

## Review Article

# Electronic Cigarette and Atherosclerosis: A Comprehensive Literature Review of Latest Evidences

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Coronary artery diseases (CAD), also known as coronary heart disease (CHD), are the world's leading cause of death. The basis of coronary artery disease is the narrowing of the heart coronary artery lumen due to atherosclerosis. The use of electronic cigarettes has increased significantly over the years. However, harmful effects of electronic cigarettes are still not firm. The aim of this article is to review the impact of electronic cigarette and its role in the pathogenesis of atherosclerosis from recent studies. The results showed that several chemical compounds, such as nicotine, propylene glycol, particulate matters, heavy metals, and flavorings, in electronic cigarette induce atherosclerosis with each molecular mechanism that lead to atherosclerosis progression by formation of ROS, endothelial dysfunction, and inflammation. Further research is still needed to determine the exact mechanism and provide more clinical evidence.

## 1. Introduction

Coronary artery diseases (CAD), also known as coronary heart disease (CHD), are the world's leading cause of death [1]. The basis of coronary artery disease is the narrowing of the heart coronary artery lumen due to atherosclerosis. CAD may appear as one of several manifestations, ranging from stable angina, unstable angina, myocardial infarction, and sudden cardiac death [2]. The American Heart Association reported that in 2016, 15.5 million people above 20 years old in the United States were affected by CAD, and the prevalence was shown to increase with age [3]. In Indonesia, it is suspected that by the year 2013, there will be more than 2.6 million CAD patients, and the number of cases is expected to rise significantly in recent years [4].

CAD is multifactorial, affected by both genetic and lifestyle factors [5]. One of the most significant modifiable risk factors of CAD is cigarette smoking. Cigarette smok-

ing is a habit widely known to be harmful to health. Smokers can be differentiated into active and passive smokers depending on whether the smokers are voluntarily and directly involved with tobacco use. In recent years, many different alternatives to tobacco smoking can be found in the market, including smokeless tobacco, hookah (also known as shisha), and electronic cigarettes (also known as vaping) [6, 7]. Electronic cigarettes (e-cigarette) are especially recognized since they were marketed as a "healthier" substitute to tobacco smoking [8]. Around 2.3-3.7% million US adults were estimated to be current e-cigarette users [7, 9]. In Indonesia, 10.9% of adults were aware of the rising use of the e-cigarette, and 2.5% of them were current e-cigarette users [10]. The number of e-cigarette users increased over the years in different parts of the world, even among the youths [11, 12]. The increasing prevalence of e-cigarette users is a concerning issue since its use is related to devastating health and socioeconomic

burdens. It is estimated that the general cost of e-cigarette smoking is twice higher than traditional tobacco smoking [13]. Principally, an e-cigarette is an electronic device capable of burning specialized liquids contained in a cartridge, generating aerosol and vapor smoke [14].

Smoking has been widely known to cause various complications affecting different system organs. The growing scientific evidence also implied the same findings for e-cigarette smoking. The use of e-cigarettes is recently more recognized as a cause of different public health problems. E-cigarette use causes cough and wheezing and promotes oxidative stress while generating harmful substances and wastes harmful to the environment and surrounding people [15]. E-cigarette smokers were found to inhale toxic and carcinogenic compounds in the e-cigarette vapor [16]. Overlapping with tobacco cigarette in some aspects, e-cigarettes were recorded to negatively impact respiratory, digestive, hematologic, and obstetric organ tissues while also holding the potential to cause trauma, poisoning, and allergic reaction [17]. Particularly, CAD is among the main contributors of smoking-related mortality and morbidity, and past studies found that smoking was closely associated with different aspects of CAD pathogenesis, including the formation of atherosclerosis and coronary artery spasm [18].

Considering the overlapping harmful effects of tobacco and e-cigarette smoking, we conduct this literature review study to assimilate the findings of past studies regarding the effect of e-cigarette smoking on atherosclerosis as the central pathologic basis of CAD. In this study, the term “e-cigarette smoking” encompasses both active and passive e-cigarette smokers unless elaborated otherwise. First, we will concisely describe our methodology to find works of literature that we cite in the writing of our review study. Then, we will try to outline the general cardiovascular pathologies associated with e-cigarette use and revisit the pathogenesis of atherosclerosis. After that, we will review the available literature regarding the mechanism by which e-cigarette smoking affects the development of atherosclerosis and preexisting cardiovascular diseases.

## 2. Molecular Mechanism of Atherosclerosis as the Basis of Cardiovascular Disease

Atherosclerosis is the principal pathologic factor of many different types of cardiovascular diseases [1]. The endothelial cell lining the inner surface of the blood vessels is vital in secreting chemical molecules such as nitric oxide (NO) and angiotensin II to maintain circulatory homeostasis. NO is capable of preventing vascular thrombosis and inflammation. Changes in NO formation may alter vascular physiology, and it has been noted as one of the earliest features in several vascular diseases, such as atherosclerosis. Alteration in hemodynamics may incite endothelial dysfunction, subsequently progressing into cardiovascular diseases. Several risk factors, including smoking, high cholesterol plasma levels, and obesity, may aggravate hemodynamic instability. Circulatory hemodynamics and atherosclerosis were thought to be related, and this hypothesis is proved by looking at the predilection of the atherosclerotic lesion location, which is

mainly concentrated in regions with high turbulence, such as the aorta branch point. Kruppel-like factor 2 (KLF2), a protective transcription factor against atherosclerosis, is expressed when the blood flows lamina. On the other hand, turbulent blood flow will induce the endothelial cells to activate Nf-kB inflammatory pathway and undergo subsequent cytoskeletal restructuring [19–21].

Hyperlipidemia is a prominent determinant of atherosclerosis. There are two types of lipoproteins, such as low-density lipoproteins (LDLs) that are found in the circulation, and it has been long known as highly atherogenic, and high-density lipoproteins (HDLs) are the counterpart of LDL, known to be atheroprotective. HDL is deemed atheroprotective due to its capability to carry cholesterol from peripheral circulations back to the liver to be degraded. Statin, a drug class commonly prescribed to treat hypercholesterolemia, lowers LDL levels by inhibiting HMG-CoA reductase and increasing HDL levels when combined with lifestyle changes. LDL contains single apolipoprotein B (apoB) and easy to be oxidized. Atherosclerosis progression is initiated when lipids that contain lipoproteins accumulated in the tunica intima and activated the endothelium. This process leads to inflammation that known with increase of leukocyte infiltration and growth factor production [22]. Oxidized LDL is less vulnerable to degradation, and the accumulation of oxidized LDL inside a macrophage will cause the macrophage to turn into foam cells [23]. Endothelial dysfunction is an early stage of atherosclerosis progression and risk factor of other cardiovascular diseases, such as dyslipidemia.

