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Comparison impact of cigarettes and e-cigs as lung cancer risk inductor: a narrative review

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Abstract. – Smoking cigarettes contributes to lung cancer progression and the development of other respiratory diseases. E-cigs are increasingly being offered to mitigate the harmful effects of traditional cigarettes and eventually for smoke cessation. Because e-cigs do not burn tobacco, it stands to reason that vaping e-liquid is less harmful than inhaling cigarette smoke. This study critically assessed the underlying biological effects of cigarettes and e-cigs. We searched PubMed databases to elucidate the fundamental, potentially carcinogenic, molecular pathways and the possible effects of cigarettes and e-cigs products on lung cancer progression.

Cigarette smoke leads to chronic obstructive pulmonary disease (COPD), while e-cigs have contributed to lung injury. Cigarette smoke and e-cigs increase proinflammatory cytokine expression in cells and affect protein regulation, leading to an increased lung cancer risk.

E-cigs are quickly gaining popularity among consumers. Vaping-related diseases and deaths have attracted attention on a global scale. Excessive nicotine levels in e-liquid have the potential to cause severe toxicity, which can lead to neurological and brain damage and respiratory failure, as well as death. Thus, the toxic effects of e-cigs aerosol exposure are essentially identical to that caused by combustible cigarette smoking.

Key Words:
Apoptosis, Cigarette, e-Cigs, Inflammation, Lung cancer.

Introduction

The inhalation of cigarette smoke leads to the evolution of various diseases, including chronic obstructive pulmonary disease (COPD), cardiovascular diseases, and lung cancer. Currently, cigarette products are not only available in the form of conventional cigarettes (tobacco burning), but also as innovative new products based on electronic nicotine delivery systems (ENDs) or electronic cigarettes (e-Cigs) and e-cigs liquid (vape)[1,2].

Cigarettes are the best tool to deliver nicotine into the brain since they burn tobacco, so cigarettes can produce ultrafine particles that optimize nicotine absorption. However, the burning process also encourages the release of carcinogenic agents[3]. Cigarette tobacco is frequently polluted with various tumor-causing contaminants (e.g., cadmium, radioactive polonium, and mycotoxins). Furthermore, it includes toxic substances (e.g., tar, nitric oxide, alkaloids, carbon monoxide, hydrogen cyanide, and nitrosamine), which may have the most adverse consequences when smoked. Therefore, reduced tobacco consumption may eventually decrease exposure to carcinogenic chemicals and particles[4,5]. Thus, e-cigs were introduced in 2004 as an alternative for smokers and an effective method for quitting[6]. ENDs are reportedly tobacco products without combustion, nicotine and other ingredients are aerosolized before being inhaled. E-cigs create an aerosol by heating a liquid that consists of nicotine, flavoring agents, and propylene glycol or vegetable glycerine[7]. The absence of combustion significantly reduces the toxic exposure for e-cigs users compared to traditional cigarettes[8]. Thus, e-cigs were thought to be safer than inhaling cigarette smoke and will ultimately assist smokers in quitting[9], although their efficacy as a smoking cessation therapy has not been adequately demonstrated to date.

E-cigs may aid in smoking cessation, but their potential for harm must not be overlooked. Data

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on whether e-cigs are potentially hazardous are inconsistent due to differences in the model-established approach, dosage, and administration period. In comparative trials[10,11], e-cigs have cytotoxicity and activate the same signal pathways as regular cigarettes; this condition is called e-Cigs, or vaping, product use-associated lung injury (EVALI), but the additional proof is needed. As a result, a reference point must be established to investigate the safety of cigarettes and e-Cigs. Tobacco use can be addictive, and nicotine is a factor in cigarette addiction.

The rapid increase of e-cigs users as an option from conventional nicotine products demonstrates a dearth of research about the potential negative effects of e-cigs aerosols on lung function compared to conventional cigarettes. This review presents the current data (Figure 1) and continuing investigations into the oncogenic potential of e-cigs and cigarettes in this rapidly increasing field of scientific investigation, exposing crucial gaps in the understanding and areas that require more research.

This study critically assessed the fundamental, potentially carcinogenic, molecular pathways and the possible biological effects of cigarettes and e-cigs products on lung cancer progression. We compiled the results of numerous studies identified on Pubmed database using keywords, comparing the effects of e-cigs and cigarettes on lung function and looking at links between them. The keywords are "e-cigs", "cigarette", "cytotoxicity", "Inflammation", and "lung cancer". There were 573 individual results in the initial round. Some articles were eliminated by excluding *in vivo* studies, non-English studies, or comments on published works, reviews, meeting abstracts, and editorials. These led to the final product, which featured 30 main articles[10,42,43,45,48,67,79,80,84,90,92,96,97,105,107-110,117,118,129,130,133,137,140,141,149,150,151,155] (Figure 2). The bulk of publications explored the effect of cigarettes and e-cigs aerosols on cells, including inflammatory responses, viability cells, morphology cells, apoptosis, and necrosis. This review provides concrete evidence of e-cigs' and cigarettes' roles in terms of cell damage, signaling pathways, and their correlation to the progression of lung cancer.

