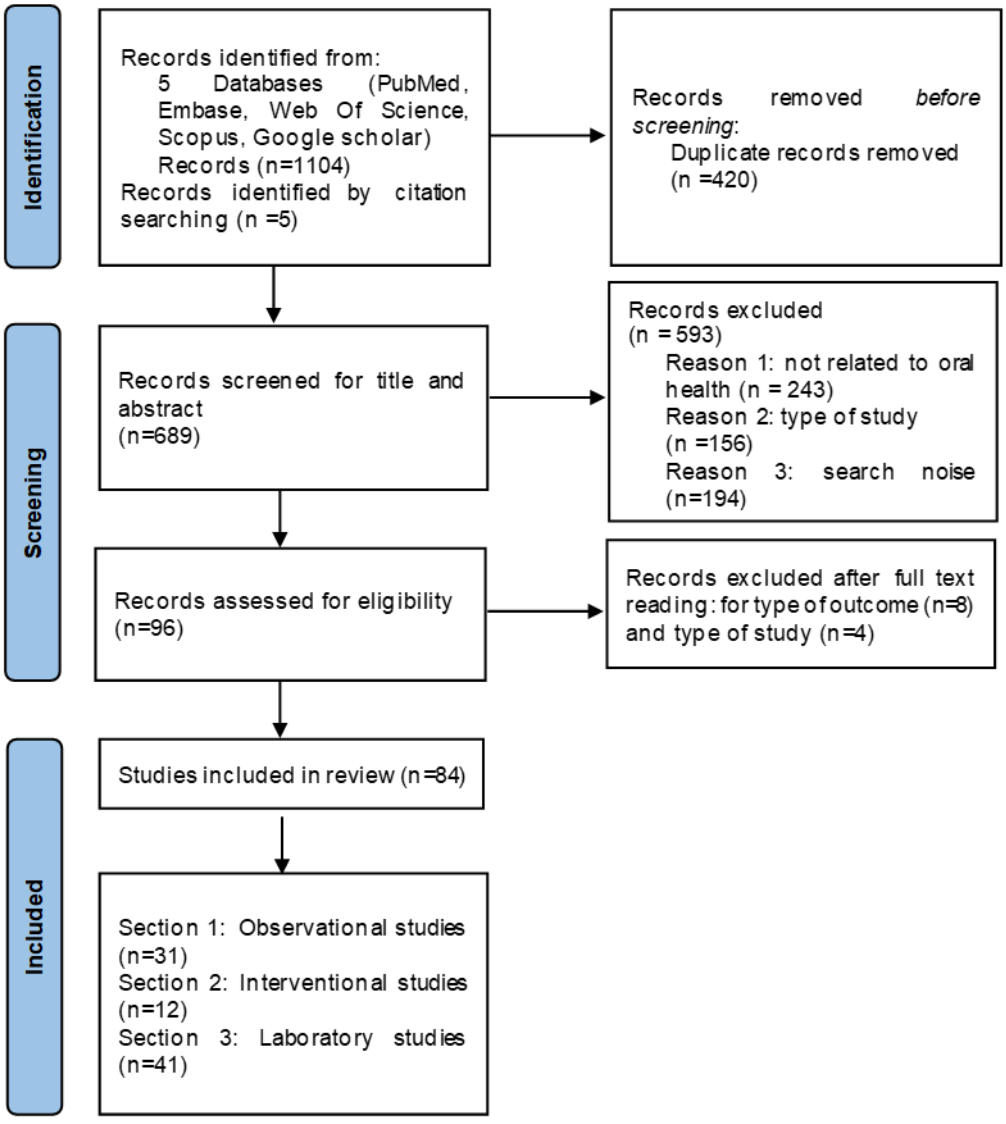

Figure 1. Prisma Flow Chart.