Endothelial dysfunction will also cause the secretion of inflammatory proteins. Several cell adhesion molecules (CAMs), including p-selectin and ICAM-1, will be upregulated by the inflammatory molecules. The increased cell adhesion molecules will aid leukocyte adherence and migration into subendothelial tissue. Several highly expressed molecules in the atheroma are interferon- $\gamma$  (IFN- $\gamma$ ) and monocyte chemoattractant protein-1 (MCP-1). The secreted IFN- $\gamma$  accelerates the progression of atherosclerosis by enhancing the formation of foam cells, while MCP-1 activates leukocyte integrin, a protein that aids cellular attachment to the endothelial surface. Macrophages that enter the intima layer of the vessel will uptake oxidized LDL and turn into foam cells while also promoting the inflammatory reaction. Macrophages aggravate the inflammation inside the atheroma by activating T cells and secreting MCP-1 and IL-1, and both molecules will trigger further upregulation of endothelial cell adhesion molecules [24]. Recently, studies have showed that endothelial dysfunction-induced smoking has a higher levels of soluble intracellular adhesion (ICAM-1), P-selectin, and E-selectin in smokers than in nonsmokers [25]. Formation of foam cells caused by the differentiation of monocyte into macrophages also promoted the chemokine secretion, such as MCP-1 and CXCL-1/2/3, leading to plaque and thrombosis formation. On the other hand, endothelial dysfunction also stimulated the proinflammatory cytokine secretion, such as IL-1 $\beta$ , IL-6, IL-8, and TNF, and activated several signaling pathways that include PI3K, Akt, and MAPK that could activate the Nf-kB as a transcription

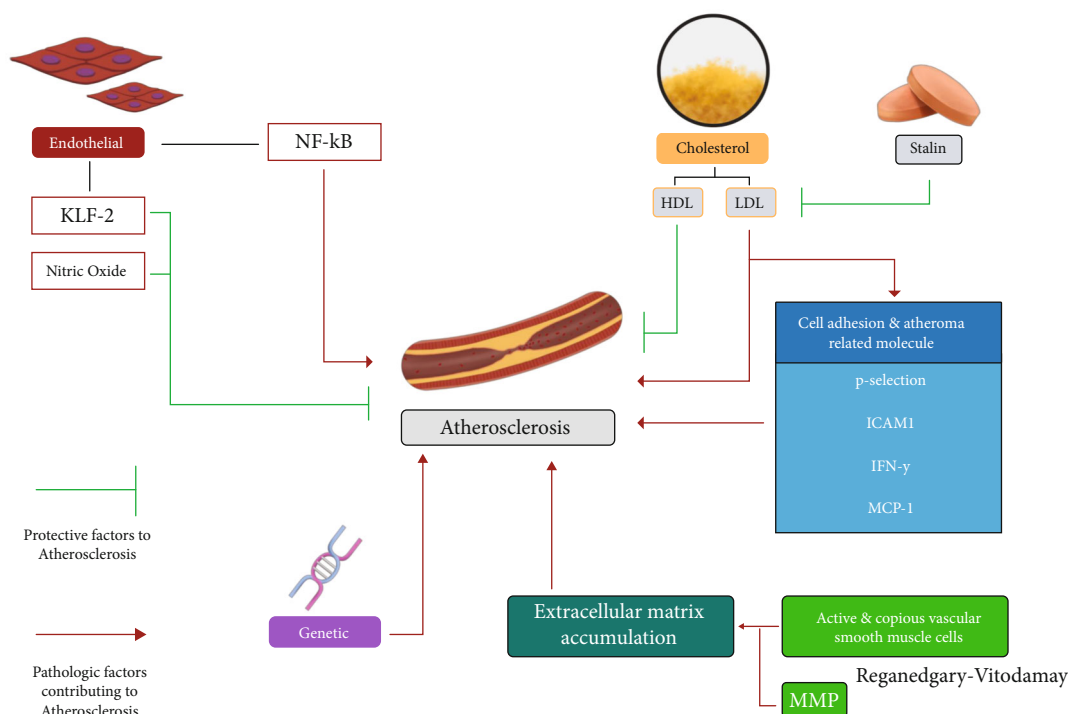


FIGURE 1: Several factors that affect atherosclerosis.

factors inducing inflammation and extracellular matrix secretion as a mediator of macrophage attachment (Figure 1) [26]. Furthermore, endothelial dysfunction also stimulated the growth factors like TGF- $\beta$ , Fibroblast Growth Factor (FGF), and Platelet-Derived Growth Factor (PDGF) that activated Nf- $\kappa$ B and Smad2/3/4 signaling pathway leading to vascular smooth muscle cell proliferation and migration [27].

Vascular smooth muscle cells (VSMC) were also involved in atherosclerosis. Inactive VSMC is contractile, expressing smooth muscle myosin heavy chain (MYH11) and smooth muscle actin alpha-2 (ACTA2) [21]. Under normal conditions, VSMC can only be scarcely found inside the tunica intima of the vessels. However, the amount of VSMC inside the intima layer of atherosclerotic vessels is copious and in an active state. The VSMCs will proliferate quite rapidly and produce extracellular matrix (ECM) in that state. The accumulation of the VSMC and the ECM will increase the size of the atheroma [21, 24]. Intima and media thickening in atherosclerosis progression is an evidence that overproliferation of VSMC induced Fibroblast Growth Factor-2 (FGF-2) and enhanced the cell migration in inflammation. There are several other agents of VSMC migration both of growth factors and extracellular matrix components, such as angiotensin II, VEGF, TNF- $\alpha$ , and collagen I/IV/VIII [28].

Extracellular matrix (ECM), such as collagens and non-collagenous proteins, has been shown to influence the function and activity of vascular cells, particularly macrophages and vascular smooth muscle cells (VSCM) [29]. Cells inside the atheroma can modify surrounding ECM by utilizing matrix metalloproteinase (MMP) enzymes. MMP is a group of zinc-dependent endopeptidases capable of disintegrating ECM proteins, and macrophages are among the biggest pro-

ducers of MMP enzymes. Several types of MMPs were found to accelerate the progression of atherosclerosis by unknown mechanisms. However, MMP enhanced macrophage accumulation inside the atherosclerotic plaque by releasing cytokines and growth factors inside the matrix. Furthermore, due to its capability to break down ECM, MMP was thought to play a role in atheroma destabilization [30, 31]. Atherosclerosis plaque formation and destabilization is controlled by MMP-9 activity and could be a predictor of cardiovascular mortality in patients with coronary artery disease [32].

Genetic is one of the least apparent risk factors of atherosclerosis. Some genetic-related conditions may foster atherosclerosis plaque progression, such as familial-type of hypercholesterolemia. Patients with this condition have abnormally high levels of LDL, related to the proprotein convertase subtilisin/kexin type 9 (PCSK9) and aberrations of apolipoprotein B (apoB). Mutation involving PCSK9 will hasten LDLR disintegration into LDL. And, due to the interaction between LDL receptor and apoB, mutations causing loss of function of any of both factors will reduce the degradation of LDL, increasing plasma levels of LDL [33].

**2.1. Chemical Compound of E-Cigarettes and Its Effect on Atherosclerosis.** Many studies have recently tried to shed light on how electronic cigarettes may impact different parts of atherosclerosis pathogenesis. Several chemicals in the e-cigarette that may contribute to atherosclerosis progression are nicotine, volatile organic compounds, oxidants, particulate matter, toxic gas compounds, and heavy metals. Different from the conventional cigarette, e-cigarette heats liquid containing propylene glycol, glycerin, nicotine, and flavoring molecules to form smoke that will be inhaled. Other chemicals generated in e-cigarettes

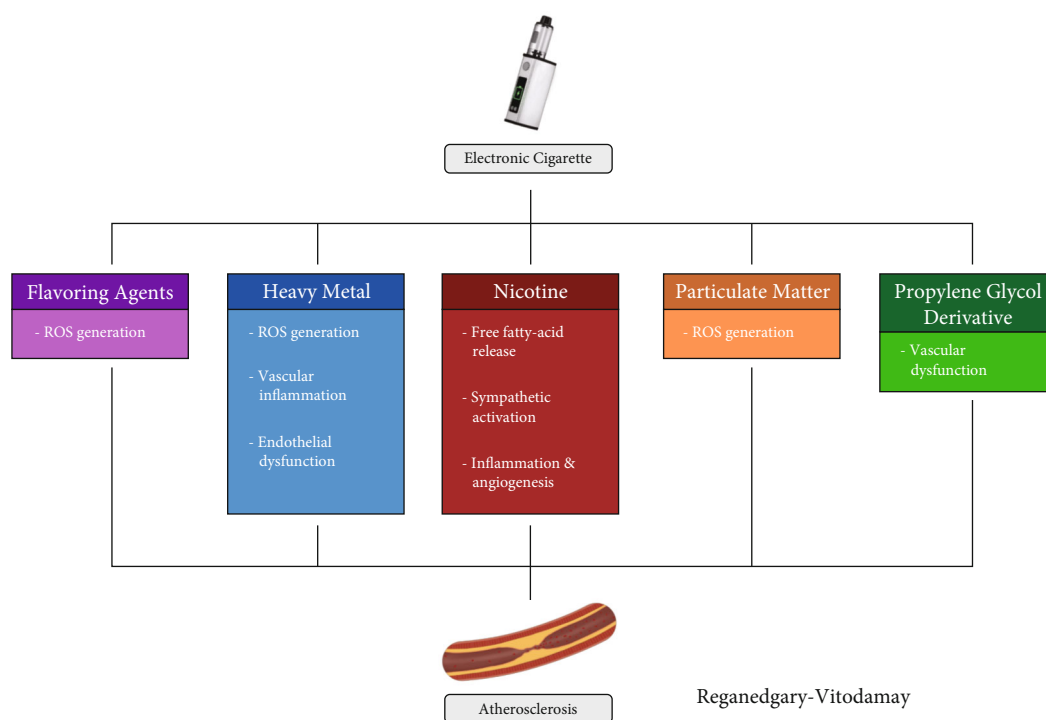


FIGURE 2: Chemical constituents of e-cigarette and their effects on atherosclerosis.