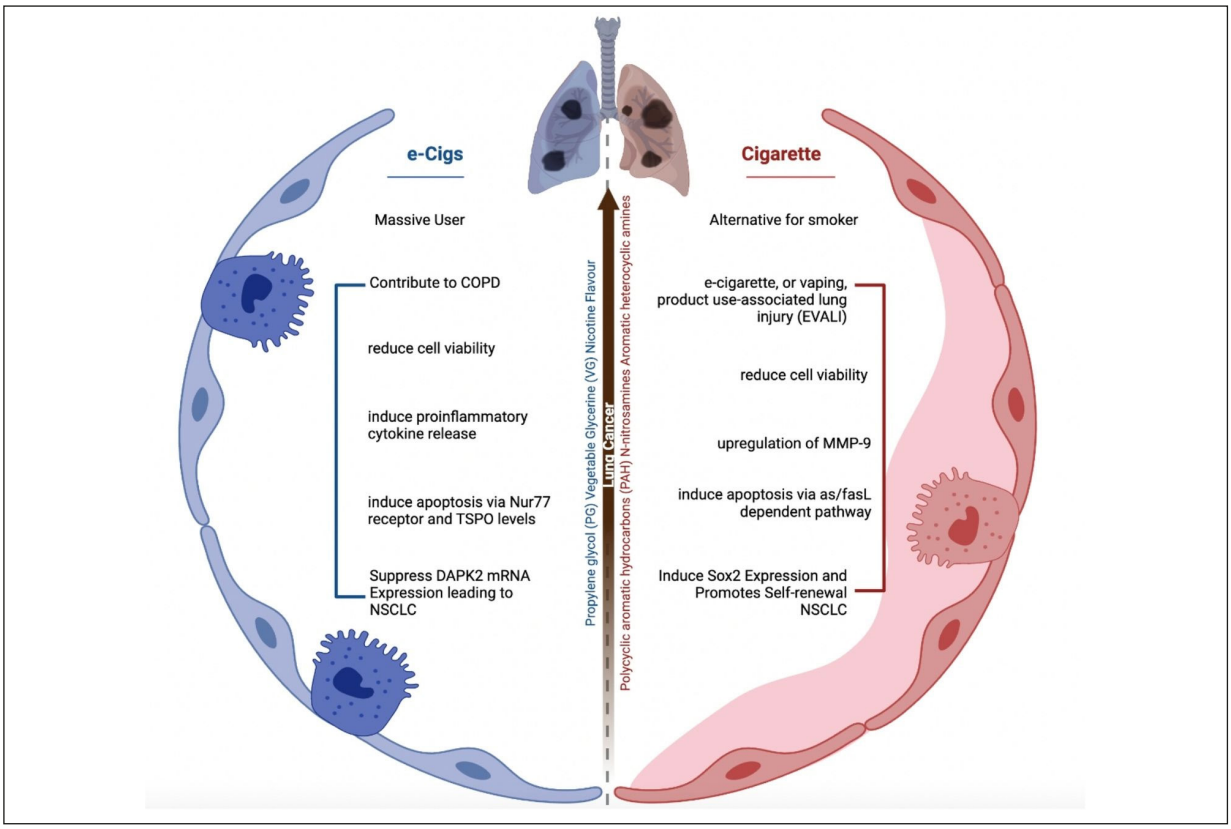

Figure 1. Comparison of the roles of e-cigs and Cigarettes in lung cancer progression. The diagram shows that cigarettes and e-cigs potentially increase the risk of lung cancer by their own pathway.

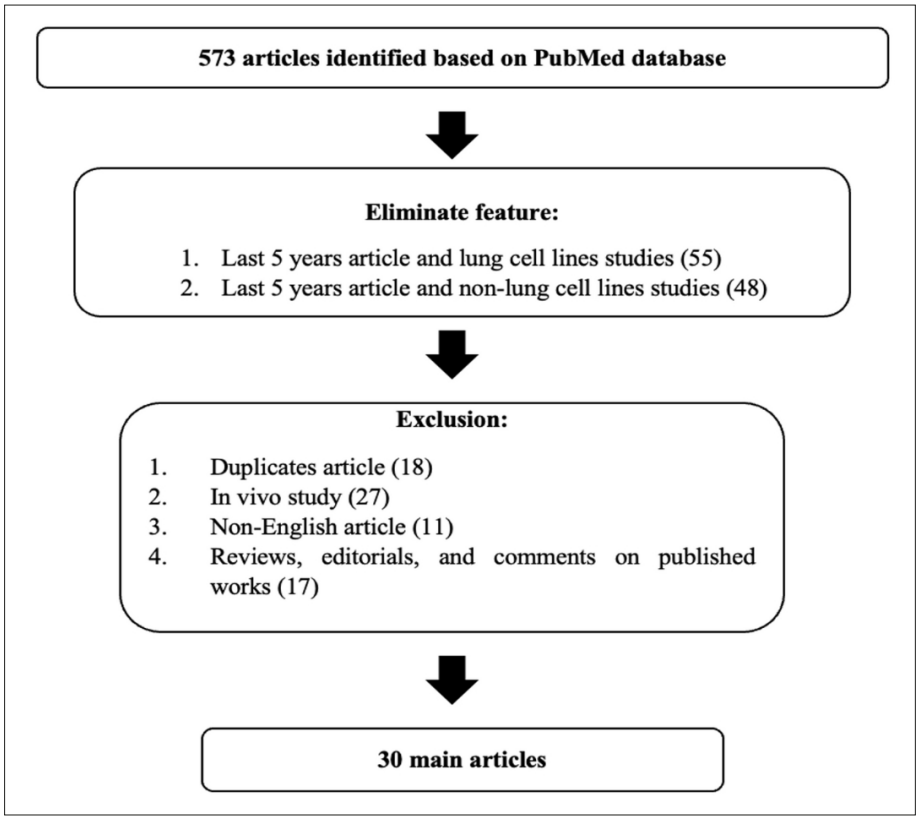

Figure 2. Flowchart of study selection.

How Cigarette and e-cigs Distribute Nicotine

Nicotine is the primary component of cigarettes and e-cigs, and most smokers require a particular level of nicotine to have a pleasurable sensation[12]. Nicotine acts as a neurotransmitter and is the primary source of nicotine dependence as an agonist of the nicotinic acetylcholine receptor (nAChR). The primary ligand-gated ion channel of each nAChR consists of five subunits found in both neurological and pulmonary systems[13]. Vertebrates have shown nine subunits (2-10) and three subunits (2-4). Different combinations of these subunits can result in various nAChRs[14]. Cigarettes are a highly effective method of administering the addictive substance nicotine. Cigarettes accomplish this by burning tobacco, which generates an aerosol of incredibly small particles that transports nicotine a long way into the lungs, where it is rapidly absorbed, and then swiftly moves through the left heart to the brain in a matter of seconds. Oxidizing agents, poisons, and carcinogens are produced during combustion[15,16].

E-cigs are designed to deliver nicotine in aerosols *via* inhalation, skin, mucosal membranes, cardiovascular system, and the digestive tract, and these are all effective routes of absorption for nicotine[17]. The first nicotine delivery systems at e-cigs devices were largely ineffective, due in part to the aerosol's enormous particle sizes that prevented it from reaching the deepest region of the lungs[18]. Newer models include rechargeable batteries and removable or refillable reservoirs that produce smaller particles and more effective nicotine delivery[19]. The e-cigs liquid, which comes in a wide variety of flavors and has varied nicotine concentrations, may be individually purchased using these refillable devices. In addition to increasing nicotine delivery, operating at a higher power (temperature) also increases the quantity of formaldehyde and other aldehydes that are created naturally when heating up propylene glycol or vegetable glycerine[20].

Compared to cigarettes, e-cigs produce aerosol by heating a liquid, often nicotine, vegetable glycerine or propylene glycol, and flavoring ingredients, without combustion[21,22]. The basic

component of an e-cigs is an atomizer, which heats a metal coil using battery power, aerosolizing an "e-liquid" by conducting it *via* a wick composed of cotton or silica and then releasing the aerosol. The coil is heated, and a plume of droplets is pulled out of the device, conveying aerosol into the oropharynx and respiratory system, resulting in high amounts of particle deposition with each puff[21,23].

