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REVIEWS

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Are e-cigarettes really a healthier alternative to smoking?

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary E-cigarettes emerged in the early 21st century as a safer health alternative to conventional cigarettes. E-cigarettes use e-liquids based on glycerine and propylene glycol. This results in smaller amounts of toxic substances in the aerosol they produce compared to traditional cigarettes. The rather short existence of such replacements does not make it clear whether they are actually better for smokers' health. The increasing number and younger age of smokers has prompted researchers to expand their research on the subject. A review of literature has shown that e-cigarettes affect many biochemical mechanisms, affecting the health of their users. They cause oxidative stress and, consequently, a cytotoxic effect; an increase in the production of mucins, taking part in lung diseases; affect the formation of DNA damage, carcinogenesis, sensitivity to chemotherapy, inflammatory response and disrupt cytokine levels in tissues. In addition, they cause thinning of the laryngeal mucosa, autophagy of middle ear epithelial cells, apoptosis of gingival fibroblasts, weakening of the tooth attachment apparatus and promote dental caries. It will take some time to test the theory of whether e-cigarettes are a healthier substitute for classic cigarettes, but based on current knowledge, one should be aware that these substances can cause adverse health effects.

Key words: vaping, electronic nicotine delivery systems, oxidative stress, carcinogenesis.

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Background

Interest in e-cigarettes

Recently, healthier alternatives have been sought for people addicted to tobacco, as it has been proven that conventional cigarettes are highly conducive to carcinogenesis [1]. E-cigarettes were invented in China in 2003. They were intended to provide smokers with the satisfaction of nicotine delivery without harmful health effects. At the beginning of the 21st century, their 'safe' substitute – e-cigarettes – emerged [2]. Currently, e-cigarettes are widely available. They are promoted as a safe replacement for cigarettes, but the problem is their very short duration of use. There are a small number of studies evaluating their safety. It will take many years to determine the effect of e-cigarettes on the development of cancer in humans [3, 4]. We already know that heating e-liquids releases carcinogenic formaldehydes, acetylaldehyde and acrolein [5, 6]. E-cigarettes, instead of fulfilling their primary function as a 'safer substitute', have begun to be used by previous non-smokers and increasingly younger people. E-cigarettes are now considered the tobacco product most commonly used by adolescents and young adults. Their availability is very high. The increasing use of e-cigarettes by the public and the unknown exact effects of smoking them have prompted researchers to check their safety [7, 8]. The first cases of head and neck cancer among people who do not smoke conventional cigarettes and do not chronically consume excessive amounts of alcohol, while being human papilloma virus negative (HPV-negative), are emerging. The only element that linked these cases was a history of smoking e-cigarettes. Two cases of squamous cell carcinoma of the tongue and one case of squamous cell carcinoma of the lower lip have been documented in individuals with a history of e-cigarette use [9, 10]. All of this prompted us to carry out a literature review examining the health impacts of e-cigarette consumption. To the best of our knowledge, this is the first comprehensive narrative review assessing the health effects of smoking e-cigarettes.

Composition of e-cigarettes

E-cigarettes deliver nicotine in aerosol form. It is dissolved in propylene glycol (PG) and vegetable glycerine (VG) [11]. Nicotine and these organic solvents, along with flavourings and other additives, form e-liquid [4]. E-cigarettes are made up of a battery, a cartridge containing e-liquid and an electronic heating atomiser. According to studies, e-cigarette aerosols generally contain fewer toxic components than conventional cigarette smoke [2], but the effects of smoking electronic cigarettes are still not as well studied as classic cigarettes.

