Review

Xenobiotics Delivered by Electronic Nicotine Delivery Systems: Potential Cellular and Molecular Mechanisms on the Pathogenesis of Chronic Kidney Disease

Pablo Scharf, Felipe Rizzetto, Luana Filippi Xavier [ID] and Sandra Helena Poliselli Farsky *

Department of Clinical and Toxicological Analyses, School of Pharmaceutical Sciences, University of Sao Paulo, São Paulo 05508-220, Brazil
* Correspondence: sfarsky@usp.br

Abstract: Chronic kidney disease (CKD) is characterized as sustained damage to the renal parenchyma, leading to impaired renal functions and gradually progressing to end-stage renal disease (ESRD). Diabetes mellitus (DM) and arterial hypertension (AH) are underlying diseases of CKD. Genetic background, lifestyle, and xenobiotic exposures can favor CKD onset and trigger its underlying diseases. Cigarette smoking (CS) is a known modified risk factor for CKD. Compounds from tobacco combustion act through multi-mediated mechanisms that impair renal function. Electronic nicotine delivery systems (ENDS) consumption, such as e-cigarettes and heated tobacco devices, is growing worldwide. ENDS release mainly nicotine, humectants, and flavorings, which generate several byproducts when heated, including volatile organic compounds and ultrafine particles. The toxicity assessment of these products is emerging in human and experimental studies, but data are yet incipient to achieve truthful conclusions about their safety. To build up the knowledge about the effect of currently employed ENDS on the pathogenesis of CKD, cellular and molecular mechanisms of ENDS xenobiotic on DM, AH, and kidney functions were reviewed. Unraveling the toxic mechanisms of action and endpoints of ENDS exposures will contribute to the risk assessment and implementation of proper health and regulatory interventions.

Keywords: diabetes mellitus; hypertension; nicotine; risk assessment; flavoring agents; volatiles organic compounds; cigarette smoking; ENDS

1. Introduction

Chronic kidney disease (CKD) is a silent outcome that occurs due to the aging process as a consequence of metabolic and vascular diseases. It occurs due to a sustained damage of renal parenchyma evolving to the chronic deterioration of renal function, which may gradually progress to end-stage renal disease (ESRD) [1]. CKD affects about 13.4% of inhabitants worldwide, leading to severe morbidity and mortality. It is more prevalent in people older than 65; nevertheless, the expectancy of progression to ESRD is higher when the disease manifests itself in younger people [2]. The aging of an organism proceeds at variable rates, being influenced by gene background, lifestyle, environmental exposure, and habits. Therefore, the etiology and incidence of CKD varies widely worldwide [3]. The disease is more prevalent in the low socioeconomic status population, and racial/ethnic/low-class minority groups in high-income countries [4]. CKD overcharges health systems worldwide, as all stages of the disease can be responsible for the impaired quality of life and the premature death of patients [5].

CKD presents a well-defined progression; however, prevention of ongoing disease is still a challenge, as symptoms occur during the latter phase of disease and early sensitive and specific biomarkers are not available. The progression of CKD, before reaching ESRD, can last for years [6]. Robust data associate CKD to previous type II Diabetes Mellitus (DM) and arterial hypertension (AH). Indeed, about 20% to 30% of DM patients evolve to

ESRD, and hypertensive patients are around 15 times more likely to develop ESRD than normotensive individuals [7,8].

Long-term exposure to environmental pollutants may lead to silent toxic effects, where symptoms are manifested at the late progression of diseases [9,10]. Cigarette smoking (CS) is responsible for severe health problems and is pointed out as the major cause of preventable deaths worldwide. It is expected that cigarette smoking causes about 7.5 million deaths/year and burdens individuals and health systems, achieving up to US $500 billion globally per year, with costs of productivity loss, illnesses and premature deaths [11]. Although massive tobacco control policies have been successful, with marked reductions in the estimated prevalence of daily smoking in the last 20 years, the number of smokers increased significantly at the global level because of population growth. Beyond that, in some countries and territories, such as China, Albania, Portugal and Latin America, smoking prevalence among adolescents of both genders has augmented substantially and represented a steady increase among young people [11–13]. CS is a severe concern to CKD onset and progression and growing epidemiological studies have pointed out an increase incidence of CKD among the healthy population or diabetic subjects [14–20].

DM incidence, especially type II, has increased worldwide during the last decades, generating a tremendous impact on public health systems [21]. Exposure to environmental pollution is associated with DM prevalence [22], including CS [23,24]. Several epidemiological studies demonstrated the high incidence of pre-diabetes or DM in heavy smokers. Furthermore, quitting smoking reduces the estimative of occurrences of the disease, especially ten years after stopping tobacco addiction [4]. DM leads to damage of blood vessels, with consequent macro and microvascular complications, which are worsened by smoking [25]. Therefore, smoking is a pivotal modifiable risk factor to prevent the onset or delay the DM complications [26]. Moreover, several studies associate the risk of smoking during pregnancy or feeding on insulin resistance and DM in the offspring. Hypoxia, oxidative stress, and inflammation in the uterus microenvironment of smoker mothers lead to epigenetic alterations related to DM genesis [27].