are acrolein, phenols, formaldehyde, crotonaldehyde, pyruvaldehyde, acetone, and acetaldehyde [34]. The chemical compounds will vary depending on the brands and the used cartridge and refill solutions. Heavy metals may be found in trace amounts [35]. Even though the number of chemicals found in e-cigarette liquid is comparably lesser than those found in a tobacco cigarette, those chemicals may undergo chemical transformations due to heat utilized by the e-cigarette, which may be potentially dangerous [36].

**2.2. Nicotine.** The nicotine in the e-cigarette is significantly associated with several different cardiovascular outcomes, such as atherosclerosis, myocardial infarction, and stroke. Plasma nicotine levels of tobacco cigarette smokers and e-cigarette smokers were equal, raising questions about the safety aspects of e-cigarettes claimed by the manufacturers [37]. An estimated 0.5-15.4 mg of nicotine are generated in the e-cigarette vapor for every 300 puffs [38]. The chronic exposure to e-cigarettes containing nicotine leads to atherosclerotic plaque formation, proved by a study in rats that found no atherosclerosis plaque formed on rats exposed to the e-cigarette with 0% nicotine [39]. The mechanism by which nicotine induces atherosclerosis appears to be caused by the FFA release from adipocytes, disrupting endothelial integrity [40].

The result of past studies indicates that nicotine is a potent sympathomimetic agent capable of stimulating the sympathetic nervous system, leading to both acute and chronic shifts in blood pressure and heart rate variability [41, 42]. Nicotine may bind with nicotinic receptors found in autonomic ganglia, brain, and sympathetic nerve terminals to stimulate the release of norepinephrine and increase adrenergic activity [43]. The increasing sympathetic nerve

activity may promote proinflammatory effects via the splenic axis pathway (discussed below) [44]. Nicotine may activate the sympathetic nervous system via  $\beta_3$  receptors, inducing a proinflammatory state and ultimately increasing the proliferation of monocytes and speeding up atherosclerosis [45, 46]. Molecular mechanism of nicotine-induced atherosclerosis is when nicotine enters the endothelial cell and increase production of ROS which activates NLRP3 inflammasome that leads to the activation of caspase-1. Activation of caspase-1 will trigger pore formation of membrane, DNA fragmentation, and release of IL-1 $\beta$  and IL-18 well known as inflammation response and promoting atherosclerosis (Figure 2) [47].

**2.3. Flavoring.** Flavoring agents can usually be found in many different e-cigarette liquid brands, comprising up to 4% of the e-cigarette fluids [48, 49]. Acetoin is the flavoring agent giving rise to the "buttery" taste of e-cigarettes, while the sweet taste is usually due to diacetyl in an exceedingly high concentration [50, 51]. Several flavoring agents, such as acetylpyridine, vanillin, diacetyl, and menthol, were capable of inducing endothelial cell dysfunction in cell culture and act as oxidants and triggered the generation of ROS, ultimately leading to oxidative stress [52]. Flavorant such as acetoin and maltol were found to trigger IL-8 release by causing ROS release, shifting the immunity into a proinflammatory state [53, 54]. Previous study has shown that flavoring compounds such as menthol and eugenol induce acute alterations in endothelial cell culture and loss of nitric oxide signaling that leads to atherosclerosis formation [55].

**2.4. Heavy Metal Particle.** The vapor of e-cigarette liquid contains variations of heavy metal particles, including

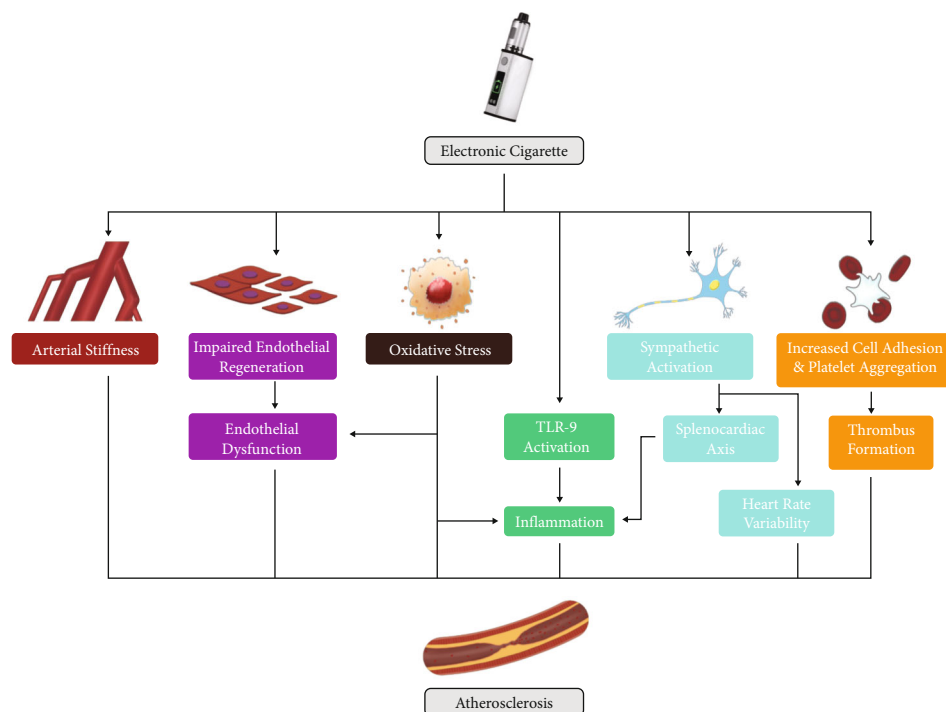


FIGURE 3: Mechanisms by which e-cigarette contributes to the pathogenesis of atherosclerosis.

aluminum, cadmium, iron, nickel, and zinc, which are contaminated even further with trace metal particles from the batteries released to the vapor through the interaction with the high temperature generated during vaping [56, 57]. The most concerning heavy metal particles are those with a diameter smaller than  $<2.5\ \mu\text{m}$ , often called fine heavy metal particles, capable of accumulating in the respiratory airway and translocating into the underlying vascular tissue and causing oxidative stress formation, vascular inflammation, and endothelial dysfunction [58, 59]. High temperature in electronic cigarette well known as release of heavy metals (cadmium, chromium, and lead) from the coil into the e-liquid and exposure to these metals can cause inflammation [60]. Recently, studies have shown that exposure of cadmium induces vascular dysfunction in the aorta of mice and increases the risk of atherosclerosis [61].