Mechanisms of toxicity

Oxidative stress

Electronic cigarettes are poorly understood, but there is already scientific evidence pointing to their harmful effects on cells. In vitro studies have noted that e-cigarette aerosol induces oxidative stress with a decrease in antioxidant glutathione in a dose-dependent [12]. There is activation of oxidative stress response pathways. Secondary to an increase in the number of unfolded proteins in the endoplasmic reticulum is the attach-

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ment of these proteins to immunoglobulin heavy-chain binding protein (BIP) with subsequent up-regulation of activating transcription factor 4 (ATF4), C/EBP homologous protein (CHOP, a.k.a. DNA-damage-inducible transcript 3), X box binding protein 1 (XBP1) and inositol-requiring enzyme 1 alpha (IRE1α). ATF4 activates oxidative stress response genes, and at the same time, CHOP promotes apoptosis by inhibiting anti-apoptotic B-cell lymphoma 2 (BCL-2 protein). IRE1α protein also activates XBP1 with a subsequent increase in the expression of protein disulfide isomerase (PDI), which catalyses protein folding. These actions are designed to restore the homeostasis disrupted by the deleterious agent, and if this fails, there is a switch to the apoptosis pathway. There is activation of many other cellular pathways, i.e. the nuclear factor kappa-light-chain-enhancer of the activated B cell (NF-κB) pathway, interleukin-6 (IL-6), C-X-C chemokine motif ligand 8 (CXCL-8), interleukin-10 (Il-10) pathways, transforming growth factor-β (TGF-β) and the hepatocyte growth factor (HGF) pathway. TGF-β and HGF pathways are involved in processes related to cell growth and differentiation [13].

Increased TGF-β activity has been shown to cause metabolic dysfunction and promote epithelial-mesenchymal transition (EMT) and excessive deposition of the extracellular matrix, resulting in metabolic dysfunction, fibrosis and cancer [14]. TGF-β causes activation of the mothers against decapentaplegic (SMAD) pathway, which includes the mothers against decapentaplegic homolog 2 (Smad2) and mothers against decapentaplegic homolog 3 (Smad3) proteins, which play an important role in tissue fibrosis and cancer formation. Smad3 causes increased levels of thrombospondin 4 (TSP-4), which stimulates angiogenesis and thus facilitates tumour growth [15, 16]. The hepatocyte growth factor activates the c-mesenchymal-epithelial transition factor (c-MET) receptor. This causes changes in cell metabolism, stimulating glycolysis [17]. Activation of the HGF/c-MET pathway promotes tumour progression by stimulating proliferation, invasiveness and angiogenesis. It is often overactivated in head and neck cancers, and overexpression of MET is an adverse prognostic factor in them [18, 19].

Activation of the NF-κ, MAPK/ERK1/2 and p38 pathways results in the production of mucins through the production of the mucin-5AC (MUC5AC) protein. The increase in mucin production occurs independently of the presence of nicotine in the smoke [20, 21]. Propylene glycol in the aerosol is suspected to be responsible for these changes [22]. Mucins are produced by the airway epithelium. Unlike the mucin-5B (MUC5B) gene, which ensures adequate ciliary transport and removal of inhaled particles from the body, MUC5AC expression is regulated by inflammatory factors [23]. MUC5A results in a much more viscous secretion that becomes difficult to remove. Excessive production of mucus causes it to lodge in the airways [23]. Mucus that is impossible to remove is the cause of airway constriction, inflammation and a source of recurrent infections [24]. Mucins are involved in the pathogenesis of lung diseases, which are associated with bronchitis and are characterised by increased sputum production and are also related to airway epithelial remodelling, i.e. cup cell metaplasia, inflammation and mucus plugging [25]. Mucins have been proven to be increased in chronic obstructive pulmonary disease, cystic fibrosis and asthma [26–28].

Cytotoxic effect

A potential effect of oxidative stress is cytotoxicity. In vitro studies have shown that e-cigarette aerosols can cause cytotoxicity. Evidence from a study on nasopharyngeal mucosal tissue cultures indicates that e-liquids are cytotoxic and cause cellular DNA damage. Moreover, fruit-flavoured e-liquids are associated with a stronger cytotoxic effect compared to tobacco-flavoured e-liquids [12, 29]. The most likely factor for this phenomenon is flavouring compounds intended to mimic fruit flavours [30, 31].