E-cigs generally contain 3 mg to 36 mg of nicotine per milliliter, or 18 mM to 112 mM, of nicotine. To hasten and boost the transport of nicotine to the brain, the majority of current generations of e-cigs contain much more nicotine (up to 60 mg/ml), which is "roughly comparable to around 1 pack of cigarettes[24]". Nicotine levels in vapers were 50 μM every 30 minutes after starting to vape. The initial nicotine concentration seen by the lung is likely much higher and may even be in the millimolar range if it is identified after 30 minutes since nicotine is most likely absorbed by the epithelium in an exponential fashion[25]. The amount of nicotine that binds to plasma proteins is less than 5%, after entering the bloodstream. Nicotine is widely disseminated throughout the body's tissues, with an average steady-state volume of distribution that ranges from 2.2 to 4.2 L/kg[26]. Adipose tissue is less receptive to nicotine than the liver, kidney, spleen, lung tissues, brain, and other organs. Due to the overexpression of nicotinic cholinergic receptors in smokers' brains compared to non-smokers, nicotine has a greater receptor-binding capability in smokers[27].

Blood nicotine levels normally peak at 120 nM after smoking and vaping[28], and nicotine consumption affects lung homeostasis as well as acting to increase addiction in the brain. Nicotine stimulates the nAChRs in the lung when it is inhaled into the lungs. It has been demonstrated that nicotine inhibits the action of the cystic fibrosis transmembrane conductance regulator (CFTR), resulting in reduced Cl^- secretion, decreased ciliary beating, and decreased hydration of the airways[29,30]. Increases in cytoplasmic Ca^{2+} prevent CFTR from functioning[31]. This results in CFTR dephosphorylation and nicotine-dependent Ca^{2+} influx through nAChRs, likely suppressing CFTR by a similar process[32]. This also encourages chemokines, cytokines, and growth factors, which may induce lung injury[33].

Nicotine, when exposed to mice, resulted in decreased lung function, enlarged alveolar spaces, emphysema, and increased airway resistance[34]. Inflammation and oxidative stress are the main mechanisms governing nicotine-induced emphysema. Furthermore, nicotine consumption increases levels of pro-inflammatory cytokines (IL-6 and TNF-α), which increase lung damage[35]. Nicotine, along with substances like alcohol, cocaine, and amphetamine, promotes mesolimbic dopamine signaling by making the ventral tegmental area (VTA) dopamine cells more excitable when they pass the blood-brain barrier[36].

Nicotine alters dopamine neuron excitability through direct effects on dopamine cell bodies as well as changes in local GABAergic and glutamatergic transmission by binding with nAChRs expressed in VTA dopamine neurons as well as on local GABAergic interneurons and afferent terminals[37]. Chronic nicotine use is linked to a lower dopaminergic state than acute exposure. Chronic nicotine exposure reduces VTA dopamine cell activity, dopamine release, and extracellular dopamine levels in human smokers. These deficiencies in dopamine transmission are assumed to be responsible for the symptoms of nicotine withdrawal, such as low mood, reduced alertness, and sleep difficulties, as well as diminished brain reward function[38]. Additionally, to its effects on the central nervous system, nicotine also significantly affects the parasympathetic nervous system, causing changes in body temperature and increased movement[39]. Thus, nicotine inhaled from any source results in considerable cellular neuronal alteration.

Cigarette and e-cigs Chemical Composition Affects Cell Viability

One Numerous factors have contributed to cigarette smoking cytotoxicity. Multiple studies (Table I) on diverse cell types have examined the impact of nicotine on numerous cellular physiological activities, among others. Despite significant investigations into the hazards of smoking cigarettes, the adverse effects of vaping are unclear. According to a new study[40], e-cigs and e-liquid flavorings produce toxicity and induce an inflammatory response and oxidative stress in lung epithelial cells. Aerosols with ENDs from a popular device induce the release of inflammatory cytokines[41].

Cell viability was determined after aerosol exposure by counting the number of living cells and measuring intracellular adenosine triphosphate (ATP) concentrations[42]. Exposure to cigarette smoke extract (CSE) for 24 h dramatically reduced cell (human bronchial epithelium cell) viabi-

Table I. Studies investigating cigarette and e-cigs chemical composition and their effects on cell.

Type	Chemical Composition	Key Finding	Cell Type	Study
Cigarettes	• Polycyclic aromatic hydrocarbons (PAHs),	Reduce viability	Human bronchial epithelium cell line BEAS-2B	Wang et al[10] Sohal et al[43] Wang et al[97]
			Human bronchial epithelium cell line NCI-H292	Herr et al[149]
	• N-nitrosamines,		Human bronchial epithelium cell line 16HBE	Zhang et al[105]
	• Aromatic heterocyclic amines		Human alveolar epithelial	Jain et al[110]
			Human alveolar macrophages	Scott et al[84]
			Human umbilical vein endothelial cells	Giebe et al[90]
		Induced necrotic and contributed to pyroptosis	Human bronchial epithelium cell line 16HBE	Zhang et al[105]
		Induce apoptosis; induce autophagy	Human middle ear epithelial cell	Go et al[79]
			Human bronchial epithelium cell line NCI-H292	Herr et al[149]
			Human alveolar macrophages	Scott et al[84]
		Increase acidification rate	Human bronchial epithelium cell line BEAS-2B	Sohal et al[43]
		Reduce wound healing	Human umbilical vein endothelial cell	Giebe et al[90]
			Non-small cell lung cancer	Zeineh et al[67]
		Induced inflammation; Increase cytokine release	Human bronchial epithelium cell line NCI-H292	Herr et al[149]
			Human alveolar macrophages	Scott et al[84]
			Human alveolar epithelial	Jain et al[110]
			Human bronchial epithelium cell line BEAS-2B	Dusautoir et al[42]
		Reduce protein expression	Non-small cell lung cancer	Jin et al[92]
		Induce oxidative stress; induce mitochondrial damage	Non-small cell lung cancer	Zeineh et a[l67]
			Human lung adenocarcinoma cell	Di vicenzo et al[117]
e-cigs	• Propylene glycol (PG),	Reduce cell viability	Human bronchial epithelium cell line BEAS-2B	Dusautoir et al[42] Sohal et al[43] Lamb et al[80]
	• Vegetable Glycerine (VG)		Human umbilical vein endothelial cell	Bhozilova et al[150]
	• Nicotine,		Human iPS cell	Bengalli et al et al[45]
	• Flavour	Increase acidification rate	Human bronchial epithelium cell line BEAS-2B	Sohal et al[43,80]
		Reduce wound healing; effect cells shape;	Human gingival fibroblast cell	Alanazi et al[48]
		and proliferation;	Human umbilical vein endothelial cell	Giebe et al[90]
		Induced inflammation; increased cytokine production	THP-1 line	
			Human bronchial epithelium cell line 16HBE	Escobar et al[96] O'Farrell et al[129]
			Human bronchial epithelium cell line BEAS-2B	Wang et al[97]
		Induced apoptotic cells; increased efferocytosis	Human bronchial epithelium cell line 16HBE	Ween et al[151]
			THP-1 line	Ween et al[155]
		Induced DNA damage; inhibits DNA repairs	Human bronchial epithelium cell line BEAS-2B	Rankin et al[130]
			Human lung adenocarcinoma cell	Rankin et al[130]
		Promote self-renewal lung cancer cells	Human lung adenocarcinoma cell	Rigg et al[137]
			Non-small cell lung cancer	Schaal et al[140]