**2.5. Particulate Matters.** Particulate matters are an air-suspended liquid and solid phase particle with different chemical characteristics. In general, particulate matter can be differentiated into primary and secondary particulate matter depending on the source of the particles [62]. Particulate matters are hypothesized to affect cardiovascular directly by increasing reactive oxygen species (ROS) generation, and excessive ROS levels were linked to altered vascular functions, inducing the death of vascular cells and disrupting arterial vasoconstriction and vasodilation [63]. Based on aerodynamic diameters, particulate matters (PMs) are classified into 4 types: thoracic particles ( $\text{PM} > 10\ \mu\text{m}$ ), coarse particles ( $\text{PM}_{2.5-10}\ \mu\text{m}$ ), fine particles ( $\text{PM} < 2.5\ \mu\text{m}$ ), and ultrafine particles ( $\text{PM} < 0.1\ \mu\text{m}$ ). Animal studies investigated about particulate matter ( $\text{PM}_{2.5}$ ) on atherosclerosis

and resulting elevation of LDL, MDA, and TNF-Alpha levels and reduction of superoxide dismutase (SOD) [64].

**2.6. Propylene Glycol.** Propylene glycol is the main constituent of most e-cigarette liquids, comprising 95% liquid formulation [65, 66]. When exposed to heat, propylene glycol may disintegrate into secondary products, including formaldehyde, acetaldehyde, and methylglyoxal [67]. Methylglyoxal was found to disrupt vascular functions and accelerate atherosclerosis [68]. Acrolein is another oxidant found in the e-cigarette liquid and has been widely studied due to its carcinogenicity [35]. Chronic exposure to acrolein was correlated with cardiovascular events [69]. Formation of thermal dehydration products from propylene glycol highly depends on temperature. High temperature will produce more aldehyde products and increase the cardiovascular disease risk [70]. Exposure of electronic cigarette that contains 70% of propylene glycol (PG) 1 hour/day and 6 days/week for 4 weeks resulted in cardiac fibrosis [71]. Furthermore, 50% propylene glycol exposed in mice induces vascular oxidative stress [72].

**2.7. Association of Electronic Cigarette and Atherosclerosis.** Arterial stiffness is associated with alterations of stress features due to modification of structural components. This modification involves a complex interaction, such as cell signaling pathways that lead to alteration of collagen and glycoproteins of the extracellular matrix of the artery wall [73]. E-cigarettes and their constituents contribute to the pathogenesis of atherosclerosis by causing different types of pathologic features of atherosclerosis. Arterial stiffness is one of the biomedical indicators of arterial wall inflammation (Figure 3). It may be measured using a PET scan to detect

the increasing metabolic activity of the inflamed arterial wall segments [74]. The findings of some studies indicated that the use of e-cigarettes is associated with increased stiffness of aortic and other arterial vessel walls [42, 74–76]. Decreased arterial stiffness has been associated with an increased risk of cardiac events [77].

Endothelial dysfunction has been accepted as the most crucial aspect also known as early stage in the atherosclerosis progression and the ensuing cardiovascular diseases [78]. Microscopically, the characteristic of endothelial dysfunction is the disrupted regeneration of the endothelial cells and the endothelial-dependent vasodilatory mechanism [79]. In the context of scientific research, endothelial dysfunction may be approximately evaluated by measuring flow-mediated dilatation (FMD) of the brachial artery. Acute use of e-cigarettes resulted in similar FMD impairment compared to the acute use of tobacco cigarettes [75, 80]. The endothelial dysfunction induced by e-cigarette smoking is comparable to tobacco cigarette smoking, and both are capable of significantly inducing endothelial inflammation and dysfunction [80–82]. Endothelial dysfunction may also be indirectly measured by evaluating circulating endothelial progenitor cell (EPC). Previous study was found that ten puffs from an e-cigarette are enough to increase the amount of EPC in circulation [41].

Tobacco smoking is known to increase oxidative stress, and so does e-cigarette smoking [83]. Recent literature discovered that e-cigarette aerosol generates oxidative stress comparable to tobacco smoke, and the reactive oxygen species (ROS) and oxidants generated by both cigarette types are similar [84]. ROS are a group of chemicals with unpaired electrons on its outermost shell, thus damaging biochemical compounds found on the surface and inside the cells. Billions of free radicals are contained within each puff of e-cigarette, and exposure to e-cigarette vapor will trigger ROS release inside the body [85, 86]. Breach of cellular antioxidant defense due to ROS may cause DNA damage [87]. The oxidization damage was thought to be caused by nicotine to a certain extent; on the other hand, the use of e-cigarettes containing nicotine was found to acutely increase plasma levels of myeloperoxidase, a type of oxidative stress marker [75].

Oxidative stress has been widely known to be closely related to endothelial dysfunction. It also has been closely associated with inflammation, another major contributor of atherosclerosis, via the peroxidation reactions, activating the monocytes and ultimately causing vessel wall inflammation [88]. Atherosclerosis has been accepted as an inflammatory disease for some period. Exposure to e-cigarette vapor is linked to inflammation and leukocyte activation [89, 90]. The concept of the splenic axis has been suggested as the central inflammatory mechanism in the pathogenesis of atherosclerosis. This concept stands on the evidence of the connection between the sympathetic nervous system, spleen, and bone marrow as a cause of atheroma formation [44]. The increased sympathetic nerve activity will activate progenitor cells residing in the bone marrow due to acute stress introduced, and the progenitor cells will migrate into the spleen and

undergo maturation into proinflammatory monocytes [45, 91]. The monocytes will then enter the circulatory system and work together with oxidants and other prothrombotic factors to speed up atherosclerosis. These pathological changes of the proinflammatory state induced by e-cigarette use persisted for several weeks to months [44, 92]. The physiological basis of the splenic axis was confirmed using  $^{18}\text{F}$ -FDG-PET/CT in several studies, a noninvasive radiologic modality used to detect active inflammation [93]. It was observed that there is an increased plasma CRP level and higher inflammatory process inside the spleen after an attack of the acute coronary syndrome, which may also be an independent future cardiovascular event [44, 74, 94].

Toll-like receptors (TLRs) are an essential group of the innate immune system that recognize each pathogen-associated molecular pattern [31]. Toll-like receptor 9 (TLR9) is one of the innate immunity receptors that is expressed on macrophages. Activation of TLR9 has been implicated in inducing IL-6 and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) secretion, vascular wall inflammation, and the transformation of macrophages into foam cells [95]. Furthermore, TLR9 plays a crucial role in the development of vascular inflammation through proinflammatory activation of macrophages in angiotensin II-induced atherosclerosis via MyDD8 pathway [31, 96]. Histopathologically, monocyte infiltrating the atherosclerotic lesion is one of the most significant components of atheroma [97]. Additionally, drug intervention focusing on blocking TLR9 hampers the progression of atherosclerosis progression, supporting the notion that TLR9 is associated with atherosclerosis [98].

Platelet plays a central role in forming thrombus in coronary artery disease. E-cigarette vapor was observed to induce platelet activation and aggregation. The use of e-cigarettes increased the formation of soluble CD40-ligand and P-selectin while also increasing platelet aggregation significantly in less than 5 minutes after single e-cigarette use [8]. The CD40 expressed on the platelet affects atherosclerosis by mediating the leukocyte recruitment and chemokine release, playing vital roles in atherosclerotic plaque formation [99]. The CD40 also transiently expressed on T cells under inflammatory conditions, especially in tumors signaling pathway [100]. Meanwhile, P-selectin is a cellular adhesion molecule involved in procoagulant activities and leukocyte activation.[101] One in vitro study found that harmful components found in the e-cigarette vapor significantly cause platelet activation, with a degree of effect compared to traditional tobacco cigarette smoking. The extent of platelet activation was found to be independent of nicotine concentration [102]. Another study conducted by Qasim et al. [103] noted the increasing activity of platelets exposed to in vitro e-cigarette vapor inhalation system with denser  $\alpha$ -granule secretion, higher phosphatidylserine expression, and higher activation of Akt, ERK, and  $\alpha\text{IIb}\beta\text{3}$  integrin. However, these findings still need further confirmation as very few studies on the impact of e-cigarette use on platelet function.