It is worth pointing out that the cytotoxic effect of electronic cigarettes is considerably lower compared to traditional cigarettes. Anita R. Iskandar et al. observed that high concentrations of nicotine did not cause cell damage in buccal epithelial cell cultures, but there was a decrease in cell cilia motility [21].

However, the changes were much smaller than those observed in the group exposed to smoke from conventional cigarettes. Low cilia mobility leads to a decrease in mucus transport, resulting in mucus retention. This, in turn, leads to reduced elimination of inhaled particles, including microorganisms from the airways. This is the primary defence mechanism of the upper and lower respiratory tracts, and insufficient elimination of microorganisms results in an elevated risk of respiratory infections [32–34].

Inflammatory reaction

The use of e-cigarette smoke components disrupts the cytokine levels in the tissue. These components cause a statistically significant increase in pro-inflammatory interleukin-1α (IL-1α), tumour necrosis factor (TNF) and strongly chemotactic CXCL-8. There is an increase in the concentration of chemotactic granulocyte-macrophage growth factor (GM-CSF) and granulocyte growth factor (G-CSF), which are responsible for chemotaxis of neutrophils and macrophages [35]. At the same time, there is a decrease in interleukin-13 (IL-13), which plays a significant role in the T helper 2 (Th2) response, though with a simultaneous increase in interleukin-4 (IL-4) [19, 21, 36].

Th2 cells that secrete effector cytokines are mainly stimulated by interleukin 4. Based on the research where the influence of classic cigarettes on animals was tested, it can be concluded that cigarette smoking primarily promotes the Th2 type immune response, but nicotine may lead to the attenuation of the allergic reaction by reducing the Th2 response [37–39]. Mishra et al. proved that the application of nicotine to Brown Norway rats sensitised with allergens resulted in a downregulation of the expression of Th2-related chemokines and cytokines in the lungs, as well as inhibition of eosinophil migration [39].

It is suspected that the secretion of IL-1α may be a part of the mechanism that senses chromatin damage and promotes an inflammatory response, as well as a tissue repair in the tissues damaged by the e-cigarette smoke [40, 41]. Within the gingival tissues, inflammatory processes are also activated. Prostaglandin-E2 and cyclooxygenase-2 levels, as well as CXCL-8, were observed to increase [41]. Cyclooxygenase 2 (COX-2) is an enzyme that converts arachidonic acid into prostaglandins, including, for example, prostaglandin E2 (PGE2). This prostaglandin is a key mediator of inflammation and angiogenesis. Studies have shown that COX-2 can promote cell proliferation, as well as participate in cell apoptosis and the process of carcinogenesis [42, 43].

COX-2 overexpression also causes an increased inflammatory response of human gingival epithelial cells (HGSCs) and leads to the destruction of the connective tissue [44]. Oxidative stress, as well as the products of this process, which are aldehydes and proteins with a carbonyl group, activate the RAGE receptor (receptor for advanced glycation end products). This receptor is associated with immune and inflammatory diseases, which include, e.g., dental pulp inflammation and periodontitis. The increased activation of this receptor as a result of e-cigarette smoke was observed. The activation of the RAGE receptor causes an inflammatory response and DNA damage. This leads to the development of inflammatory diseases of the oral cavity and the accelerated aging of epithelial cells. It has been stated that e-cigarette smokers, compared to non-smokers, have an increased expression of RAGE. It was also noted that the nicotine metabolite (nornicotine) increases the expression of RAGE in the gums of smokers, which contributes to the induction of a pro-inflammatory reaction due to the secretion of cytokines and reactive oxygen species. This, in turn, affects the destruction of periodontal tissues. All this may result in poorer outcomes of periodontal treatment in smokers [45].