lity and increased lactate dehydrogenase (LDH) release[43,44]. The toxicity of e-cigs was equivalent to reduced cell viability. This may cause by e-cigs contained-nicotine-induced metabolic disturbance, indicating the possibility of developmental harm at dosages lower than those affecting cell survival[45]. Under acute exposure conditions, this impact may result from a change in the expression of tight junction and cytoskeletal actin rearrangement, ultimately resulting in increased epithelial permeability[46].

The smoke of e-cigs that directly exposes lung cells demonstrated a stress phenotype, reduced cell viability and density, and changed cell

morphology[47]. Recent studies[48,49] indicated that exposure of human gingival fibroblasts to CSE and e-cigs aerosols altered cell shape and growth. However, CSE showed more severe effects than those observed in e-cigs aerosols. These findings corroborated previous research[50] demonstrating that e-cigs aerosols affected lower cell viability and oxidative damage than cigarette smoke. However, it is essential to note that both e-cigs and cigarettes have affected cell viability adversely.

Furthermore, cell shape was altered drastically after 24 h of CSE treatment. CSE exposure resulted in an epithelial cell-like shapeshift, decreased cell density, and decreased cell-cell interactions. In contrast, e-cigs-treated cells retained their usual morphology. These findings indicated that CSE was more cytotoxic to lung epithelial cells than e-cigs after 24 h acute exposure[10].

Cigarette Smoke Promotes Apoptotic Cell Signalling Through Nuclear Receptor (Nur77)

CSE decreased cell viability and increased apoptosis cells are critical during lung injury. Apoptotic cells increased in lung epithelial cells within CSE concentrations of 10 μg/ml[51]. CSE significantly reduced the protein expression of pro-caspase-3 and Bcl-2 but increased cleaved caspase-3, cleaved poly adenosine diphosphate (ADP-ribose) polymerase, and Bax[51-54]. CSE and e-cigs vapor increased apoptosis, even in the absence of nicotine in e-cigs vapor condensate[48]. Furthermore, flavored e-cigs vapor, damaged cell viability and led to cell death[49].

CSE can promote the overexpression of proinflammatory cytokines and activation of necrotic and apoptotic signaling pathways in mammalian cell cultures in reaction to oxidative stress[30]. CSE-induced oxidative stress triggers caspase-mediated apoptotic pathways[55]. Nicotine caspase-mediated apoptosis inhibits the phosphatidylinositol 3-kinase/Akt signaling pathway, promoting cell survival and proliferation[56]. Cigarette smoke produces oxidation, leading to apoptosis, whereas nicotine upregulates Akt protein, resulting in the phosphorylation of downstream substrates that enhance cell survival and tumor growth[57].

Nicotine, a component of tobacco, promotes nuclear receptor 77 (Nur77) expression in human lung cancer cells[58]. CSE strengthened the interaction between Nur77 and Bcl-2. CSE promoted Beclin-1 separation from Bcl-2, increasing autophagy[59]. Proapoptotic and antiapoptotic Bcl-2 family proteins share a domain called the Bcl-2 homology 3 (BH3) motif, which is involved in apoptosis regulation[60,61]. The orphan nuclear receptor Nur77 is primarily a transcription factor that regulates the expression of numerous genes in the nucleus. Nur77 is a nucleoprotein that translocates from the nucleus to the cytoplasm to exert biological effects[62]. Nur77 is required for inflammation and cancer cell proliferation, differentiation, and apoptosis[63].

Nur77, *via* its ligand-binding site, interacts with the Bcl-2 homology 3 (BH3) (Bcl-2 family proteins) peptide-binding crevice and turns antiapoptotic proteins into proapoptotic proteins. The Bcl-2 family of proteins plays a critical role in regulating programmed cell death[64]. Previously, Nur77 interacted with Bcl-2 (Figure 3B) and might switch the function of Bcl from protective to pro-death; moreover, certain stimuli could control the interaction of Nur77 and Bcl-2 to trigger cell apoptosis. Nur77 expression is increased in pulmonary tissue and cells exposed to CSE, and Nur77 induces autophagy by binding to Bcl-2 and decreasing the affinity of Beclin-1 for Bcl-2. The proapoptotic Bax-like subfamily causes cell death *via* the caspase cascade by creating holes in the mitochondrial outer membrane and controlling mitochondrial cytochrome c release. Antiapoptotic proteins, through its BH3 domain, the BH3-only protein BAD interacts with Bcl-2 family proteins and possesses a transmembrane Bcl-2 homology domain that localizes them to the mitochondrial membrane[59].

Exposure to CSE affects the expression of 18 kDa translocator protein (TSPO) and is associated with mitochondrial/cellular functions. One critical function of TSPO is its involvement in programmed cell death and other cellular activities[65]. Additionally, TSPO regulates mitochondrial membrane potential and reactive oxygen species (ROS) production (Figure 3B). Excessive activation of TSPO *via* these mechanisms finally results in cell death[66]. The activities of TSPO are described as time-dependent in the presence of CSE. CSE exposure for 30, 60, and 120 min showed increased cell death levels by 19%, 42%, and 76%, respectively. Similarly, additional TSPO-related activities include ATP synthase activity (ADP/ATP ratio), cardiolipin peroxidation, mitochondrial membrane potential collapse, cell death (mainly apoptosis and necrosis), and cyclic adenosine monophosphate (cAMP) levels, all found to be time-dependently sensitive to CSE exposure[67].