AH is also a highly prevalent disease and is one of the leading causes of premature death worldwide [28]. Unquestionably repeated exposure to combustible product released by CS leads to AH and can display different mechanisms on AH genesis [29], such as (I) modifying the metabolism and the reactivity of endothelial and muscles of vessels wall [30]; (II) causing systemic inflammation and atherosclerosis; (III) oxidative stress [31]; (IV) impairing renal filtration which activates the renin-angiotensin and aldosterone system [32]; and (V) activating the sympathetic nervous system and hypothalamus-pituitary-adrenal gland axis with consequent release of vasoconstrictors [33].

Based on the incidence of DM and AH in smokers, one could expect a positive correlation between smoking and CKD. Indeed, smoking is an inducer and accelerating agent on the progression of established CKD in adults and young people, and smoking is considered a modifiable lifestyle factor for the prevention of CKD [34,35]. Moreover, products released by CS cause direct noxious effects in renal cells, and the main mechanisms are an unbalanced redox system and induction of inflammation. The intracellular downstream effects elicited by reactive oxidative species (ROS) and inflammatory mediators amplify the inflammatory process and activate cellular death pathways in renal cells [36,37].

The toxicity of CS is associated with the release of nicotine and products generated during the combustion process, which reached temperatures around 650 °C. It generates more than 8000 compounds, and almost 70 are classified as carcinogens [38]. Indeed, tobacco-released products can trigger several deleterious effects and impair multiple function, such as hematopoiesis [39], autoimmune and inflammatory responses [40,41], metabolism [42], respiratory functions [43] and so on. As a possible harm reduction tool to current smokers, tobacco products lacking the combustion process have emerged worldwide [44,45]. These products named electronic nicotine delivery systems (ENDS) include e-cigarettes, pods, and heated tobacco products that can release nicotine and other chemicals by a heating process [46]. However, knowledge about the toxicity of ENDS is still limited, and further

experimental and epidemiological data are required for the risk assessment of the possible chronic effects of these devices and their possible association with diseases onset, such as CKD. Although ENDS lack combustion, they can release nicotine, byproducts from thermal degradation (acrolein and carbonyl compounds), and flavoring agents that can trigger potential toxic effects related to several pathological conditions [45,47].

Based on the growing consumption of tobacco products, including ENDS, here we review the current knowledge of the mechanism underlying the toxic actions of xenobiotics released by ENDS and their role on CKD pathophysiology. We focused on the role of nicotine, solvents employed as vehicles, and toxic substances generated by ENDS devices in the genesis of CKD, centering the attention on mechanisms of DM, AH, and the damage of renal cells.

2. Electronic Nicotine Devices Systems (ENDS): A Rising Concern for CKD Pathogenesis?

Based on the recognized hazardous effects of tobacco combustion, a wide array of nicotine replacement therapies has been used to aid tobacco cessation in a therapeutic context for over 30 years, including gums, transdermal patches, nasal spray, oral inhalers, and tablets [44]. The first ENDS emerged in the 60′s decade also as an alternative to delivering nicotine by airways, in pulses, as occurs in cigarette addiction. They were proposed as harm reduction agents; nevertheless, the enormous technological advances in vaping nicotine and a increased number of commercialized devices led to widespread employment over the world in the last decade [46].

All ENDS devices have a rechargeable battery, and, in some cases, an atomizer is necessary to heat the nicotine content. Nicotine can be stored in a cartridge filled with a liquid that can be exchanged, or in special tobacco sticks, known as heat-not-burn tobacco systems [45]. Both systems use glycerin and propylene glycol as humectants; nevertheless, several flavorings can be used for commercial appeal. In some cases, liquids and cartridges are filled with flavorings without nicotine [47].

Conventional cigarettes burn tobacco and generate smoke and ashes during the combustion process; differently, ENDS are heated at much lower temperatures when compared to conventional cigarettes, generating vapor [48]. Although ENDS deliver much lower amounts of tobacco combustion products, the heating process can generate byproducts from thermal degradation or compounds released from batteries supply, for which toxicity has not been described [45]. Indeed, recent epidemiological evidence has provided controversial data, such as on AH [49,50] as DM [51,52].

Considering the importance of CKD as a public health problem and the growing employment of ENDS worldwide, it is pivotal to evaluate if such exposures can evoke cellular and molecular mechanisms related to CKD onset and progression. Notably, further experimental, clinical, and epidemiological data about the acute and chronic use of ENDS are required to assess their real toxicity. Therefore, we selected the main compounds delivered by ENDS devices and depicted their potential toxic mechanisms involved in CKD pathogenesis.