It was also found that e-cigarette vapour extracts induce the expression of CD11b and CD66b (factors affecting adhesion and

migration to the site of inflammation) in neutrophils isolated from the peripheral blood of healthy non-smokers. Moreover, e-cigarette extract stimulates the neutrophil matrix to release neutrophil elastase and metalloproteinase-9 [46].

Wu et al. proved in their research that exposure to e-liquids can lead to a condition of reduced immunity, and thus increased susceptibility to bacterial infections [47].

What is more, it was observed that exposure to e-cigarette vapour resulted in greater virulence of methicillin-resistant *Staphylococcus aureus*. It was concluded that e-liquids may contribute to the promotion of biofilm formation and cause changes in the surface charge of this bacterium, which may result in increased drug resistance [48]. This may suggest that the growth in the frequency of e-cigarette use may contribute to the increased virulence of bacteria and increase their resistance to drugs [47].

Carcinogenesis

Smoking e-cigarettes causes DNA damage [6]. Hyun-Wook Lee et al., in a study in mice, showed that after exposure to e-cigarette smoke, DNA-damaging agents are produced that induce O^6-methy l-deoxyguanosine and, to an even greater extent, cyclic *γ*-hydroxy-1,N2-propane-deoxyguanosine (*γ*-OH-PdG) in the lungs, bladder and heart [49]. Moon-shong Tang et al. showed that nicotine can induce these in cultured human bronchial and bladder epithelial cells [11]. In addition, by studying DNA repair by excision of nucleotides (NER) and DNA repair by excision of bases (BER) in lung tissues, they verified that the activity of these mechanisms is reduced in mice exposed to e-cigarette smoke. The levels of DNA repair proteins in the lungs are also reduced [49].

DNA strand breaks occur, including a particularly dangerous double strand break (DSB). Vicky Yu et al. found that in cells exposed to e-cigarette smoke, there is an increased tail length and number of foci of the DNA double-strand break marker (*γ*-H2AX) regardless of nicotine concentration [50]. Attempts to repair the damage often result in non-homologous splicing of chromosome ends, which can lead to karyotype abnormalities, gene inactivation or fusion genes [51].

Smoking e-cigarettes also promotes cancer by increasing the metabolism of benzo(a)pyrene to its carcinogenic metabolites. It has been proven that e-cigarette aerosol can increase the rate of metabolism of benzo(a)pyrene to genotoxic products. The authors found that e-cigarette aerosol appears to induce the activity of enzymes (CYP1A1 and 1B1) that contribute to the conversion of benzo(a)pyrene (BaP) into its genotoxic forms. Significantly, this is one of the first studies to suggest that e-cigarettes can affect carcinogenic processes in the context of the carcinogens present in tobacco [52].

The aerosol condensers of e-cigarettes (EACs) significantly increase the rate of metabolism of BaP to genotoxic products and also induce the expression of cytochrome P-450s, probably through activation of the aryl hydrocarbon receptor (AhR). AhR activation leads to the transcription of cytochrome 1A1 (CYP1A1) and CYP1B1, which, in turn, encode proteins that convert polycyclic aromatic hydrocarbons into genotoxic metabolites [52].

In e-cigarette users, exposure to e-liquids results in notable gene expression changes in the affected cells. The most frequently altered transcripts include those of cancer-related genes. E-cigarette smoking impacts the activation level of various signalling pathways within the cell. The Wnt/Ca2+ pathway, a less familiar pathway than the canonical Wnt/B-catenin pathway, is significantly suppressed under the influence of e-cigarette use. WNT5A protein functions as a ligand binding to the cell surface receptor. In this pathway, Ca2+ ions mediate instead of utilising B-catenin as an intracellular mediator. There is also activation of protein kinase C (PKC), which has important functions in the process of development, as well as other molecular effects. It has been observed to be suppressed in several types of tumours. However, in tongue squamous cell tumours, activating the Wnt/Ca2+/PKC pathway leads to an increased capacity of cells to migrate. Tumour-associated fibroblasts and endothelial cells generate WNT5A, and it is probable that they create a concentration gradient of WNT5A through chemotaxis, thereby boosting tumour invasion of nearby tissues. Activation of PKC is hypothesised to play a larger role than an increase in intracellular calcium levels in head and neck cancers. While the role of this signalling pathway is not yet well understood, down-regulation of the tumour suppressor genes neurogenic locus notch homolog protein 1 (NOTCH1) and hect domain and RCC1-like domain-containing protein 2 (HERC2) occurs, while up-regulation of BCL2-related athianogen 3 is implicated in tumorigenesis [53, 54].