3.2. Observational Studies

3.2.1. Data Synthesis

A total of 31 studies were observational (Table 1): 10 were cross-sectional surveys using questionnaires (7 were self-administered, 2 were in-person/audio computer-assisted, and 1 was an interview) [41,45–50,53,57,58,112,113]; 6 studies included a cross-sectional observation with periodontal clinical examination (mainly BOP and other periodontal indicators) [30,33,36,40,43,44]; 5 studies focused on the previously mentioned

parameters, but were related to implants [28,29,32,34,46]; 5 studies included both a questionnaire and a clinical examination [38,42,56,57], and in 1 of these, the examination consisted of an oral HPV test [39]; 3 studies analyzed caries variables [43,51,54]; 1 study examined oral mucosal lesions , and the last evaluated breath odor [37].

All participants were adults (age > 18 years), except for five studies that included younger patients [39,47,48,54,114]. Age varied among the studies conducted using surveys, where children, early adolescents, young adults, middle adults, and older adults were questioned, and those using cross-section studies with clinical examinations, which were performed mainly on young adults and middle adults. Four studies included participants with systemic diseases [35,47,48,50], while all the others included only healthy participants. Additionally, in 13 studies, participants with recent dental treatments or pharmacological therapies were excluded (from 1 to 6 months before the clinical assessment).

Ten surveys included questions on socio-demographic status, self-perceived oral health and/or oral health practice [31,39,42,47,49,50,52,53,57,114]. Of these, six studies analyzed data from national surveys on smoking habits, with a sample size ranging from 4618 [51]to 456,343 subjects [45]. Another study was a national questionnaire survey about self-reported oral lesions that differentiated the type of smoking and even the differences among subjects infected by COVID-19 [48]. Different characteristics of ECS were described in two papers, which were both derived from the same questionnaire performed by the NIH in the USA between 2016 and 2018, called PATH (Population Assessment of Tobacco and Health). The first [112] focused on self-perceived oral health in the first wave of the PATH survey, while the second one [40]focused on new gingivitis cases before the third wave. A third study used the PATH survey from the 2013–2014 database and focused on adolescents' oral health and smoking status. Another study recalled ECS from the NHANES (National Health and Nutrition Examination Survey) performed in 2015–2016 and collected oral cells for HPV testing [39]. One study from a national Japanese survey considered HTP and periodontitis using two questions: if periodontal disease is present, and if it has been treated [58]. Several studies described data regarding the "smoking session", including duration and daily frequency. The effect of ENDS on periodontal parameters (i.e., BOP, PI, PPD, CAL) was examined in nine cross-sectional studies, while peri-implant parameters (i.e., BOP, PPD) were exanimated in five studies. From these 14 studies, 9 studies further analyzed salivary inflammatory biomarkers or receptors of crevicular fluid. The sample size ranged from 57 [61] to 160 subjects [31].

3.2.2. Risk of Bias across Studies

Most observational studies (87%) were rated with a moderate risk of bias (Supplementary File S1). The participant selection procedure was rated at a moderate risk of bias (68%) because a detailed history of smoking habits was not considered, which could have influenced the results.

3.2.3. Main Results of Included Studies

Vaping has been indicated to harm oral health, with a general decrease in self-perceived oral health status. In one study [45], the daily use of e-cigarettes was reported to be more detrimental than intermittent use. In contrast, in another study[56], its use was described as a valuable option for CS quitters, although it may be a risk factor for pain in the cheek and broken teeth [52]. Non-smokers, CS, and ECS with higher education level showed more knowledge and awareness regarding the potential negative effects of smoking on oral health [62].

Cross-sectional studies, including clinical examinations, compared ECS with CS, NS, and OS. Vaping is associated with unfavorable effects on periodontal and peri-implant parameters, causing an increase in inflammatory biomarkers/receptors, especially if compared with NS. The use of ENDS was associated with an increased expression of NF-kappa B ligand receptor activator and osteoprotegerin in the gingival crevicular fluid [69]. Both vapers and smokers exhibited unfavorable effects on oxidative stress markers and

inflammatory cytokines, such as GSHPx and 8-OHdG [61], even if worse results were reported in CS [89]. Moreover, one study reported a significant association between e-cigarette use and the presence of oral HPV-16 [39].