The sympathetic nerve regulates the physiology of the cardiovascular system. Recent evidence consisted of findings

regarding the hyperactivated sympathetic state in e-cigarette users, affecting several aspects of cardiovascular health such as blood pressure [104]. Heart rate variability (HRV) measures sympathetic nervous system hyperactivation, and HRV has long been associated with cardiovascular events [105]. In chronic e-cigarette users, aspects of HRV pointed to the predominant activation of the nervous system accompanied by decreased vagal tone, a pattern known to be involved in recent and future cardiovascular events [106]. The change in sympathetic nerve activity contributes to the incidence of CAD by hastening the progression of atherosclerosis via the splenocardiac axis. The increasing sympathetic nerve activity triggers an inflammatory pathway contributing to atherosclerosis via the release of proinflammatory monocytes by the spleen [75].

**2.8. E-Cigarettes: Future Considerations.** The emission of e-cigarette vapor has given rise to several environmental concerns. Even though the number of chemicals contained in e-cigarette vapor was less than tobacco cigarette smoke [107], the dangerous chemicals contained within e-cigarette smoke may cause adverse effects to people surrounding the smoker. The particulate matter in the e-cigarette smoke may contaminate the active smoker's air and cause systemic effects if inhaled by the passive smokers, especially the smaller fraction of particulate matter [108]. The propylene glycol emitted by electronic cigarettes has a shorter half-life time (10-20 seconds) than propylene glycol emitted by tobacco cigarettes (1.4 h); it still poses a dangerous threat when vaping is done in a small room with poor ventilation [66].

Information gathered by studies regarding the impact of e-cigarette vapor to passive surrounding passive smokers may be of value to determine the future direction of public health policy and regulatory developments [109]. Since the beginning of their creation, the e-cigarette has been claimed as a healthy alternative to tobacco smoking, developed to help in smoking cessation [110]. In Indonesia, a study by Aminullah forecasted that the rising use of e-cigarettes would replace traditional tobacco cigarette smoking, which will be influenced by tax incentives, technological development, and stricter tobacco regulation by the government [111]. Public exposure to e-cigarette advertisements and marketing is associated with an increased chance of e-cigarette smoking on nonsmokers, adolescents, and youth due to the illusion of "perceived safety" of e-cigarettes.[11, 112] Thus, government-imposed marketing restriction on e-cigarettes was thought to be beneficial in decreasing e-cigarette consumption. Other perceived factors contributing to the increased use of e-cigarettes are the customization options available to suit personal preference and the similarity of e-cigarettes to tobacco cigarettes compared to traditional nicotine replacement therapy [12]. However, due to its copious harmful effects, the use of e-cigarettes as a substitute for tobacco cigarette smoking is still not recommended since the harms outweigh the questionable benefits compared to the standard nicotine replacement therapy. E-cigarettes should be studied further before being widely implemented as an alternative to standard nicotine replacement therapy in routine clinical practice.

### 3. Conclusion

E-cigarette is associated with several noxious compounds, such as nicotine, propylene glycol, particulate matter, heavy metals, and flavorings, that lead to atherosclerosis progression. Every single one of these toxic compounds has its own molecular mechanism associated with cardiovascular disease risk factor by ROS formation, endothelial dysfunction, and inflammation. Even though e-cigarettes are believed to be the safer substitute for tobacco smoking, several studies proved that it is still potentially harmful. Further research is still needed to determine the clinical use and harms of e-cigarettes and their effect on cardiovascular system.

### Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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### References

- [1] G. A. Roth, M. D. Huffman, A. E. Moran et al., "Global and regional patterns in cardiovascular mortality from 1990 to 2013," *Circulation*, vol. 132, no. 17, pp. 1667-1678, 2015.
- [2] M. M. Álvarez-Álvarez, D. Zanetti, R. Carreras-Torres, P. Moral, and G. Athanasiadis, "A survey of sub-Saharan gene flow into the Mediterranean at risk loci for coronary artery disease," *European Journal of Human Genetics*, vol. 25, no. 4, pp. 472-476, 2017.
- [3] D. Mozaffarian, E. J. Benjamin, A. S. Go et al., "Heart disease and stroke statistics-2016 update: a report from the American Heart Association," *Circulation*, vol. 133, no. 4, pp. e38-360, 2016.
- [4] Pusdatin, *Situasi Kesehatan Jantung*, Kementerian Kesehatan, 2014.
- [5] F. Wright and K. Fessele, "Primer in genetics and genomics, article 5-further defining the concepts of genotype and phenotype and exploring genotype-phenotype associations," *Biological Research for Nursing*, vol. 19, no. 5, pp. 576-585, 2017.
- [6] E. K. O'Brien, L. Hoffman, M. A. Navarro, and O. Ganz, "Social media use by leading US e-cigarette, cigarette, smokeless tobacco, cigar and hookah brands," *Tobacco Control*, vol. 29, no. e1, pp. e87-e97, 2020.
- [7] M. Mayer, C. Reyes-Guzman, R. Grana, K. Choi, and N. D. Freedman, "Demographic characteristics, cigarette smoking, and e-cigarette use among US adults," *JAMA Network Open*, vol. 3, no. 10, article e2020694, 2020.
- [8] C. Nocella, G. Biondi-Zoccai, S. Sciarretta et al., "Impact of tobacco versus electronic cigarette smoking on platelet function," *The American Journal of Cardiology*, vol. 122, no. 9, pp. 1477-1481, 2018.