The «Rho family GTPases signalling pathway» is dysregulated in both traditional cigarette and e-cigarette smokers. This pathway comprises a cluster of GTP-binding proteins that govern multiple functions in the cell, including apoptosis, transcriptional regulation and tumour formation while controlling neutrophil activation and phagocytosis. The chief function attributed to this pathway is organising the actin cytoskeleton, although it is suspected that this protein family may also play a part in DNA damage repair [55].

Development of cancer cell resistance to cisplatin treatment

Some of the individual components present in e-cigarette aerosols have been shown to reduce the sensitivity of cancer cells to chemotherapy; these include: nicotine and reactive oxygen species [56, 57]. Jimmy Manyanga et al. analysed the effect of e-cigarette exposure on the viability of head and neck squamous cell carcinoma cells after cisplatin treatment. Exposure to aerosol extracts from e-cigarettes led to a significant increase in the viability of head and neck squamous cell carcinoma cells after cisplatin treatment, regardless of whether the liquid contained nicotine or was nicotine-free. This study also demonstrated that the increase in viability of these cells was caused by an increase in cisplatin resistance induced by the presence of e-cigarette aerosol extracts. It was interesting to find that it was the non-nicotine-based mechanisms that predominated in the decrease in cell death [58].

A key role in the development of cisplatin resistance was played by reduced accumulation of the cytostatic in tumour cells. Responsible for this was a decrease in the mRNA expression of the copper transporter 1 (CTR1) transporter, responsible for cellular uptake of cisplatin, and a significant increase in the expression of ATPase copper-transporting alpha (ATP7A) and ATP-binding cassette transporter (ABC) family proteins: ABCG2, ABCA1, ABCC1 and ABCC2 [58].

Several studies have shown that transporters belonging to the ABCB, ABCC and ABCG subfamilies, such as: ABCB1 (P-gp), ABCC1 (multidrug resistance protein 1), ABCG2 (pathogenesis-related protein), are responsible for the development of multidrug resistance (MDR) [59–62]. These proteins often show increased expression within tumour-lesioned tissues. Their mechanism of action is based on an increase in the excretion of cytostatic drugs from tumour cells, resulting in a reduced drug concentration within pathological cells, leading to a reduction in the effectiveness of therapy [63]. The role of ABC transporters in the development of MDR is not limited to the mechanism described above. Modification of the distribution of ABC transporters to intracellular or extracellular compartments to enhance drug sequestration has also been observed, as well as their involvement in tumour cell proliferation, invasion and defence against regulatory anticancer pathways [64].

In a study by Ziya Salturk et al., a higher incidence of squamous cell metaplasia was found in the larynx of an animal model. However, the study group was too small to reach statistical significance [65].