Two studies [43,51]concluded that both CS and ECS reflect a higher occurrence of untreated caries and a higher caries risk than do non-ECS [54]. In one study, statistically significant differences were found in oral mucosal lesion prevalence comparing ECS and FS [35], and in another study, ECS showed a 1.5 higher odds of reporting oral lesions than NS [48].

Female subjects accounted for 51% of the sample of survey-based cross-sectional studies, 17% of surveys that included a clinical evaluation, and only 7% of cross-sectional studies based on clinical evaluation.

3.2.4. Meta-Analysis

Meta-analyses of six studies [31,41,46,49,57,114] on self-perceived gingivitis were performed (Figure 2). The total number of subjects considered was 562.837. High heterogeneity was observed ($T^2 = 9.47$ $I^2 = 99.32\%$), and three papers described an association between self-reported gingivitis and ENDS use.

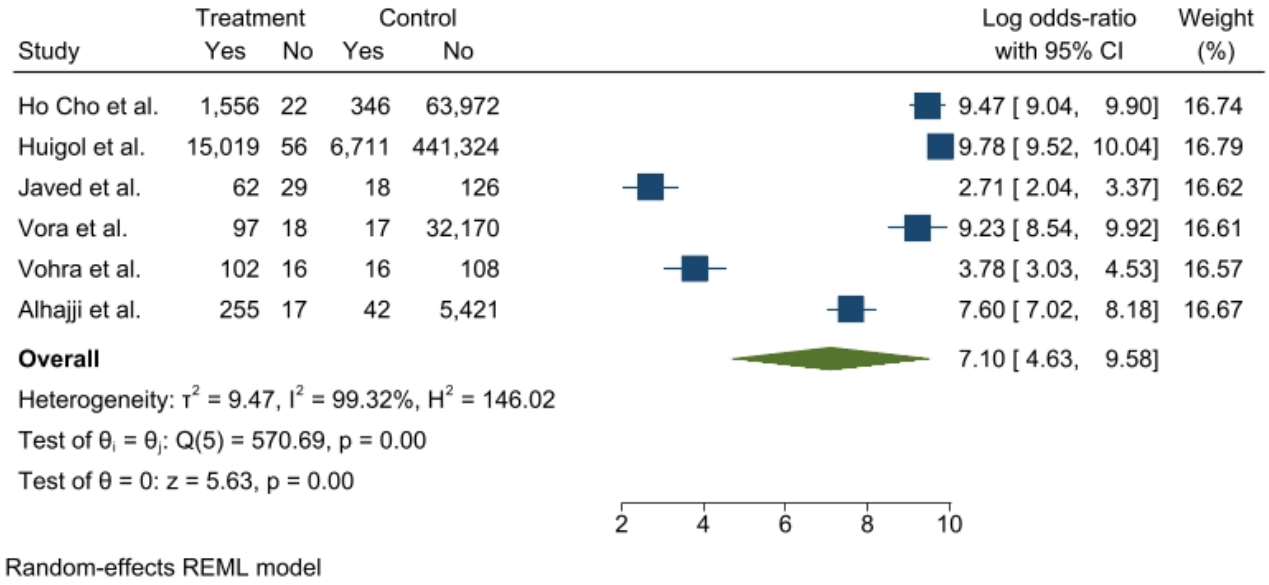

Figure 2. Forest plot of the included observational studies reporting self-perceived gingivitis (ECS = treatment, non-ECS = control) [31,41,46,49,57,114].

BOP was registered in three studies [40,41,57] including a total of 319 subjects; bleeding on probing was associated with ENDS (Figure 3), with a gain in high heterogeneity of $T^2 = 8.68$ $I^2 = 99.13\%$.