CSE operates similarly to synthetic ligands in activating TSPO. Stimulation of TSPO reverses the ATP synthase proton pump in the inner mitochondrial membrane, resulting in oxidative stress and ROS generation, resulting in cardiolipin peroxidation-associated cytochrome c binding and release. Simultaneously with cardiolipin peroxidation, an increase in ROS results in changes to the mitochondrial permeability transition pore and Ca^{2+} efflux into the cytosol[68-70]. After the collapse of dissipation of the mitochondrial membrane potential ($\Delta\psi M$), changes in outer mitochondrial membrane (OMM) channels such as Bax/Bak occur, resulting in the release of cytochrome c into the cytosol. This series of events primarily activates the apoptotic cascade, including the creation of apoptosomes, and ultimately culminates in cell death[70,71].

E-cigs Promote Apoptotic Cell Signaling Through the Fas/FasL-Dependent Pathway

E-cigs in epithelial lung cells through vapor exposure can induce apoptosis. In healthy lungs, airway cells undergo a basal turnover *via* apoptosis, and alveolar macrophages would generally clear these away to prevent the accumulation of apoptotic debris, which can induce inflammation. The removal of apoptotic cells by macrophages 'efferocytosis' is the last stage of apoptosis. In healthy tissues, apoptotic cells are hardly visible without being absorbed by phagocytes, indicating that their clearance happens simultaneously with the process of apoptosis[72]. COPD patients and smokers have a higher risk of airway cell apoptosis, and the capacity of alveolar macrophages to efferocytosis is increased[73,74]. E-cigs vapor exposure (ECVE) inhibits bacterial phagocytosis in differentiated macrophages and causes a significant decrease in efferocytosis. This impact is not reliant on the nicotine rate or flavor of e-Cigs[75].

CSE-exposed on alveolar macrophages of patients with COPD exhibit a decreased capacity for efferocytosis *via* decreased expression of dead cell identification receptors, including the following CD44, CD3[76], SR-A[77] and SR-B1 (CD36)[78], and LRP-1/CD9[75,76]. While after vapor exposure to e-Cigs, nicotine, including propylene glycol (PG) and vegetable glycerin (VG), drastically lowered the dead cell recognition receptor CD44[73]. Consequently, e-cigs may influence the expression of apoptotic cell recognition receptors on the surface of macrophages, resulting in a reduction in efferocytotic capability, which, together with an increase in bronchial epithelial apoptosis, may cause increased inflammation in the airways.

E-cigs tobacco-flavored e-liquid vapor strongly induces cyclo-oxygenase-2 (*COX-2*) expression[79]. Hence, it might promote the *COX-2*-induced autophagy pathway and be antiapoptotic for cell survival. The mitochondrial function intimately connects to apoptotic cells. Stimulation of apoptosis can cause alterations in the integrity of the mitochondrial membrane, and cytochrome C is released into the cytoplasm, activating the downstream effector caspase-3 and resulting in cell death[51,80].

E-cigs vapor contains a variety of potentially harmful substances, such as formaldehyde, acetyl aldehyde, and acrolein, which trigger apoptosis *via* lipid peroxidation[81]. Certain carcinogens are released during vaporization due to the heat or voltage generated by the e-cigs battery[82]. The vapor from e-cigs has been estimated to contain up to 7 × 1011 free radicals in each puff[83,84]. In nicotine-free liquid, nicotine-free and nicotine-containing condensate significantly increase ROS production and trigger apoptosis[83,85]. Additionally, reactive aldehydes promote the build-up of 4-hydroxynonenal, which induces Fas-mediated apoptosis (Figure 3) and p53-dependent pathways[20,84].

E-cigs operate similarly to synthetic ligands by binding to death receptors to recruit one of two pivotal death domain-containing adaptor proteins (Figure 3A). It starts signaling through the cytoplasmic death domain to trigger the apoptosis pathway. Then, the Fas-associated protein with the death domain controls cell death (FADD) by recruiting caspase-8 to form the death-inducing signaling complex (DISC). DISC mediates autocatalytic processing, propagating the death signal through proteolysis of effector caspase-386. Following their cleavage, these caspases promote the breakdown of poly ADP-ribose polymerase (PARP). DNA damage is caused when PARP is activated by attaching to DNA ends or strand breaks. It has also been claimed that PARP may contribute to cell death by diminishing the cell's supply of nicotinamide adenine dinucleotide (NAD) and ATP[87].

Cigarettes and e-cigs Activate Proinflammatory Signaling in Lung Cells

The proinflammatory phenotype of cells is characterized by a significantly increased expression of cytokines and adhesion molecules. Inflammation occurs due to the sustained participation of