- [9] H. Dai and A. M. Leventhal, "Prevalence of e-cigarette use among adults in the United States, 2014-2018," *JAMA*, vol. 322, no. 18, pp. 1824-1827, 2019.
- [10] K. M. Palipudi, L. Mbulo, J. Morton et al., "Awareness and current use of electronic cigarettes in Indonesia, Malaysia, Qatar, and Greece: findings from 2011-2013 global adult tobacco surveys," *Nicotine & Tobacco Research*, vol. 18, no. 4, pp. 501-507, 2016.
- [11] D. S. Mantey, M. R. Cooper, S. L. Clendennen, K. E. Pasch, and C. L. Perry, "E-cigarette marketing exposure is associated with E-cigarette use among US youth," *Journal of Adolescent Health*, vol. 58, no. 6, pp. 686-690, 2016.
- [12] V. N. Simmons, G. P. Quinn, P. T. Harrell et al., "E-cigarette use in adults: a qualitative study of users' perceptions and future use intentions," *Addiction Research and Theory*, vol. 24, no. 4, pp. 313-321, 2016.
- [13] L. Kock, L. Shahab, R. West, and J. Brown, "E-cigarette use in England 2014-17 as a function of socio-economic profile," *Addiction*, vol. 114, no. 2, pp. 294-303, 2019.
- [14] R. Grana, N. Benowitz, and S. Glantz, "A. E-cigarettes: a scientific review," *Circulation*, vol. 129, no. 19, pp. 1972-1986, 2014.
- [15] G. St Helen and D. L. Eaton, "Public health consequences of e-cigarette use," *JAMA Internal Medicine*, vol. 178, no. 7, pp. 984-986, 2018.
- [16] M. A. Kaisar, S. Prasad, T. Liles, and L. Cucullo, "A decade of e-cigarettes: limited research & unresolved safety concerns," *Toxicology*, vol. 365, pp. 67-75, 2016.
- [17] A. Tzortzi, M. Kapetanstradaki, V. Evangelopoulou, and P. Beghrakis, "A systematic literature review of E-cigarette-related illness and injury: not just for the respirologist," *International Journal of Environmental Research and Public Health*, vol. 17, no. 7, p. 2248, 2020.
- [18] R. A. Stallones, "The association between tobacco smoking and coronary heart disease," *International Journal of Epidemiology*, vol. 44, no. 3, pp. 735-743, 2015.
- [19] M. A. J. Gimbrone and G. García-Cardena, "Vascular endothelium, hemodynamics, and the pathobiology of atherosclerosis," *Cardiovascular Pathology*, vol. 22, no. 1, pp. 9-15, 2013.
- [20] M. A. J. Gimbrone and G. García-Cardena, "Endothelial cell dysfunction and the pathobiology of atherosclerosis," *Circulation Research*, vol. 118, no. 4, pp. 620-636, 2016.
- [21] I. Tabas, G. García-Cardena, and G. K. Owens, "Recent insights into the cellular biology of atherosclerosis," *The Journal of Cell Biology*, vol. 209, no. 1, pp. 13-22, 2015.
- [22] E. Mannarino and M. Pirro, "Molecular biology of atherosclerosis," *Clinical Cases in Mineral and Bone Metabolism*, vol. 5, no. 1, pp. 57-62, 2008.
- [23] J. Hurtubise, K. McLellan, K. Durr, O. Onasanya, D. Nwabuko, and J. F. Ndisang, "The different facets of dyslipidemia and hypertension in atherosclerosis," *Current Atherosclerosis Reports*, vol. 18, no. 12, p. 82, 2016.
- [24] A. R. Fatkhullina, I. O. Peshkova, and E. K. Koltsova, "The role of cytokines in the development of atherosclerosis," *Biochemistry (Moscow)*, vol. 81, no. 11, pp. 1358-1370, 2016.
- [25] R. Carnevale, V. Cammisotto, F. Pagano, and C. Nocella, "Effects of smoking on oxidative stress and vascular function," in *Smoking Prevention and Cessation*, IntechOpen, London, 2018.
- [26] A. O. Jackson, M. A. Regine, C. Subrata, and S. Long, "Molecular mechanisms and genetic regulation in atherosclerosis," *IJC Heart & Vasculature*, vol. 21, pp. 36-44, 2018.
- [27] P.-Y. Chen, L. Qin, N. Baeyens et al., "Endothelial-to-mesenchymal transition drives atherosclerosis progression," *The Journal of Clinical Investigation*, vol. 125, no. 12, pp. 4514-4528, 2015.
- [28] W. T. Gerthoffer, "Mechanisms of vascular smooth muscle cell migration," *Circulation Research*, vol. 100, no. 5, pp. 607-621, 2007.
- [29] D. A. Chistiakov, I. A. Sobenin, and A. N. Orekhov, "Vascular extracellular matrix in atherosclerosis," *Cardiology in Review*, vol. 21, no. 6, pp. 270-288, 2013.
- [30] R. Mohindra, D. K. Agrawal, and F. G. Thankam, "Altered vascular extracellular matrix in the pathogenesis of atherosclerosis," *Journal of Cardiovascular Translational Research*, vol. 14, no. 4, pp. 647-660, 2021.
- [31] T. Li, X. Li, Y. Feng, G. Dong, Y. Wang, and J. Yang, "The role of matrix metalloproteinase-9 in atherosclerotic plaque instability," *Mediators of Inflammation*, vol. 2020, Article ID 3872367, 13 pages, 2020.
- [32] S. Holm Nielsen, L. Jonasson, K. Kalogeropoulos et al., "Exploring the role of extracellular matrix proteins to develop biomarkers of plaque vulnerability and outcome," *Journal of Internal Medicine*, vol. 287, no. 5, pp. 493-513, 2020.
- [33] K. Musunuru and S. Kathiresan, "Surprises from genetic analyses of lipid risk factors for atherosclerosis," *Circulation Research*, vol. 118, no. 4, pp. 579-585, 2016.
- [34] T. Muthumalage, T. Lamb, M. R. Friedman, and I. Rahman, "E-cigarette flavored pods induce inflammation, epithelial barrier dysfunction, and DNA damage in lung epithelial cells and monocytes," *Scientific Reports*, vol. 9, no. 1, pp. 1-11, 2019.
- [35] T. Cheng, "Chemical evaluation of electronic cigarettes," *Tobacco Control*, vol. 23 Suppl 2, p. ii11-7, 2014.
- [36] A. Darville and E. J. Hahn, "E-cigarettes and atherosclerotic cardiovascular disease: what clinicians and researchers need to know," *Current Atherosclerosis Reports*, vol. 21, no. 5, p. 15, 2019.
- [37] M. L. Goniewicz, M. Gawron, D. M. Smith, M. Peng, P. Jacob III, and N. L. Benowitz, "Exposure to nicotine and selected toxicants in cigarette smokers who switched to electronic cigarettes: a longitudinal within-subjects observational study," *Nicotine & Tobacco Research*, vol. 19, no. 2, pp. 160-167, 2017.
- [38] M. L. Goniewicz, J. Knysak, M. Gawron et al., "Levels of selected carcinogens and toxicants in vapour from electronic cigarettes," *Tobacco Control*, vol. 23, no. 2, pp. 133-139, 2014.
- [39] J. Espinoza-Derout, X. M. Shao, C. J. Lao et al., "Electronic cigarette use and the risk of cardiovascular diseases," *Frontiers in Cardiovascular Medicine*, vol. 9, pp. 1-15, 2022.
- [40] A. Ghosh, L. Gao, A. Thakur, P. M. Siu, and C. W. K. Lai, "Role of free fatty acids in endothelial dysfunction," *Journal of Biomedical Science*, vol. 24, no. 1, p. 50, 2017.
- [41] L. Antoniewicz, J. A. Bosson, J. Kuhl et al., "Electronic cigarettes increase endothelial progenitor cells in the blood of healthy volunteers," *Atherosclerosis*, vol. 255, pp. 179-185, 2016.
- [42] K. F. Franzen, J. Willig, S. Cayo Talavera et al., "E-cigarettes and cigarettes worsen peripheral and central hemodynamics as well as arterial stiffness: a randomized, double-blinded pilot study," *Vascular Medicine*, vol. 23, no. 5, pp. 419-425, 2018.