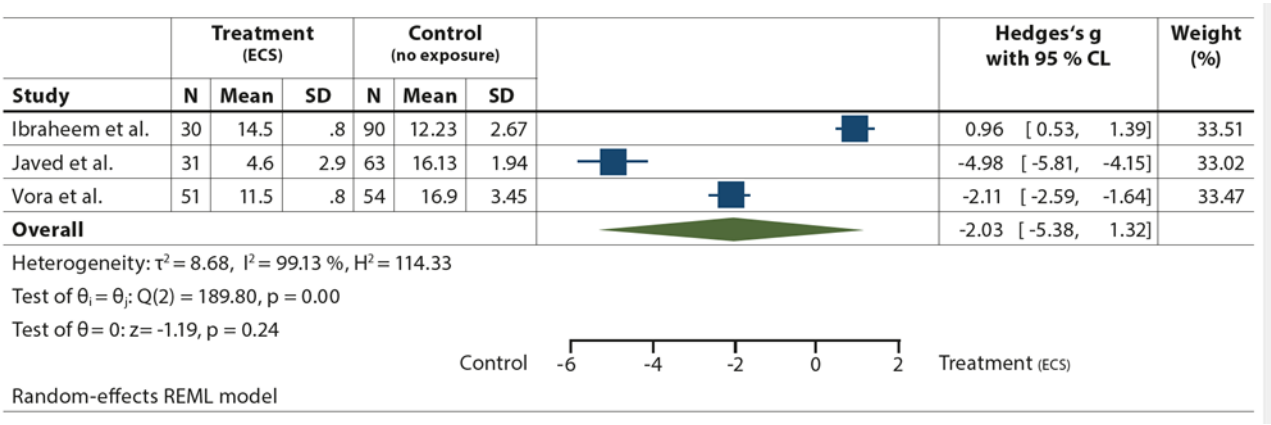

Figure 3. Forest plot of the included observational studies on BOP (ECS = treatment, Non-ECS = control) [40,41,57].

3.3. Interventional Studies

3.3.1. Data Synthesis

Twelve studies were included in this category [59,60,62,63,65–68,70]. All subjects enrolled were adults; sample sizes ranged from 10 to 172 (Table 2). The results of the age categories were as follows: 54% of the studies were conducted on young adults, 9% on average adults and young adults, 28% on both young and average adults, and finally, 9% included all age categories.

Five studies evaluated the effects of ENDS on periodontal parameters, investigating inflammatory markers [59,60,63–65]. Seven studies re-evaluated the periodontal or peri-implant parameters after a specific treatment [60,63,64,66,68,69,100]. One study [67] assessed the blood flow after vaping using a Doppler laser. The last study evaluated periodontal parameters in subjects that switched or did not switch from cigarettes to HTP [70]. Of the 772 subjects (the sum of participants in all these studies), 83% were male. In one study, including 20 subjects, the participant's sex was not specified [105].

3.3.2. Risk of Bias across Studies

Four studies [66,68,70,100] were RCTs and were rated with an overall "some concern" risk of bias, according to the ROB-2 tool (Supplementary File S1). The remaining eight studies [59,60,63–65,67,68] were assessed using ROBINS-I and evaluated with a moderate bias risk (Supplementary File S1).

3.3.3. Main Results of Included Studies

A worsening of the periodontal condition was observed, mainly in CS compared to ECS and NS. However, one study found that the severity of periodontal disease was significantly greater after 6 months of using both CS and ECS compared to NS [106]. In a sample of 20 former CS who switched to electronic cigarettes, the percentage of sites with BOP increased statistically after 2 weeks [105]. In the studies comparing different parameters after periodontal treatments, the results were as follows: scaling and root planning produced an anti-inflammatory effect more pronounced in NS than in ECS and CS [61]; photodynamic treatment is as effective as non-surgical therapy in the management of periodontal inflammation in ECS [66]; another study [68], which evaluated peri-implant sites, affirmed that photodynamic therapy with adjunctive mechanical debridement reduced PI and PPD, but an increase in BOP was still observed in both ECS and CS; ECS was considered a risk indicator for peri-implantitis [64]; finally, an antimicrobial treatment added to photodynamic therapy was more effective in ECS with peri-implantitis compared to the photodynamic therapy alone [100]. One study [70] compared switchers and non-switchers from CS to HTP using a multicenter design, and all the participants received a scaling and

root planning treatment that had a positive effect on periodontal health, but possibly obscured the beneficial effect of quitting CS.