3. Nicotine

Nicotine (3-(1-methyl-2-pyrrolidinyl) pyridine) is a water-soluble alkaloid and the main component found in tobacco leaves [53]. Nicotine is promptly absorbed by the lungs and biodistributed. Pharmacokinetics studies designed to assess the nicotine uptake by electronic aerosol devices showed similarities in nicotine absorbed from conventional cigarettes. Both caused a rapid increase in plasma concentration (minutes) with similar Tmax and Cmax, and a half-life of around 60–90 min [54]. About 80% of nicotine is metabolized to cotinine in the liver microsomes, mainly by the isoform CYP2A6 enzyme; cotinine is further metabolized by the same enzyme to trans-3-hydroxycotinine. Furthermore, nicotine is also metabolized to norcotinine via N-demethylation by CYP2A6 and CYP2B6 at low and high substrate concentrations, respectively. Gene polymorphism of CYP2A6 leads to differences in nicotine metabolism and smoking behavior [55].

Nicotine binds to nicotine acetylcholine receptors (nAChRs), widely distributed in central and peripheral nervous systems and on a diversity of peripheral cells, such as including epithelium, endothelium, immune (neutrophils, monocytes, macrophages, DC, B cells, and T cells), cancer, astrocytes, and oligodendrocytes [56–59]. nAChRs are transmembrane pentameric ligand-gated ion channel members of the Cys-loop superfamily. The receptor comprises five distinct subunits, which form a central aqueous pore that allows cation (Ca^{2+}, Na^+, K^+) transportation, an extracellular domain that binds to ligands, a transmembrane and an intracellular domain [60,61]. Agonist binding on nAchR displays rapid conformational changes on the three-dimensional structures of the receptors. It leads to ion channels opening to the influx of cations and rapid cell depolarization [60]. Seventeen subunits of nAChRs are characterized, in which 12 subunits are known neuronal-type nAChRs (α2–α10 and β2–β4) and five subunits are muscle-type nAChRs (α1, β1, δ, γ and ε) [62]. Beyond their channeling activity, nAChRs activation mediates diverse intracellular events involving signaling through PI3-kinase, ERK1/2, AKT, and CREB pathway, and mediates proteolysis and mitochondrial permeability [63]. The extraordinary diversity and distribution of nAChR isoforms, associated with different affinities to ligands, results in numerous functional responses to agonists [57–59,64]. In physiological conditions, nAChRs bind to acetylcholine and trigger neuron depolarization and the parasympathetic autonomic nervous system in the peripheral systems [65]. It displays pivotal roles in the homeostasis of different systems, such as cardiovascular, respiratory, central nervous, and immune [66]. In comparison to acetylcholine, nicotine causes longstanding activation of nAchR, accompanied by rapid receptor desensitization [60,67]. Therefore, chronic nicotine exposure causes adaptations on the central nervous system, including the upregulation of nAChR subtypes. As a consequence, a withdrawal syndrome develops during attempts to quit smoking.

Data have associated nicotine exposure and AH incidence and pointed out different and interconnected mechanisms due to the high distribution and diversity of nAchR on cells involved in the complex genesis of AH, such as:

(I)   Different mechanisms of action of nicotine on the vascular and cardiac autonomic nervous system have been broadly shown. For instance, nicotine directly affects the cardiac autonomic nervous system and mediates cardiac autonomic ganglion transmission [68,69]. Notably, nicotine during pregnancy results in autonomic dysfunction and increased blood pressure in the offspring, leading to structural–functional modifications in the arterial wall and heart [70]. Nicotine also impairs the baroreflex sensitivity to sodium nitroprusside by disrupting adenosine A(2A) receptor-mediated facilitation of reflex cardiac sympathetic excitation [71];

(II)   Activation of nAChRs in adrenal gland chromaffin cells induces the release of catecholamine into blood, which acts in peripheral vessels receptors and elevates the blood pressure [72];

(III)   Long-lasting exposure to nicotine affects target genes correlated to blood pressure control. Elevation of the blood pressure in mice by nicotine administration was associated with reduced expression and activity of renal 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) in renal cortical collecting duct cells. 11β-HSD2 catalyzes the conversion from active into inactive glucocorticoids and favors the expression and occupancy of mineralocorticoids receptors. The suppression of 11β-HSD2 by nicotine was dependent on the suppression of C/EBPβ (CCAAT/enhancer-binding protein-β) and activation of Akt protein kinase phosphorylation (pThr308Akt/PKB) by kidney cells [73]. Furthermore, exposure to oral nicotine for 28 days increased blood pressure, impaired glomerular filtration rate and fraction excretion of sodium, and augmented sympathetic cardiac modulation in mice with reduced renal Klotho gene expression [74]. The gene encodes a single-pass transmembrane protein expressed predominantly by the distal convoluted tubules in the kidneys and is related to calcium-phosphorus metabolism, ion channel regulation, intracellular signaling pathways, and longevity. Klotho deficiency is associated with a syndrome that resembles human aging, acute

kidney injury and renal fibrosis. Moreover, the overexpression or replacement of klotho protects against or ameliorates such injury [75,76]. Therefore, the association of nicotine actions on the expression of the Klotho gene by distal tubules cells deserves further investigation to provide knowledge to the comprehension of nicotine on the genesis of AH and CKD;