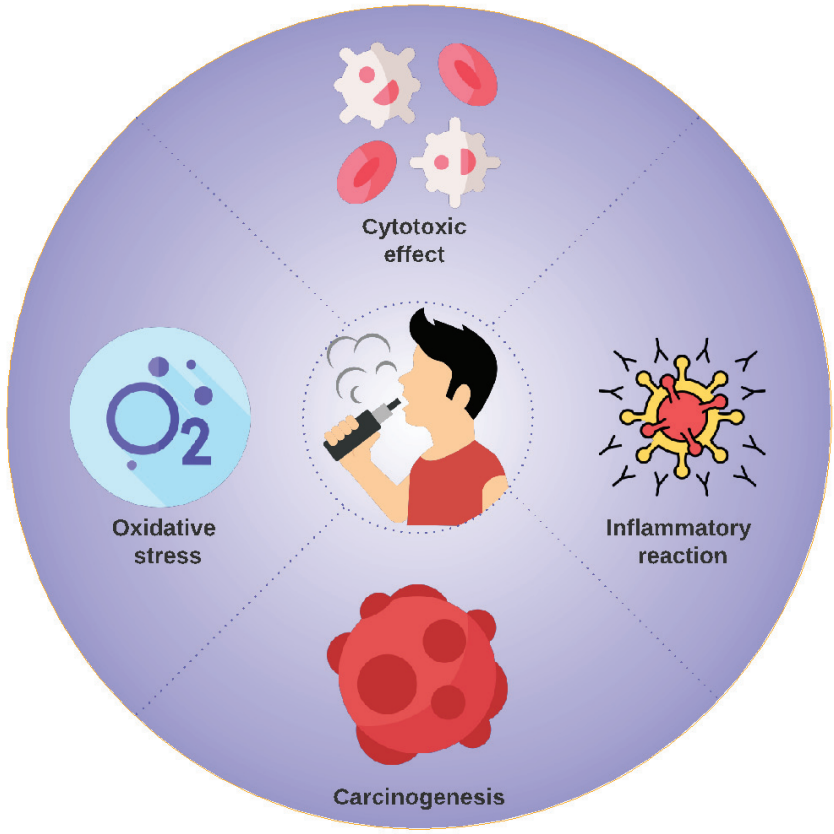

Figure 1. Summary of mechanisms of the action of e-cigarettes in vivo

Organ-specific effects of e-cigarette smoking

Larynx

The effects of e-cigarettes on the larynx are not well understood. Several studies have explored the impact of e-cigarette smoke on laryngeal cells. E-cigarette smoke components lead to damage of vocal fold fibroblasts, although to a lesser extent than traditional cigarettes. Cell viability is reduced to cytotoxic levels in the presence of e-cigarette smoke [66]. Histologically, components of e-cigarette smoke cause thinning of the mucosal layer. A decrease in cytokeratin 13 expression suggests damage to the basal layer. There is a decrease in cell adhesion, as indicated by the lowered levels of E-cadherin. Epithelial layers that come into direct contact with aerosol lose their structure and integrity. It has been demonstrated that exposure to e-cigarette smoke leads to an increase in mucin 1 (MUC1) gene expression and mucin production [67].

The inflammatory response to e-cigarette smoke is characterised by an increase in IL-4, a major component of the Th2-type inflammatory response, and a concomitant, although statistically insignificant, decrease in anti-inflammatory IL-10 [19]. Additionally, there is an upregulation of C-C motif chemokine 11 (CCL11) and IL-6, which stimulate eosinophil migration and may contribute to asthma exacerbations. At the same time, there is a decrease in the expression of the C-C motif chemokines (CCL) such as CCL5, CCL7, C-X3-C motif chemokine ligand 1 (CX3CL1), interleukin-23A (IL-23A), interleukin-21 (IL-21) and G-CSF, which are responsible for recruiting monocytes and neutrophils, consequently delaying the defence response to pathogens [67].