Due to the heterogeneity of the studies, a meta-analysis could not be performed.

3.4. Laboratory Studies

3.4.1. Data Synthesis

Of the 41 included studies (Table 3), 8 evaluated the effect of ENDS on commensal bacteria growth or *Streptococcus mutans* adhesion to enamel [75,76,82,83,88,92,94,102]; 3 evaluated bacterial composition/diversity [87,95,97], 9 considered metabolic or morphological changes of gingival fibroblasts or gingival endothelial cells after ENDS exposure [71,87,88,95–97,99,100,105]; 6 studied the effect of ENDS on oral cancer cells or gene deregulation in oral epithelial cells [84,86,90,103,104]; and 11 evaluated the effects of vaping on heterogeneous outcomes: *C. albicans* growth, microbial community changes, gene pathways of normal human oral keratinocytes, and whitening effect on extracted teeth [44,71,73,78–80,85,98,103,104,107]. Four studies [108–111] evaluated the effect of HTP on human cells for biological and genetical alterations.

3.4.2. Risk of Bias across Studies

All the studies resulted in an overall "probably low" risk of bias.

3.4.3. Main Results of the Included Studies

Articles regarding the effects of ENDS on cariogenic bacteria [82,92,95] concluded that flavored liquids from e-cigarette are detrimental to oral health, and an effect on enamel similar to that of gelatinous sweets or acidic drinks has been speculated [72]. Studies concerning periodontal issues have considered human gingival fibroblasts, oral mucosa cells, or periodontium cells exposed to aerosols derived from electronic or conventional cigarettes, using unexposed cells as the control. ENDS with a longer exposure time and higher nicotine concentration induced a harmful modulation of cellular activities and promoted the expression of apoptotic and cytotoxic pathways. Exposure to e-vapors is not as harmful as exposure to cigarette smoking [44]. Studies investigating ENDS and oral cancer have been conducted on oral epithelial cells and concluded the following: ENDS increases the resistance to chemotherapy [90]; the use of e-cigarettes seems to be safe for oral cells and should be suggested as an aid to smoking cessation [84]; ENDS-exposed cells exhibit deregulation of critically important genes that could enhance cell invasion and inflammatory effects [74,85,89]; propylene glycol contained in EC liquid could inhibit bacterial-induced inflammation in the oral cavity and mask the reduced formation of apurinic/apyrimidinic (AP) sites, indicating DNA damage [86].

Similarly, two studies on HTP confirmed gene modifications when oral cells were exposed to HTP [108,109]. When compared to ECS and CS, HTP seems to modify oral cell function [111]. With respect to CS exposure, HTP was not associated with the apoptotic pathway, although clinical effects on oral cells could not be excluded [110]. Two studies analyzed the effects of vaping on oral candida, concluding that *C. albicans* carriage would be higher in ECS and CS than in NS [77,114]. No firm conclusions could be reached regarding oral microbial changes after vaping or smoking exposure: one study questioned the proper safety of electronic cigarettes [115], and another concluded that ENDS might be less harmful to the oral microbiota than conventional cigarettes because they did not reduce the carriage of methicillin-susceptible *Staphylococcus aureus* [32]; a similar conclusion was drawn from another study that affirmed that *S. aureus* is promoted by EC vapors, enhancing periodontitis [76]. One study[116] stated that there are significant differences in the composition and diversity of the oral bacterial community in ECS and NS, with a significant increase in *Veillonella* and *Haemophilu*s species in ECS, while another study pointed out that the microbiome of ECS with mild periodontitis seems healthier, but not compared to NS [101]; the possible dysbiosis of ECS may lead to periodontal disease [93].

Two other studies on oral bacterial growth in ECS stated that steam promotes streptococci in the oral biofilm [75,102].

3.4.4. Meta-Analysis

The meta-analysis was performed by combining data from four studies reporting the apoptosis rate of human gingival fibroblast after 24 h of exposure to e-cigarette vapor or air (i.e., no exposure), as shown in Figure 4 [72,95,97,105]. The number of independent repetitions under the same conditions was considered as a sample size. A high heterogeneity was observed ($T^2 = 8.10$ $I^2 = 91.50\%$).