(IV) Nicotine affects the mechanisms of endothelial cells on the control of blood pressure and leads to kidney inflammation. Chronic exposure to nicotine by an oral route further increased the blood pressure of rats evoked by high-diet obesity, related to endothelial activation and inflammation. In this context, nicotine augmented the expression of superoxide in endothelial cells and impaired endothelial nitric oxide synthase (eNOS), an endothelial-derived relaxing factor. Indeed, several nAChR subunits are identified in endothelial cells, and their activation leads to downstream signaling that mediates endothelial proliferation, survival, migration, angiogenesis, blood pressure, and inflammation [77,78]. Furthermore, peritoneal macrophages of nicotine-treated obese rats further released tumor necrosis factor (TNF) α and interleukin (IL) 1β and presented higher expression of CD36 [79]. In addition, the role of systemic nicotine as an inducer of renal inflammation was shown, as a continuous infusion of nicotine for two weeks in spontaneously hypertensive rats caused marked infiltration of CD161a$^+$ monocyte into kidneys and premature hypertension. The renal infiltration of cells was correlated to the augmented secretion of the chemotactic cytokine monocyte-chemoattractant-protein-1 (MCP-1) and the membrane expression of the adhesion molecules very-late antigen-4 (VLA-4) and CD161a ligand Lectin-LikeTranscript-1 (LLT1) by renal cells [32];

(V) Nicotine alters the renin-angiotensin-aldosterone system (RAAS) homeostasis. Chronic nicotine administration elevated plasma renin activity in rats subjected to a high-salt diet, and nicotine administration increased plasma angiotensin-converting enzyme activity, with consequent enhancement of conversion of angiotensin I to angiotensin II [80]. Moreover, nicotine exposure inhibited aldosterone production by the adrenal gland, which led to compensatory RAAS activation upon chronic exposures [81,82]; and

(VI) Nicotine modulates the cholinergic central nervous system and activates the hypothalamic-pituitary-adrenal (HPA) axis, which increases blood pressure by sympathetic stimulation [83].

The fine-tuning mediation of nicotine on neuroendocrine systems is extensively shown. In this way, nicotine displays several mechanisms on glucose and insulin homeostasis and may cause dual opposite effects dependent on concentrations and lasting exposures [84].

As previously described, nAchR activation induces catecholamines release and HPA activation [72,85] Secreted catecholamines mobilize glucose primarily from stored skeletal muscle and liver glycogen [85]. Augmented levels of cortisol in the blood cause: (I) liver gluconeogenesis, with the consequent decrease on glucose uptake; (II) a permissive role for catecholamine-induced glycogenolysis and/or inhibition on insulin-stimulated glycogen synthesis; (III) modulation on functions of pancreatic α and β cells to regulate the secretion of glucagon and insulin. Therefore, elevated catecholamines and glucocorticoids levels lead to hyperglycemia and insulin resistance [85].

More recently, it has proposed a novel pathway on glucose control by nicotine in the brain, by the interconnection of diabetes-associated transcription factor 7 like 2 (TCF7L2) and nAchRs in the ventral region of the medial habenula. Indeed, the medial habenula is a major cholinergic pathway in the brain [86] that maintains a polysynaptic connection with the pancreas [87], and expresses TCF7L2. Activation of medial habenula by nicotine disrupts blood glucose homeostasis, reflected by elevated fasting blood glucose and glucagon levels, which was not detected in animals deficient in TCF7L2 [88].

Islet β cell senescence is a hallmark of DM. Senescent β cells permanently loose proliferative capacity. They are characterized by shortened telomeres, higher expression of senescent markers, such as p16, p21, and p19, elevated secretion of multiple pro-inflammatory

cytokines, including TNF, IL-6, MCP1, and IL-1β, increased cell size, high glucose uptake, and mitochondrial dysfunction [89]. Direct nicotine exposure led to β cells senescence by local accumulation of reactive oxygen species (ROS) [90], reinforcing the ability of nicotine to induce oxidative stress, as yet had been proposed as a toxic mechanism in other tissues [91–93]. Nevertheless, the hazardous role of nicotine on Islet β cells may depend on concentration and schedule of exposures. Stimulation of nAChR by nicotine, especially α7nAChR, increased insulin secretion and reduced cytokine-induced apoptosis in human and murine islet cells [94]. Moreover, in vivo administration of nicotine ameliorated the diabetic phenotype in rodent obese models and type I DM [95,96]. A proposed mechanism to these beneficial effects is the re-establishment of cell homeostasis, by modulating the stress endoplasmic reticulum and activation of inositol requiring enzyme 1α [97].