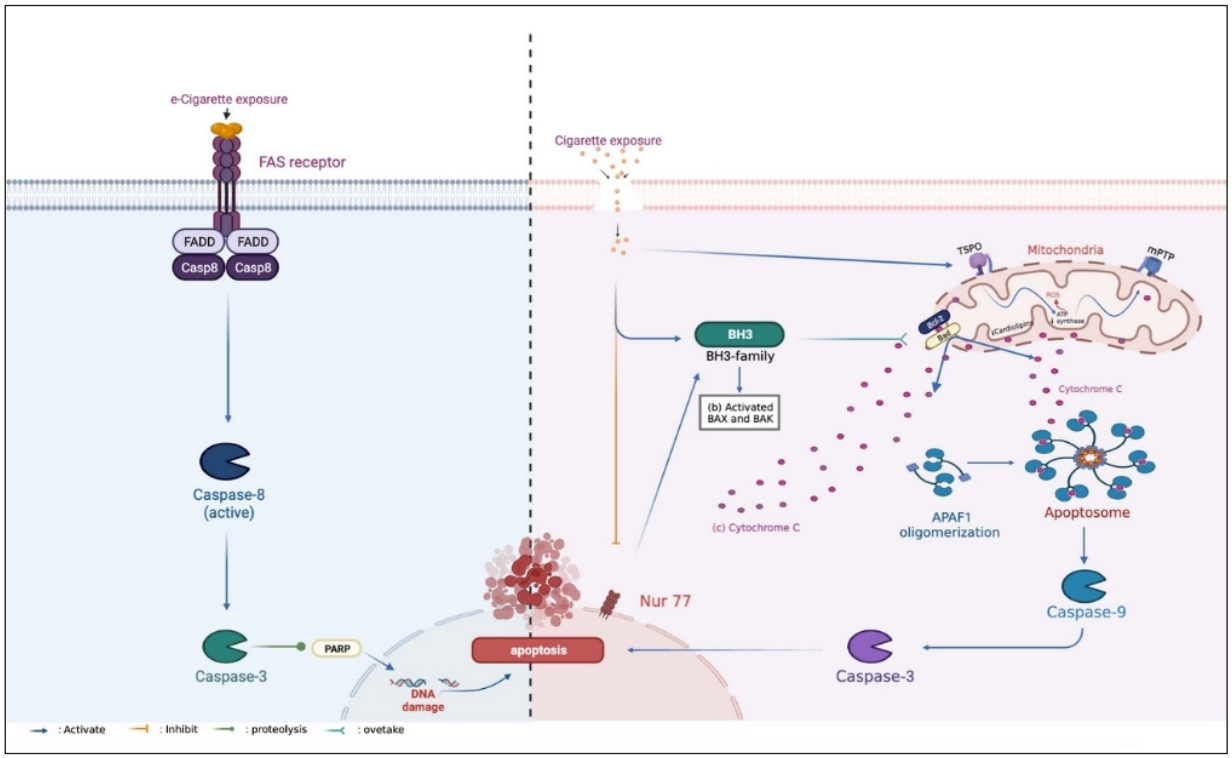

Figure 3. e-cigs vapor and cigarette smoke-induced apoptotic signaling. **A**, e-cigs vapor binds to the FAS receptor, and activation of caspase stimulates PARP and inhibits DNA repair. **B**, Cigarette smoke inhibits Nur77, which interacts with the BH3 peptide-binding crevice and turns antiapoptotic proteins into propoptotic proteins. **B**, In response to CSE, TSPO expression on the OMM increases, followed by a decrease in ATP synthase activity, ROS generation, and cardiolipin peroxidation. The propoptotic Bax-like subfamily induces cell death *via* the caspase cascade by creating holes in the mitochondrial outer membrane and controlling mitochondrial cytochrome c release.

critical inflammatory cells, such as neutrophils, T cells, macrophages, and lung epithelial cells, which release proinflammatory mediators, such as interleukin (IL)-1B, IL-8, IL-6, and tumor necrosis factor-α (TNF-α)[88-90]. The nuclear translocation of nuclear factor-κB (NF-κB) plays a critical role in regulating cytokine production[91,92]. IL-8 is a proinflammatory cytokine that works as a chemoattractant for neutrophils, ultimately influencing the inflammatory response. IL-8 is required for chronic inflammation and cancer development[93]; however, IL-6 is related to inflammation and various chronic illnesses[94].

Based on enzyme-linked immunosorbent assay, the levels of proinflammatory cytokines (IL-6 and IL-8) in CSE-exposed lung epithelial cells increased after 24 h exposure[44]. Furthermore, e-cigs exposure in lung epithelial cells showed a slight increase in IL-6 gene expression[95], but no changes in IL-8 protein levels were significantly detected, and cytochrome P450 CYP1B1 was upregulated in CSE and e-cigs exposure[50,96,97]. CSE and e-cigs vapor can induce inflammation in the lungs. CSE treatment stimulated the release of CXCL8 in lung epithelial cells in a concentration-dependent manner[98]. E-cigs exposure caused CXCL8 release at the highest concentration, whereas CSE-induced chemokine secretion from both airways. Additionally, the toxicity of e-cigs was comparable at 5% and 10% exposure[43,99].

Cigarettes Smoke Suppresses DAPK2 mRNA Expression Leading to Lung Cancer

CSE in high concentrations can lead to pyroptosis in lung epithelial cells. Pyroptosis is a programmed cell death process activated by an inflammasome[100]. NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) is the most well-studied inflammasome and plays a vital role in immune-related sensing[101,102]. Cigarette smoke activates NLRP3, and the activated NLRP3 inflammasome stimulates caspase-1 cleavage. Then, caspase-1 activation might target downstream molecules, boo-

sting IL-1 and IL-18 levels. Additionally, caspase-1 may cleave gasdermin-D, resulting in pyroptosis[103]. Activators of the inflammasome, such as extracellular ATP, ROS, and other damage-associated molecular patterns, are enhanced in the airway of COPD patients[104]. Once the inflammasome is active, the inflammasome-mediated caspase-1 is also activated, which breaks down the cell membrane's integrity and eventually causes the release of several inflammatory cytokines, including IL-1 and IL-18[105,106].

CSE-induced cytotoxicity and inflammation enhance oxidative stress and are mediated by the mitogen-activated protein kinase (MAPK) pathway. CSE-induced inflammation is mediated by the c-Jun N-terminal kinase (JNK), p38, NF-κB, and extracellular signal-regulated kinase 1/2 (ERK1/2) pathways[107-110] by activating p38 and ERK1/2. CSE promotes inflammation in endothelial cells[111]. However, a previous study44 discovered that CSE treatment elevated ERK1/2 and JNK phosphorylation in bronchial epithelial cells.

CSE-generated oxidative stress impairs the ability of cells to counteract increasing oxidants, triggering further inflammation, mucus hypersecretion, and proteolytic activity[55,104,112]. It blocks the activity of a number of antioxidant enzymes, including glutathione, the oxidant scavenger Nrf2, and superoxide dismutase (SOD), which increases lipid peroxidation and triggers the production of proinflammatory cytokines through NF-κB activation. Increased ROS levels enhance the phosphorylation of suppressor of mothers against decapentaplegic (Smad), a critical activator of the epithelial-mesenchymal transition (EMT) signaling[113,114].

CSE exposure significantly increased the number of inflammatory cells in the airways and lung tissue considerably, with a predominance of macrophage-like cells (neutrophils and lymphocytes) and an influx of neutrophils around the bronchial walls typically connected with airway wall destruction, a hallmark pathophysiological aspect of lung injury[115]. CSE activates pro-inflammatory agents, including TNF-α, IL-6, IL-8, and neutrophil elastase[42,116]. Inflammatory cytokines cause damage to and alter the structure and function of the airway wall. It is assumed that airway remodeling in COPD is related to active EMT signaling[110].

CSE upregulated matrix metalloproteinase-9 (MMP-9) gene expression and decreased E-cadherin expression in lung cancer cell lines. E-cadherin is a protein involved in cell-cell adhesion and an atypical epithelial marker. Additionally, cigarette smoke (CS) increased SNAIL1, a transcription factor that acts as a negative regulator of E-cadherin expression[117]. MMPs also contribute to establishing the tumor microenvironment, which is essential for the cancer cell to initiate the cascade of events necessary for cancer growth and metastasis[118]. MMP-9 is one of the MMPs that promote tumor development, and various studies[117,120] have established a link between its expression and the metastatic process[119]. Notable is the possibility that forkhead box class O 3a is responsible for these impacts on lung cells.