- [43] H. R. Middlekauff, J. Park, and R. S. Moheimani, "Adverse effects of cigarette and noncigarette smoke exposure on the autonomic nervous system: mechanisms and implications for cardiovascular risk," *Journal of the American College of Cardiology*, vol. 64, no. 16, pp. 1740–1750, 2014.
- [44] P. Libby, M. Nahrendorf, and F. K. Swirski, "Leukocytes link local and systemic inflammation in ischemic cardiovascular disease: an expanded "cardiovascular continuum"," *Journal of the American College of Cardiology*, vol. 67, no. 9, pp. 1091–1103, 2016.
- [45] P. Dutta, G. Courties, Y. Wei et al., "Myocardial infarction accelerates atherosclerosis," *Nature*, vol. 487, no. 7407, pp. 325–329, 2012.
- [46] N. L. Benowitz and A. D. Burbank, "Cardiovascular toxicity of nicotine: implications for electronic cigarette use," *Trends in Cardiovascular Medicine*, vol. 26, no. 6, pp. 515–523, 2016.
- [47] X. Wu, H. Zhang, W. Qi et al., "Nicotine promotes atherosclerosis via ROS-NLRP3-mediated endothelial cell pyroptosis," *Cell Death & Disease*, vol. 9, no. 2, article 171, 2018.
- [48] R. Z. Behar, W. Luo, K. J. McWhirter, J. F. Pankow, and P. Talbot, "Analytical and toxicological evaluation of flavor chemicals in electronic cigarette refill fluids," *Scientific Reports*, vol. 8, no. 1, p. 8288, 2018.
- [49] P. A. Tierney, C. D. Karpinski, J. E. Brown, W. Luo, and J. F. Pankow, "Flavour chemicals in electronic cigarette fluids," *Tobacco Control*, vol. 25, no. e1, pp. e10–e15, 2016.
- [50] E. J. Zaccone, J. A. Thompson, D. S. Ponnoth et al., "Popcorn flavoring effects on reactivity of rat airways in vivo and in vitro," *Journal of Toxicology and Environmental Health. Part A*, vol. 76, no. 11, pp. 669–689, 2013.
- [51] K. E. Farsalinos, K. A. Kistler, G. Gillman, and V. Voudris, "Evaluation of electronic cigarette liquids and aerosol for the presence of selected inhalation toxins," *Nicotine & Tobacco Research*, vol. 17, no. 2, pp. 168–174, 2015.
- [52] G. Wölkart, A. Kollau, H. Stessel et al., "Effects of flavoring compounds used in electronic cigarette refill liquids on endothelial and vascular function," *PLoS One*, vol. 14, no. 9, article e0222152, 2019.
- [53] J. Gerloff, I. K. Sundar, R. Freter et al., "Inflammatory response and barrier dysfunction by different e-cigarette flavoring chemicals identified by gas chromatography-mass spectrometry in e-liquids and e-vapors on human lung epithelial cells and fibroblasts," *Applied In Vitro Toxicology*, vol. 3, no. 1, pp. 28–40, 2017.
- [54] T. Muthumalage, M. Prinz, K. O. Ansah, J. Gerloff, I. K. Sundar, and I. Rahman, "Inflammatory and oxidative responses induced by exposure to commonly used e-cigarette flavoring chemicals and flavored e-liquids without nicotine," *Frontiers in Physiology*, vol. 8, p. 1130, 2018.
- [55] J. L. Fetterman, R. M. Weisbrod, B. Feng et al., "Flavorings in tobacco products induce endothelial cell dysfunction," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 38, no. 7, pp. 1607–1615, 2018.
- [56] S. Gaur and R. Agnihotri, "Health effects of trace metals in electronic cigarette aerosols-a systematic review," *Biological Trace Element Research*, vol. 188, no. 2, pp. 295–315, 2019.
- [57] V. K. Mishra, K. H. Kim, P. Samaddar, S. Kumar, M. L. Aggarwal, and K. M. Chacko, "Review on metallic components released due to the use of electronic cigarettes," *Environmental Engineering Research*, vol. 22, no. 2, pp. 131–140, 2017.
- [58] M. Williams, A. Villarreal, K. Bozhilov, S. Lin, and P. Talbot, "Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol," *PLoS One*, vol. 8, no. 3, article e57987, 2013.
- [59] H. Nakane, "Translocation of particles deposited in the respiratory system: a systematic review and statistical analysis," *Environmental Health and Preventive Medicine*, vol. 17, no. 4, pp. 263–274, 2012.
- [60] J. Ebersole, V. Samburova, Y. Son et al., "Harmful chemicals emitted from electronic cigarettes and potential deleterious effects in the oral cavity," *Tobacco Induced Diseases*, vol. 18, pp. 1–16, 2020.
- [61] T. F. Oliveira, P. R. Batista, M. A. Leal et al., "Chronic cadmium exposure accelerates the development of atherosclerosis and induces vascular dysfunction in the aorta of ApoE<sup>-/-</sup> mice," *Biological Trace Element Research*, vol. 187, no. 1, pp. 163–171, 2019.
- [62] M. R. Miller, C. A. Shaw, and J. P. Langrish, "From particles to patients: oxidative stress and the cardiovascular effects of air pollution," *Future Cardiology*, vol. 8, no. 4, pp. 577–602, 2012.
- [63] F. He and L. Zuo, "Redox roles of reactive oxygen species in cardiovascular diseases," *International Journal of Molecular Sciences*, vol. 16, no. 11, pp. 27770–27780, 2015.
- [64] H. C. Lee and T. H. Lin, "Air pollution particular matter and atherosclerosis," *Acta Cardiologica Sinica*, vol. 33, no. 6, pp. 646–647, 2017.
- [65] S. Talih, R. Salman, R. el-Hage et al., "Characteristics and toxic emissions of JUUL electronic cigarettes," *Tobacco Control*, vol. 28, no. 6, pp. 678–680, 2019.
- [66] C. L. Marcham and J. P. Springston, "Electronic cigarettes in the indoor environment," *Reviews on Environmental Health*, vol. 34, no. 2, pp. 105–124, 2019.
- [67] S. Klager, J. Vallarino, P. MacNaughton, D. C. Christiani, Q. Lu, and J. G. Allen, "Flavoring chemicals and aldehydes in E-cigarette emissions," *Environmental Science & Technology*, vol. 51, no. 18, pp. 10806–10813, 2017.
- [68] C. Nigro, A. Leone, G. Raciti et al., "Methylglyoxal-glyoxalase 1 balance: the root of vascular damage," *International Journal of Molecular Sciences*, vol. 18, no. 1, p. 188, 2017.
- [69] N. DeJarnett, D. J. Conklin, D. W. Riggs et al., "Acrolein exposure is associated with increased cardiovascular disease risk," *Journal of the American Heart Association*, vol. 3, no. 4, 2014.
- [70] N. L. Benowitz and J. B. Fraiman, "Cardiovascular effects of electronic cigarettes," *Nature Reviews. Cardiology*, vol. 14, no. 8, pp. 447–456, 2017.
- [71] F. Mayyas, H. Aldawod, K. H. Alzoubi, O. Khabour, A. Shihadeh, and T. Eissenberg, "Comparison of the cardiac effects of electronic cigarette aerosol exposure with waterpipe and combustible cigarette smoke exposure in rats," *Life Sciences*, vol. 251, p. 117644, 2020.
- [72] M. Kuntic, M. Oelze, S. Steven et al., "Short-term e-cigarette vapour exposure causes vascular oxidative stress and dysfunction: evidence for a close connection to brain damage and a key role of the phagocytic NADPH oxidase (NOX-2)," *European Heart Journal*, vol. 41, no. 26, pp. 2472–2483, 2020.
- [73] A. Avolio, "Arterial Stiffness," *Pulse*, vol. 1, no. 1, pp. 14–28, 2013.
- [74] J. M. Tarkin, F. R. Joshi, and J. H. F. Rudd, "PET imaging of inflammation in atherosclerosis," *Nature Reviews. Cardiology*, vol. 11, no. 8, pp. 443–457, 2014.