Nicotine is the tobacco compound most highly correlated with metabolic dysfunction in offspring of tobacco addict mothers. Exposure of pregnant mice to nicotine caused several systemic effects in the mother and offspring, including insulin resistance [98–100]. Robust investigations support that nicotine intake leads to glucocorticoid overexposure in the mother. Exacerbated glucocorticoid actions lead to intrauterine neuroendocrine programming changes in offspring switching them susceptible to metabolic diseases [98,101]. Moreover, chronic nicotine exposure to dams causes oxidative stress and toxicity in target cells. It promotes post-translational histones in perivascular adipose tissue and β-cells [102,103]. Recently, it was found that a pre-diabetic state in offspring of nicotine-exposed dams was associated with downregulated transcription factor sterol regulatory element-binding protein-1c (SREBP-1c), peroxisome proliferator-activated receptor-α (PPAR-α), and insulin receptor in the liver [99,104]. SREBP-1c transduces the insulin signal and induces the expression of a family of genes involved in glucose utilization, fatty acid synthesis, and PPAR-α regulates glucose synthesis during fasting states and gluconeogenesis [105].

Beyond evoking mechanisms related to DM or AH, nicotine directly acts on kidney cells. Indeed, nAChR isotypes are highly distributed in the kidney [106,107]. Some investigations show α7nAChR activation by agonists protects renal against ischemia/reperfusion injury by eliciting anti-inflammatory actions [106–108]. Conversely, in vitro and in vivo investigations describe the toxicity of nicotine in renal cells, mainly by triggering oxidative stress and inflammation. These effects impair the viability and function of renal tubular and endothelial cells, alter renal hemodynamics, and compromise overall kidney function [109,110].

The connection between immune cells and cholinergic innervation in kidney lesions was demonstrated in different experimental models of spontaneously hypertensive rats. Administration of nicotine-induced premature hypertension, renal expression of the sodium-potassium chloride co-transporter, increased renal sodium retention, and an influx of CD161a$^+$/CD68$^+$ macrophages into the renal medulla. Bilateral renal denervation and depletion of CD161a$^+$ immune cells abolished the toxicity caused by nicotine [32,111]. Moreover, sustained elevated expression of the unphosphorylated form of signal transducer and activator of transcription-3 (U-STAT3) was detected in kidneys of nicotine-exposed mice and was related to the sustained transcription of genes linked to remodeling and inflammation in the kidney during injury [112,113]; and incubation of nicotine with human cell kidney led to ROS generation and activation of NLRP6 inflammasome and endoplasmic reticulum (ER) stress [114].

Nicotine exposure exacerbates diabetic nephropathy, which is a leading cause of CKD. Expansion of mesangial, a precursor of glomerular sclerosis, is a hallmark of diabetic nephropathy [115]. Also, nicotine exposure further enhances the mesangial cell proliferation caused by hyperglycemia, dependent on enhanced Wnt/β-catenin downstream in primary human renal mesangial cells [116]. Indeed, DM leads to up activation of Wnt1/β-catenin signaling. The activation of the signaling pathway promoted podocyte injury, the epithelial–mesenchymal transition of podocytes, along with renal injury and fibrosis [117,118]. Moreover, nicotine binds to podocytes, causes an unbalance of the redox system, and activates inflammatory and apoptotic pathways. DM mice exposed to nicotine

presented proteinuria and reduced glomerular podocyte synaptopodin. Synaptopodin is a crucial stabilizer of the podocyte cytoskeleton [119]. As podocytes are pivotal to maintaining the structure and function of the glomerular filtration barrier, the hazardous mechanisms described by nicotine actions assuredly contribute to CKD.

Considering nicotine released by CS and ENDS presents high bioavailability, prompt reaching peripheral and central systems, the mechanisms elicited above can be triggered by both tobacco products. It is pivotal novel epidemiological and experimental data that could clarify the real role of these novel tobacco devices on the genesis of AH, DM, and CKD. Indeed, e-cigarette consumption caused alteration in the renal functions with changes in pivotal parameters, such as urea and creatinine, histological changes in the renal tissue. Altogether, these symptoms point out the possible nephrotoxic effects due to nicotine delivered by these devices [120].

4. ENDS Vehicles and Its Thermal Degradation Byproducts

Humectants are employed in ENDS devices to generate aerosols/vapor upon the heating process. Propylene glycol (PG) and vegetable glycerin (VG) is the most common vaporizing carriers employed in these devices. They favor the delivery of flavorings and nicotine [121]. The addition of PG and VG is widely employed in the food industry, presenting almost no toxicity when used for ingestion, however, when there are modifications in the route of administration, toxic effects are observed. In vitro studies show PG or VG alters cell growth and survival and impairs DNA repair functions [122,123]. On the other hand, intramuscular injection of glycerol is used as an experimental model of rhabdomyolysis-induced acute kidney injury, which is reduced by anti-oxidant administration [124]. Upon the heating process, PG and VG can generate byproducts with recognized toxicities, including reactive aldehydes and volatile organic compounds, such as acrolein, acetaldehyde, and formaldehyde [125]. It is noteworthy to mention, these later compounds are also found in the CS.