Middle ear

The middle ear is connected to the nasopharyngeal cavity by the Eustachian tube and is vulnerable to infection and contamination. E-liquids have a dose-dependent cytotoxic effect on middle ear epithelial cells [68, 69]. Tobacco-flavoured e-liquids are suspected to induce autophagy in middle ear epithelial cells by activating pathways associated with COX-2 [70] and MUC-5 activation. In the case of menthol flavour, cells enter the apoptosis pathway by activating the mucin 4 (MUC4) and aquaporin-4 (AQP4) gene and inactivating the epithelial sodium channel (EnaC) protein family [69]. These changes suggest an increased risk of developing otitis media in e-cigarette smokers. Tobacco-flavoured e-liquid increases the expression of CYP4F3, Interleukin 1 receptor-like 1 (IL-1RL1), COX-2 and CXCL-8, associated with inflammation, as well as genes associated with cancer and neuronal damage. In contrast, with menthol flavour, there was an upregulation of interleukin-24 (IL-24) and clusterin (CLU), associated with apoptosis, and CYP4F3, CCL26 and IL-1RL1, associated with inflammation. There was a down-regulation of the Cadherin 8 (CDH8) and Sidekick Cell Adhesion Molecule 2 (SDK2) genes, which are involved in cell adhesion and may promote cancer, as well as the immunity-related gene IFITM1 [70].

Periodontal diseases

Smoking conventional cigarettes has been linked to periodontal disease [71, 72]. The effect of e-cigarettes on this area is not yet well understood, but new evidence is emerging that points to the harmful effects of e-cigarettes. The components of e-cigarette smoke are cytotoxic and cause apoptosis of gingival fibroblasts [73, 74]. Collagen I production is reduced, which may lead to weakening of the tooth-attachment apparatus [74]. There is a significant increase in the inflammatory response under the influence of activation of RAGE receptors and increased production of PGE2 and CXCL-8. Under the influence of menthol, there is activation of transient receptor potential ankyrin 1 (TRPA1), which intensifies pro-inflammatory, pro-fibrotic and pro-carcinogenic reactions. Significantly, liquids with added flavours have a worse effect on gingival epithelial cells [45].

E-cigarettes cause dysregulation of oral bacterial flora. They cause inhibition of the growth of colonies of the commensal bacteria *Streptococcus sanguinis* and *Streptococcus gordonii*, while they have no inhibitory effect on *Streptococcus mutans*,

the bacterium best known for causing dental caries. In addition, e-cigarette aerosol, regardless of nicotine content, promotes biofilm formation by S. mutans. These changes may lead to oral imbalance and secondarily promote dental caries in e-cigarette users [75]. There is also the development of other potentially gingival pathogenic bacteria, including Veillonella and Porphyromonas, and increased susceptibility to periodontal disease [76].

Table 1. Pathophysiological effects of e-cigarettes on organs

Organ	Pathophysiological change
Larynx	Thinning of the mucous membrane
Middle ear	Autophagy of middle ear epithelial cells
Periodontium	Apoptosis of gingival fibroblasts, weakening of the tooth attachment apparatus, promote caries

Limitations of the study

The main limitation of this study is the lack of studies showing the long-term effects of e-cigarette use. Available studies include only in vivo studies. Despite thorough screening, we have been unable to find animal studies or human observational studies. This is insufficient for a full assessment of the problem. Therefore, this national review is based only on in vivo studies, which are not sufficient to carry out an accurate assessment of the effects of e-cigarettes on the human body.

We attempted to include all important studies in this study, although we may have missed some studies. This is another limitation of the study.

Conclusions

Recently, interest in e-cigarettes and the effects of smoking them has increased. Initially, as a replacement for conventional cigarettes, they were seen as safer measures. Currently, we do not have detailed studies about the consequences of their long-term use, but reports have begun to emerge about the increasing number of adverse effects of these substances. A review of literature has shown that e-cigarettes induce oxidative stress, which can result in cytotoxic effects; contribute to an increase in the production of mucins, which are involved in the pathogenesis of lung disease; disrupt cytokine levels in tissues, causing an inflammatory response; induce DNA damage; promote tumour formation and metastasis; and may reduce sensitivity to chemotherapy. A number of works have shown that for people who previously smoked classic cigarettes, e-cigarettes may be a better substitute, but this theory is still being tested. It is currently known that for non-smokers, reaching for these substances is combined with significantly adverse health effects.

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Conflicts of interest: The authors declare no conflicts of interest.

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