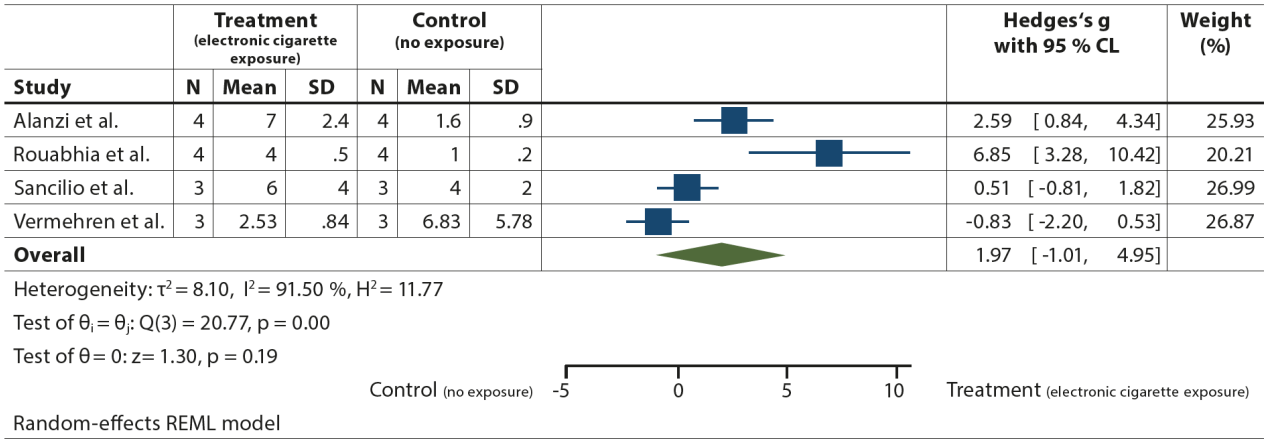

Figure 4. Apoptosis of human gingival fibroblasts after 24 h exposure to EC versus no exposure [72,95,97,105].

4. Discussion

The present review explored vaping and heat-related products concerning oral health, investigating the comprehensive effects of ENDS and HTP on different clinical and cellular variables and offering an overview of the current literature through observational, interventional, and laboratory studies. Other recent reviews [42,116,117] have focused only on periodontal parameters and revealed data consistent with those reported in the present study, underlying that the results must be considered with caution because of the heterogeneity of the articles and the scarcity of RCTs.

The cross-sectional studies based on surveys highlighted that the responders often need to be aware of the potentially harmful effects of alternative tobacco products [36,42,45,59]. This outcome underlines need for dental professionals to provide complete smoking counseling, which should become a routine practice. Nevertheless, these surveys were judged as having a high-moderate risk of bias. While the national surveys could investigate the younger population, the same cannot be said for clinical examinations, in which mainly adults were evaluated. In regards to waterpipe (the term includes narghile, hookah, shisha, and hubble-bubble) smokers, similar detrimental effects on oral health as to those noted for ENDS were found [31]. This last category seems quite challenging to study, as waterpipes are often used in social contexts, and daily use is rare, even if a substantial use, especially in Saudia Arabia, is reported [31]. Dual smokers and former smokers were studied only in observational studies, but no clear conclusions could be made regarding these categories, as the definition of how long a subject is considered a dual smoker or how much time should pass before being labeled as a former smoker are not uniform among studies. Few studies have been found dealing with HTP and oral health; this could have a country-specific explanation, as HTP is more widespread in Japan and the USA, but less so in Europe, where its use has recently increased [116].

Another finding of the review is that there is ahigh variability observed in laboratory studies: different results, cell lines, bacterial strains, and oral cancer cells were considered.