Acrolein is a highly reactive unsaturated aldehyde, which displays dose-dependent toxicity. Acrolein is generated from the thermal degradation and reaction of glycerol, and its formation can increase by 28-fold when glycerol e-liquid composition reaches 80%, which is a current concern during ENDS exposures [126,127]. Acrolein exposures activate/inactivate several pathways related to AH, as follows: (I) acrolein activates the transient receptor potential ankyrin 1 (TRPA1), a non-selective cation channel, and increases vascular permeability and leukocyte extravasation, leading to microvascular endothelial dysfunction [128,129]; moreover, TRPA1 activation can also increase the release of the hypertensive neuropeptide Substance P [130]; (II) acrolein reacts with structural molecules and disturbs the cellular redox balance, not only by increasing ROS production but also by depleting the antioxidant enzyme glutathione [131]; (III) higher and chronic acrolein exposures can also suppress eNOS phosphorylation and induce the Activating Transcription Factor-2 (ATF-2) expression, which leads to increased expression of the angiotensin 1 receptor in arteries [132,133]. Indeed, experimental models exposed to acrolein displayed increased diastolic and systolic values, followed by higher blood pressure and arrhythmias [134].

Acrolein exposures and detection of its urinary metabolites N-acetyl-S-(3-hydroxypropyl)-L-cysteine (3-HPMA) and N-acetyl-S-(carboxyethyl)-L-cysteine (CEMA) present a positive correlation with the development of DM and insulin resistance [135,136]. Although the precise mechanism involved in the diabetogenic potential of acrolein remains unclear, these events are closely related to the capacity of acrolein to activate oxidative stress and systemic inflammation, which directly affects glucose metabolism and insulin resistance [133,136].

Acetaldehyde and formaldehyde are volatile compounds routinely related to carcinogenic outcomes [137]. However, both chemicals evoke hemodynamic alterations in experimental models, such as altered heart rate, increased blood pressure, and impaired cardiac contractibility [138,139]. Furthermore, these chemicals lead to oxidative burst, which triggers inflammatory responses and systemic toxic effects. Higher levels of acetaldehyde and formaldehyde are found in the course of metabolic syndromes and DM [140]. Although

both compounds are generated under homeostasis, it was observed that the administration of exogenous formaldehyde was able to induce hyperglycemia in rats, followed by a deficiency in insulin signaling [139]. Formaldehyde exposures into experimental animals induced proximal tubule necrosis and increased the concentration of malonaldehyde, indicating the activation of redox signaling [141]. The latter observation was corroborated by an impaired renal function of formaldehyde-exposed rats, characterized by increased urea and creatinine levels, and altered renal structure caused by a marked enhancement in Bowman's space [142].

5. Flavoring Agents

Flavorings are chemical substances constantly added to ENDS, surpassing more than 7000 flavors that are used to make products more attractive to consumers [143]. Although many of the added flavorings in ENDS are recognized as safe (GRAS) by the FDA, these compounds are safe for ingestion, but not for inhalation after heating. The heating processes to inhalation generates ultrafine and toxic particles from flavoring compounds, wherein absorption by the lungs directly leads to harmful systemic effects [144]. The most common flavors added to stimulate consumption reach a vast range of options, such as minty, sweet, fruity, peppery, and buttery flavors [145]. Other flavors are employed to enhance the user experience, which includes menthol, cinnamaldehyde, vanillin and diacetyl. Tobacco products containing menthol can reduce the irritation caused by nicotine and other aerosolized products, once menthol modulates sensorial perception, leading to deeper inhalation and exposure to higher amounts of nicotine and other toxic particles [146].

Menthol and cinnamaldehyde are flavoring agents shared with conventional and combustible cigarettes. Although the systemic effects of inhaled flavorings are still unclear, the presence of menthol and cinnamaldehyde in nicotine-containing devices directly affects nicotine metabolism, nAChR expression, and distribution [146–148]. Both cinnamaldehyde and menthol can inhibit the main nicotine-metabolizing enzyme, CYP2A6. In fact, impaired nicotine metabolism and clearance favor addictive behaviors, leading to increased tobacco consumption and exposure to the aforementioned xenobiotics [149,150].

Beyond the direct effects on nicotine metabolism, cinnamaldehyde can directly activate TRPA1, which is widely expressed in neural and non-neural cells, such as endothelial, myocytes, and renal tubular cells [151]. Clinical and translational reports show a deleterious effect led by TRPA1 activation [151,152]. TRPA1 expression is directly associated with more severe cases of renal tubular, the expression of the DNA damage and oxidative stress marker 8-hydroxydeoxyguanosine (8-OHdG), indicating that TRPA1 activation plays a pivotal role in renal dysfunction [151]. It was observed that TRPA1 activation evoked higher ROS production and activation of mitogen-activated protein kinase (MAPK) and nuclear factor *kappa* B (NFκB) pathways, which resulted in IL-8 secretion by the human proximal tubular cells HK-2 [152]; beyond the lung microenvironment, cinnamaldehyde present in e-cigarettes displays higher cardiotoxicity; in vitro experiments testing the cytotoxicity of cinnamaldehyde in endothelial and in human-induced pluripotent stem cell-derived cardiac myocytes (hiPSC-CMs) indicated cinnamaldehyde increases cell death and impairs cellular metabolism and functions [153,154]; cinnamaldehyde drives to increased DNA damage even in non-cytotoxic concentrations, which highlights its cumulative cell damage [155].