- [75] M. Chaumont, B. de Becker, W. Zaher et al., "Differential effects of E-cigarette on microvascular endothelial function, arterial stiffness and oxidative stress: a randomized crossover trial," *Scientific Reports*, vol. 8, no. 1, pp. 1–9, 2018.
- [76] I. Ikonomidis, D. Vlastos, K. Kourea et al., "Electronic cigarette smoking increases arterial stiffness and oxidative stress to a lesser extent than a single conventional cigarette: an acute and chronic study," *Circulation*, vol. 137, no. 3, pp. 303–306, 2018.
- [77] L. M. Van Bortel, S. Laurent, P. Boutouyrie et al., "Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity," *Journal of Hypertension*, vol. 30, no. 3, pp. 445–448, 2012.
- [78] K. P. Haptonstall, Y. Choroomi, R. Moheimani et al., "Differential effects of tobacco cigarettes and electronic cigarettes on endothelial function in healthy young people," *American Journal of Physiology. Heart and Circulatory Physiology*, vol. 319, no. 3, pp. H547–H556, 2020.
- [79] T. Kondo, Y. Nakano, S. Adachi, and T. Murohara, "Effects of tobacco smoking on cardiovascular disease," *Circulation Journal*, vol. 83, no. 10, pp. 1980–1985, 2019.
- [80] R. Carnevale, S. Sciarretta, F. Violi et al., "Acute impact of tobacco vs electronic cigarette smoking on oxidative stress and vascular function," *Chest*, vol. 150, no. 3, pp. 606–612, 2016.
- [81] M. A. Kaiser, H. Villalba, S. Prasad et al., "Offsetting the impact of smoking and e-cigarette vaping on the cerebrovascular system and stroke injury: is metformin a viable countermeasure?," *Redox Biology*, vol. 13, pp. 353–362, 2017.
- [82] I. M. Olfert, E. DeVallance, H. Hoskinson et al., "Chronic exposure to electronic cigarettes results in impaired cardiovascular function in mice," *Journal of Applied Physiology*, vol. 124, no. 3, pp. 573–582, 2018.
- [83] C. Anderson, A. Majeste, J. Hanus, and S. Wang, "E-cigarette aerosol exposure induces reactive oxygen species, DNA damage, and cell death in vascular endothelial cells," *Toxicological Sciences*, vol. 154, no. 2, pp. 332–340, 2016.
- [84] C. A. Lerner, I. K. Sundar, R. M. Watson et al., "Environmental health hazards of e-cigarettes and their components: oxidants and copper in e-cigarette aerosols," *Environmental Pollution*, vol. 198, pp. 100–107, 2015.
- [85] H. B. Lim and S. H. Kim, "Inhalation of e-cigarette cartridge solution aggravates allergen-induced airway inflammation and hyper-responsiveness in mice," *Toxicology Research*, vol. 30, no. 1, pp. 13–18, 2014.
- [86] J. Zhao, Y. Zhang, J. D. Sisler et al., "Assessment of reactive oxygen species generated by electronic cigarettes using acellular and cellular approaches," *Journal of Hazardous Materials*, vol. 344, pp. 549–557, 2018.
- [87] V. Ganapathy, J. Manyanga, L. Brame et al., "Electronic cigarette aerosols suppress cellular antioxidant defenses and induce significant oxidative DNA damage," *PLoS One*, vol. 12, no. 5, article e0177780, 2017.
- [88] U. Förstermann, N. Xia, and H. Li, "Roles of vascular oxidative stress and nitric oxide in the pathogenesis of atherosclerosis," *Circulation Research*, vol. 120, no. 4, pp. 713–735, 2017.
- [89] S. Chatterjee, J. Q. Tao, A. Johncola et al., "Acute exposure to e-cigarettes causes inflammation and pulmonary endothelial oxidative stress in nonsmoking, healthy young subjects," *American Journal of Physiology. Lung Cellular and Molecular Physiology*, vol. 317, no. 2, pp. L155–L166, 2019.
- [90] A. Higham, N. J. W. Rattray, J. A. Dewhurst et al., "Electronic cigarette exposure triggers neutrophil inflammatory responses," *Respiratory Research*, vol. 17, no. 1, p. 56, 2016.
- [91] M. Laukova, P. Vargovic, L. Csaderova et al., "Acute stress differently modulates  $\beta_1$ ,  $\beta_2$  and  $\beta_3$  adrenoceptors in T cells, but not in B cells, from the rat spleen," *Neuroimmunomodulation*, vol. 19, no. 2, pp. 69–78, 2012.
- [92] T. Heidt, H. B. Sager, G. Courties et al., "Chronic variable stress activates hematopoietic stem cells," *Nature Medicine*, vol. 20, no. 7, pp. 754–758, 2014.
- [93] H. Emami and A. Tawakol, "Noninvasive imaging of arterial inflammation using FDG-PET/CT," *Current Opinion in Lipidology*, vol. 25, no. 6, pp. 431–437, 2014.
- [94] H. Emami, P. Singh, M. MacNabb et al., "Splenic metabolic activity predicts risk of future cardiovascular events: demonstration of a cardiosplenic axis in humans," *JACC: Cardiovascular Imaging*, vol. 8, no. 2, pp. 121–130, 2015.
- [95] M. I. Dushkin and G. G. Kovshik, "Effect of toll-like receptor agonists on the formation of macrophage/foam cells upon acute peritonitis in mice," *Bulletin of Experimental Biology and Medicine*, vol. 156, no. 1, pp. 49–52, 2013.
- [96] J. Hansen, C. Brandt, A. R. Nielsen et al., "Exercise induces a marked increase in plasma follistatin: evidence that follistatin is a contraction-induced hepatokine," *Endocrinology*, vol. 152, no. 1, pp. 164–171, 2011.
- [97] A. Ghattas, H. R. Griffiths, A. Devitt, G. Y. H. Lip, and E. Shantsila, "Monocytes in coronary artery disease and atherosclerosis: where are we now?," *Journal of the American College of Cardiology*, vol. 62, no. 17, pp. 1541–1551, 2013.
- [98] D. Fukuda, S. Nishimoto, K. Aini et al., "Toll-like receptor 9 plays a pivotal role in angiotensin II-induced atherosclerosis," *Journal of the American Heart Association*, vol. 8, no. 7, article e010860, 2019.
- [99] N. Gerdes, T. Seijkens, D. Lievens et al., "Platelet CD40 exacerbates atherosclerosis by transcellular activation of endothelial cells and leukocytes," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 36, no. 3, pp. 482–490, 2016.
- [100] J. Liu, J. Xu, T. Zhang et al., "Decoding the immune microenvironment of clear cell renal cell carcinoma by single-cell profiling to aid immunotherapy," *Frontiers in Immunology*, vol. 13, pp. 1–14, 2022.
- [101] S. J. Bielinski, C. Berardi, P. A. Decker et al., "P-selectin and subclinical and clinical atherosclerosis: the multi-ethnic study of atherosclerosis (MESA)," *Atherosclerosis*, vol. 240, no. 1, pp. 3–9, 2015.
- [102] S. Hom, L. Chen, T. Wang, B. Ghebrehiwet, W. Yin, and D. A. Rubenstein, "Platelet activation, adhesion, inflammation, and aggregation potential are altered in the presence of electronic cigarette extracts of variable nicotine concentrations," *Platelets*, vol. 27, no. 7, pp. 694–702, 2016.
- [103] H. Qasim, Z. A. Karim, J. C. Silva-Espinoza et al., "Short-term E-cigarette exposure increases the risk of thrombogenesis and enhances platelet function in mice," *Journal of the American Heart Association*, vol. 7, no. 15, 2018.
- [104] R. S. Moheimani, M. Bhetraratana, K. M. Peters et al., "Sympathomimetic effects of acute E-cigarette use: role of nicotine and non-nicotine constituents," *Journal of the American Heart Association*, vol. 6, no. 9, 2017.

- [105] R. S. Moheimani, M. Bhetraratana, F. Yin et al., "Increased cardiac sympathetic activity and oxidative stress in habitual electronic cigarette users: implications for cardiovascular risk," *JAMA Cardiology*, vol. 2, no. 3, pp. 278–284, 2017.
- [106] S. Hillebrand, K. B. Gast, R. de Mutsert et al., "Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: meta-analysis and dose-response meta-regression," *EP Europace*, vol. 15, pp. 742–749, 2013.
- [107] J. Margham, K. McAdam, M. Forster et al., "Chemical composition of aerosol from an E-cigarette: a quantitative comparison with cigarette smoke," *Chemical Research in Toxicology*, vol. 29, no. 10, pp. 1662–1678, 2016.
- [108] C. Protano, P. Avino, M. Manigrasso et al., "Environmental electronic vape exposure from four different generations of electronic cigarettes: airborne particulate matter levels," *International Journal of Environmental Research and Public Health*, vol. 15, no. 10, p. 2172, 2018.
- [109] H. Chang, "Research gaps related to the environmental impacts of electronic cigarettes," *Tobacco Control*, vol. 23 Suppl 2, p. ii54-8, 2014.
- [110] P. Hajek, A. Phillips-Waller, D. Przulj et al., "A randomized trial of E-cigarettes versus nicotine-replacement therapy," *The New England Journal of Medicine*, vol. 380, no. 7, pp. 629–637, 2019.
- [111] E. Aminullah, "E-cigarette as disruptive innovation: forecasting of conventional cigarette substitution in Indonesia," *STI Policy and Management Journal*, vol. 4, no. 2, 2019.
- [112] P. Pokhrel, P. Fagan, L. Kehl, and T. A. Herzog, "Receptivity to e-cigarette marketing, harm perceptions, and e-cigarette use," *American Journal of Health Behavior*, vol. 39, no. 1, pp. 121–131, 2015.