In any case, most of the cell line studies focused on human gingival fibroblasts, showing that e-liquids increased apoptosis and the appearance of necrosis biomarkers compared with those in unexposed cells [95,96,103]. Studies based on bacterial strains focused on commensal oral streptococci such as *S. mutans* [75,94]. It has been found that flavored e-liquids are often sweeter and stickier than unflavored ones, promoting bacterial adhesion and reducing normal commensal flora, with dysbiosis of the oral microbiome [82,83,94]. Regarding studies on oral cancer cells [108], conclusive hypotheses could not be drawn, since some papers suggested that ENDS and HTP might be possible alternatives to cigarette smoking. In contrast, other studies concluded that its effects are similar to those of conventional smoking [109–111].

The risk of bias assessment resulted in low risk. At the same time, the meta-analysis, although conducted on only a few studies, confirmed that electronic cigarette smoking may have a detrimental role for oral commensal bacteria.

A major limitation of this systematic review is the high heterogeneity among the studies, reflecting the lack of standardized study designs. Most studies compare ENDS or HTP with traditional cigarettes to determine whether vaping is safer/less harmful for oral health than is cigarette smoking [30,32,33,40,41,57,63]. However, the comparisons are often simplistic and the conclusions uncertain, as the content of e-liquids (nicotine percentage, flavorings, etc.) is profoundly different from that of conventional cigarettes. Moreover, the time of use of ENDS is very different from that of cigarettes, making it challenging to compare with the precise definitions of heavy and light smokers established for conventional cigarette smokers. A further limitation is the sex of subjects enrolled in the available studies. The surveys included samples of both sexes, but most of the enrolled e-cigarette users were female. In contrast, the studies that included clinical assessments and interventional studies were conducted almost entirely on males [59–62,65]. The question then arises regarding how the sex variable might have influenced the results and how the results obtained on male subjects may be extended to young women, who represent the majority of e-cigarette users in Western countries. In addition, many clinical studies performed on men were conducted in Saudi Arabia [31,33,48–50,59,60,63,64,66,89], where other smoking habits, such as the use of shisha and water pipes, are common and may have affected the results. Finally, the appearance of ENDS in the market has increased the number of dual smokers, which is a confounding factor that should be evaluated.

To overcome the above limitations and draw conclusions about the role of ENDS in oral health, further studies using standardized methodologies and taking into account all the specific details related to ENDS, such as the type of electronic cigarette, e-liquid composition, and time of use, are needed.

The main strength of this review is that it is the first, to the knowledge of the authors, to provide a broad overview of the effects of different e-cigarettes on oral health, including both clinical and self-assessment health studies, as well as in vitro studies, providing the reader with a complete picture of current knowledge.

5. Conclusions

ENDS vaping is a relatively recently introduced activity, and current investigations cannot provide sufficient evidence to confirm its effect on oral health; in fact, the findings from this review can only offer hypotheses on the harms of ENDS use. The self-perceived appearance of gingivitis and BOP noted by e-smokers cannot provide conclusive findings of ENDS use. In vitro studies show that electronic cigarettes containing nicotine appear to promote detrimental cellular pathways in human gingival fibroblast. Higher nicotine percentages and flavored e-liquids seem to have a detrimental effect on periodontal and peri-implant tissues through pathways similar to those of conventional cigarette smoke; these e-liquids may additionally represent a caries risk factor.

As a consequence of these findings, comprehensive vaping counseling should be provided to all smoking patients, investigating the type of habit in terms of duration, nicotine

percentage, and additional flavorings accessed. Particular attention should be paid to dual smokers.

In conclusion, both ENDS and HTP have a potential detrimental effect on periodontal and peri-implant parameters, and laboratory tests confirmed the presence of carcinogenic and inflammatory biomarkers. Flavored e-liquids may also be a caries risk factor. Research is necessary to assess the long-term effects of alternative tobacco products on oral health.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app13179654/s1, Supplementary Files for "Electronic Cigarettes: A Systematic Review for Dental Practitioners".

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Abbreviations

Acronyms	Terms
ENDS	electronic nicotine delivery systems
ECS	electronic cigarette smokers
HTP	heated tobacco products
CS	cigarettes smokers
NS	non-smokers
DS	dual smokers
OS	other smokers (waterpipe, shisha, etc.)
FS	former smokers

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