Diacetyl is a member of organic diketones and is widely employed in the food industry to add buttery-based flavors to food [156]. Diacetyl has been detected in several ENDS; in some e-cigarettes, the aerosols can reach a concentration of 239 µg/e-cigarette [157]. With the exponential growth of novel ENDS flavors, it was observed that out of 51 e-cigarettes tested, 47 had detectable concentrations of diacetyl or its substitutes [157]. Diacetyl is the most common example of safe flavoring by oral ingestion, but not for inhalation [156]. Although the effects of inhaled diacetyl on ENDS users remain elusive, retrospective studies assessing the occupational exposures to heated and inhaled diacetyl indicate its potential toxicity, especially to the airways [158,159]. Diacetyl can interact with structural proteins,

especially arginine-rich proteins, causing cellular damage and leading to aggregated and misfolded proteins, which in turn can trigger autophagy-mediated cell death [160,161]. Diacetyl exposure also evokes higher ROS production, formation of the DNA adducts deoxyguanosine, and in some cases, causing cell death by excessive ROS-induced damage [160,162].

6. Ultrafine Particles

In addition to the toxic effects directly caused to the ENDS user, aerosolized substances can release toxic compounds into the environment and generate secondhand exposures to bystanders [163]. Although particulate matter (PM) from combustible cigarettes is widely discussed, in particular $PM_{2.5}$, the ultrafine particles (≤ 0.1 μm in diameter) have emerged as a great public health problem regarding indoor air quality along with the increasing consumption of ENDS [164,165].

The knowledge of the effects of ENDS consumption on indoor air quality and the assessment of delivery particles to the users requires further investigation. Nevertheless, ultrafine particles emitted during ENDS use can increase up to 10-fold in comparison to basal levels, reaching 7.2×10^3 to 6.2×10^4 particles/cm^3 [166]. The ultrafine particle emission by ENDS is affected by several factors, such as the ENDS device generation, heating temperature, device voltage, and also e-liquid/tobacco-based stick composition [167]. Higher voltage devices generate more particles than low voltage devices [168,169]. Besides, the chemical composition of ENDS directly influences the concentration of emitted particles, including nicotine content, flavors, and the PG/VG ratios, which evoke higher particle releases by increased concentrations of chemicals [166].

The toxicity of ultrafine particles is based on their size and charge. Most inhaled ultrafine particles can reach deeper regions of the lung than larger particles (1–2.5 μm) [170]. Besides, positively charged ultrafine particles are up to 40 times more likely to penetrate cells than negatively charged particles [171]. Ultrafine particles translocate through the alveolar epithelium through diffusion [171]. Once these particles reach the lung vasculature, or lymphatic circulation, the inhaled ultrafine particles can trigger systemic inflammation, leading to vascular dysfunction and accumulation in the liver and kidney to exert their toxic effects [170,172,173].

Ultrafine particles generated by ENDS and released in secondhand exposures can increase intracellular calcium in the vasculature, evoking contractile dysfunction and disturbing heart rate, leading to arrhythmias [173,174]. These deleterious effects are related to the onset of oxidative stress and the activation of inflammatory pathways. Indeed, the ROS production evoked by ultrafine particles reacts with NO and shortens its endothelial bioavailability [175–177]. Several studies reported that ultrafine particles increase blood pressure and lead to coagulation-related changes [176,177]. The direct interaction of ultrafine particles with endothelium also causes vascular inflammation and sustains atherosclerosis establishment [170].

Although the effects of ultrafine particles released by ENDS on carbohydrate metabolism and pathophysiological mechanisms of DM are still limited, studies have shown the toxic potential of ultrafine particles present in air on DM outcomes [178,179]. DM patients who inhaled ultrafine carbon-based particles showed changes in coagulation parameters, in addition to higher levels of platelet activation and IL-6, enhancing hemodynamic dysfunction [180,181]. Indeed, ultrafine particles present in air pollution increase the risk of AH and DM [176,181].

Based on the mechanism involved on the toxicity of ultrafine particles and how these pollutants can trigger CKD-based diseases, it is possible to consider that, once ENDS are a growing source of first and secondhand ultrafine particles, the cumulative exposure can favor CKD onset and also exacerbate cardiovascular and metabolic dysfunction.