A smoking-related study group[92] showed aberrantly expressed genes, and the most significant one is death-associated protein kinase 2 (DAPK2). DAPK2 expression is substantially correlated with nonsmall cell lung cancer (NSCLC). DAPK is a member of the serine/threonine kinase family, and members of the DAPK family have vital roles in inducing apoptosis and acting as a tumor suppressor in various cancers[121-123]. CSE suppresses DAPK2 mRNA (Figure 4) and protein expression by altering the degree of N^6-methyladenosine (m^6A) modification on DAPK2, which alters the m^6A homeostasis, mediated by m6A "writer" methyltransferase 3 (METTL3) and "reader" YTH m^6A RNA-binding protein 2 (YTHDF2)[92]. m^6A is the most prevalent mRNA alteration, and its dysregulation contributes to the development of a variety of malignancies, including NSCLC[124,125].

Cigarette smoking increases the amount of modified m^6A of DAPK2 in NSCLC (Figure 4B) by upregulating the METTL3 enzyme, and the m6A reader YTHDF2 recognizes and binds directly to the m^6A site on DAPK2 mRNA, hence decreasing tumor suppressor DAPK2 gene stability. Thus, the downregulation of DAPK2 expression increases malignant phenotypes of NSCLC cells *in vitro* and *in vivo* by activating the oncogenic NF-κB signaling pathway. Finally, it promotes tumor cell growth and migration in the lungs.

E-cigs Vapor Induces Sox2 Expression and Promotes Self-Renewal of Lung Cancer Cells

E-cigs elicit a significant release of inflammatory mediators and nicotine-induced cytotoxicity in alveolar macrophages[89]. E-cigs increased proinflammatory cytokine secretion response in cells, such as MCP-1, IL-6, IL-8[11,126], and TNF-α[127]. E-cigs vapor increased the levels of mutagenic oxidative DNA on lesion 8-oxo-dG[9,128]. DNA damage and genotoxicity produced by e-cigs ae-

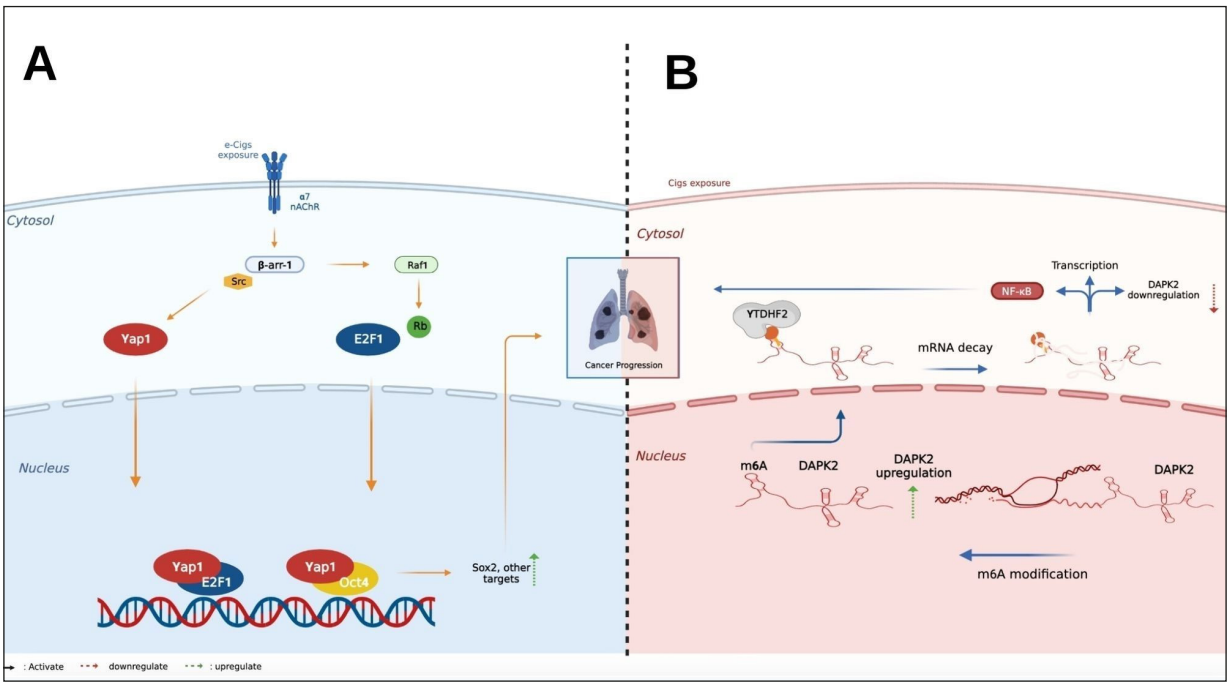

Figure 4. e-cigs vapor and cigarette smoke promote cancer cell progression. **A**, Nicotine-mediated upregulation of Sox2 via α7 nAChR promotes the self-renewal of NSCLC cells. Nicotine binds to the α7 nAChR receptor, and activation of Src *via* the α7 nAChR induces Raf-1 activation in an β-arr1-dependent way. **B**, Cigarette smoke leads to aberrant m6A of DAPK2 in the development and progression of NSCLC cells by upregulating the METTL3 enzyme, and the m6A reader YTHDF2.

rosol exposure are equivalent to those caused by combustible cigarette smoking[129,130].

E-cigs have been shown to amplify respiratory illnesses by enhancing microbial adhesion to the airways[131]. Toxins such as aldehydes are produced when the chemical makeup of e-cigs flavors is heated[132]. Flavoring compounds induce lung toxicity by disrupting the airway epithelium and causing oxidative stress and immunological responses, spreading signaling cascades inside the cell[133]. Tobacco-related lung illnesses Tobacco-related lung diseases are distinguished by increased fibronectin accumulation, which nicotine can trigger[134]. Plasma fibronectin levels increased significantly after exposure to e-cigs aerosols[9].

Exposure to e-cigs vapor activates human neutrophils. e-cigs vapor enhanced CD11b and CD66b expression on neutrophils and altered their morphology; these are indicators of neutrophil activation. E-cigs vapor (with and without nicotine) increased neutrophil *MMP-9* and CXCL8 secretion and the activity of *MMP-9* and neutrophil elastase (NE)[84,99]. CXCL8 inhibits C-X-C motif receptor (CXCR) 1 and 2 expressions in a dose-dependent manner[11,99]. When these chemotactic receptors are suppressed to modulate neutrophil inflammatory responses, these cells become adherent to inflammatory sites with the highest chemokine concentrations[99,135]. The activation of p38 MAPK was connected to these pro-inflammatory alterations and its expression was elevated in the lungs of COPD patients[136].

E-cigs vapor induces lung cancer cell proliferation and inhibits caspase-mediated apoptosis[137]. In contrast, e-cigs vapor inhibits the proliferation of epithelial airway cells[138]. E-cigs contain nicotine that increases the potential of lung tumor progression. A recent study[139] demonstrated that nicotine might promote the self-renewal of NSCLC cells. Nicotine-mediated Sox2 induction and possibly self-renewal of lung adenocarcinoma stem-like cells[140,141]. Nicotine binding to the α7 nAChR recruits β-arr-1 and activates Yap1, a target of Src and a member of the Src family[140].

Nicotine binds to the α7 nAChR receptor, and activation of Src *via* the α7 nAChR induces Raf-1 activation in an β-arr1-dependent way (Figure 4A). Raf-1 then phosphorylates the Rb tumor suppressor protein, which usually is attached to *E2F1* during cellular quiescence. However, separating hyperphosphorylated Rb from *E2F1* enables it to activate multiple proliferation and survival promoters. Rb phosphorylates and separates from *E2F1*, increasing *E2F1* transcriptional acti-

vity[142,143]. Additionally, *Yap1* interacts with *E2F1* and promotes the expression of its downstream targets, indicating that nicotine induces *Sox2* expression in NSCLC cells *via Yap1* and its interaction with transcription factors, such as *E2F1* or Oct4, which promote NSCLC cell self-renewal[140].

Discussion

E-cigs products have been promoted using a variety of platforms, including TV, social media, and product displays. Flavors added were shown to entice both adolescents and adults to use electronic cigarettes. Adolescents value flavors the most in these products and are more likely to start smoking flavored electronic cigarettes. Thus, flavors reduce harm perceptions while increasing readiness to try and begin using electronic cigarettes. Electronic cigarette flavors boost product attractiveness among adults and adolescents, which is a key reason why adults utilize the product[6].

E-cigs products are swiftly becoming a new craze among people; from 2012-2017, the number of users increased by more than doubled throughout the EU and US (7.2-14.6%)[43,144]. Currently, electronic cigarette product consumption ranges from 0.2% to 27% among European adults. Curiosity was the most often mentioned reason for starting to use electronic cigarettes, whereas reasons for continuing to use electronic cigarettes varied. Non-users of electronic cigarettes regard them as a trendy and fashionable product that mimics the smoking habit while being reasonably safe to use[145].

Vaping is a dangerous practice. The main ingredients that form the e-liquid are propylene glycol and/or vegetable glycerin, which are usually considered safe for consumption, but we do not yet know what happens when they are inhaled. According to the Surgeon General, nicotine in e-cigarettes can impair the growing brain. Although little is known about inhaling flavor compounds, some flavoring substances are plain toxic when inhaled[146]. There might also be a variety of additional substances in the liquids that users vape. There are no controls yet on what e-liquids include, and contaminants may exist. Vaping-related diseases and fatalities have garnered international attention. According to the Centres for Disease Control and Prevention, 2,758 incidents of lung injury and 64 fatalities have been linked to e-cigarette use in 46 states and the US Virgin Islands as of 2020.

Recent studies[34] have shown that exposure to e-cigarettes increases inflammation agent production, enlarges the lung alveolar spaces, and results in emphysema. Since the ingredients in e-cigarettes still contain high nicotine, which is similar to those in conventional cigarettes, it stands to reason that the risks they represent will also be similar. The toxicity effect of e-cigarettes is lower when compared to conventional cigarettes. However, e-cigarettes have a cytotoxic effect and activate the same signaling pathways as conventional cigarettes[147]. Both traditional and electronic cigarette usage raises one's risk of exposure to free radicals, which can increase reactive oxygen species (ROS)[41], which leads to cell death and stimulates hypermethylation of the gene promoter region. This may result in transcriptional silencing of the tumor suppressor gene, which is involved in the cell cycle and increases the potential for lung cancer[148].

Conclusions

According to the findings of the literature evaluation and analysis, both electronic cigarettes and cigarettes have the potential to increase the risk of lung cancer. The toxicity produced by e-cigs aerosol exposure is equivalent to that caused by combustible cigarette smoking. CSE and e-cigs aerosols alter cell shape and growth, induce apoptosis and inflammation, and increase lung cancer risk. CSE induces apoptosis *via* the Nur77 receptor and the 18 kDa TSPO levels, whereas e-cigs induce apoptosis *via* the Fas/FasL pathway. In addition, CSE and e-cigs increased proinflammatory cytokine expression in cells, such as IL-6, IL-8, and TNF-α, which affect pulmonary function. E-cigs promote *MMP-9* regulation. CSE promotes tumor cell growth and migration in the lungs, whereas e-cigs promote NSCLC cell self-renewal.

One frequent misconception is that vaping is risk-free. Poisoning from unintentional absorption of liquid nicotine is another potential health impact related to the usage of e-cigs (reported symptoms include vomiting, tachycardia, and headache). Severe toxicity may develop from excessive nicotine concentrations in e-liquid, resulting in harm to our lungs, respiratory failure, brain and neuromuscular injury, and even death. E-cigs are dangerous. On the other hand, cigarettes are exceedingly dangerous. Thus, it is believed that cigarette smokers can now try utilizing e-cigs to help them quit if they have tried a number of methods to stop smoking without success.

New e-cigs research should not be disregarded in order to help address issues regarding the safety and effectiveness of using e-cigs to stop smoking. The in-vitro exposure-focused study has to be expanded. Additionally, in-vitro exposure can aid in determining how much e-cigs can directly affect cells without the involvement of any other external factors like sex, age, activity level, diet, or lifestyle. The level of confidence in a proposed solution is positively correlated with the extent of research conducted on a particular issue. It is important to acknowledge that limiting the interpretations of individual study results in the absence of a conclusive resolution may have the adverse effect of aggravating the situation, undermining the trust of the general public in scientific research, and conceivably impeding efforts toward smoking cessation. Researchers in the field of tobacco, despite having differing viewpoints, are united in their aim to reduce the occurrence of both morbidity and mortality.

Conflict of Interest
The authors declare that they have no conflict of interest.

Ethics Approval
No ethical approval is needed for this study.

Authors' Contributions
The analysis was conceptualized and designed by XAA, MIB, and RL. XAA wrote the original manuscript and supplied the data. HG provided analysis tools. MIB and RA review and editing the manuscript, supervision. RA supervision. All authors reviewed the final manuscript.

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Data Availability
Not applicable.

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