7. Conclusions and Future Perspectives

The consumption of ENDS worldwide has grown exponentially, but the toxicity generated by chronic exposures to these devices is still unknown. Potentially harmful

compounds released by ENDS can directly modulate cellular and molecular mechanisms related to chronic and multi-mediated disease onset, such as CKD. Although the precise mechanisms related to the interaction between ENDS use and CKD onset require further investigation, the possible pathways involved, and the xenobiotics released by ENDS are summarized in Figure 1. The elucidation of how ENDS and its released toxic substances can trigger systemic conditions which favor CKD onset and progression will provide novel data regarding the toxicity of non-combustible tobacco products, making it possible to improve the risk assessment policies and alert the investigations of CKD incidence in consumers.
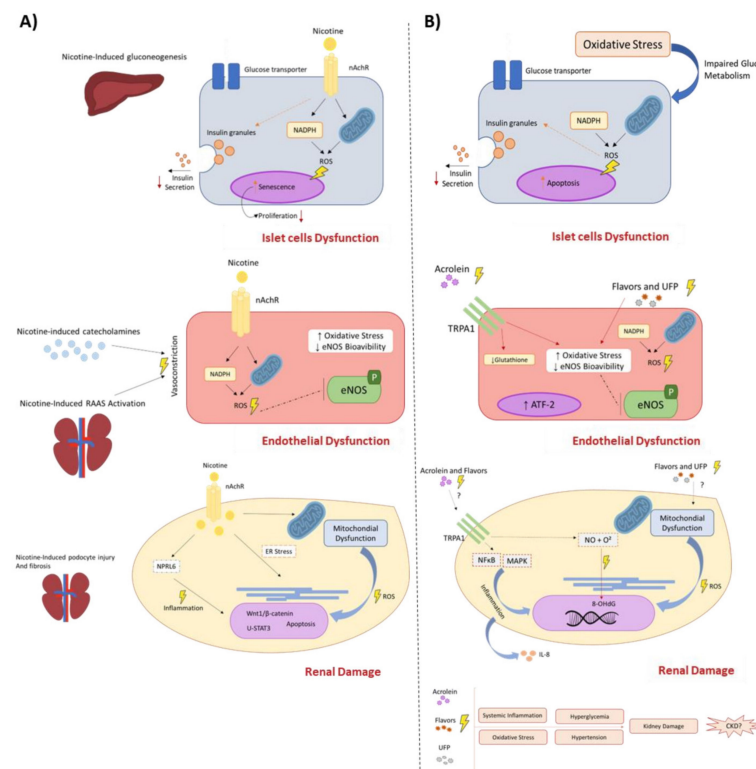

Figure 1. Potential cellular and molecular mechanism triggered by nicotine and compounds generated by ENDS and their role on CKD pathophysiology. ENDS release several chemical compounds, including nicotine, ultrafine particles, flavoring, and other harmful and potentially harmful constituents generated by thermal degradation. Thus, these compounds are absorbed by the lungs and reach systemic circulation to exert their toxicity and favor the onset of CKD and its related disorders. Although the harmful and direct effects of nicotine are well known and reported in clinical and experimental studies (**A**), other xenobiotics released by ENDS, such as acrolein, ultrafine particles (UFP), and flavorings possess the potential to trigger deleterious effects, leading to cumulative damages and favor CKD onset (**B**), however further data are required. The direct interaction of tobacco-released compounds with the endothelium increase reactive oxygen species (ROS), decreases endothelial nitric oxide species (eNOS) [73,74,126–129,170] and leads to an inflammatory response mediated or not by nicotinic receptor activation (nAChRs) or stress sensors receptors (TRPA1) [75,123–125,146,147], evoking endothelial dysfunction, impaired vascular relaxation, and increasing blood pressure. Directly or indirectly, these xenobiotics can impair glucose metabolism by affecting β islet cell homeostasis [85,86,90] and mitochondrial function in an ROS-dependent manner, culminating in insulin resistance and Diabetes Mellitus type II onset [95,100,135]. Finally, the kidneys are affected by the systemic inflammatory response, increased blood pressure, and higher levels of ROS, which increase mesangial cell proliferation, activate programmed cell death pathways on tubular cells, and impair mitochondrial function [109–115,135–137]. Once the kidneys are responsible for filtration, these xenobiotics accumulate on renal structures and cause inflammation and oxidative stress. Altogether, these mechanisms decrease glomerular filtration rate (GFR) and kidney function, leading to the late establishment of CKD.

References

1. Akchurin, O.M. Chronic Kidney Disease and Dietary Measures to Improve Outcomes. *Pediatr. Clin. N. Am.* **2019**, *66*, 247–267. [CrossRef]
2. Chou, Y.H.; Chen, Y.M. Aging and renal disease: Old questions for new challenges. *Aging Dis.* **2021**, *12*, 515–528. [CrossRef] [PubMed]
3. Neves, J.S.; Correa, S.; Baptista, R.B.; Vieira, M.B.; Waikar, S.S.; Mc Causland, F.R. Association of prediabetes with ckd progression and adverse cardiovascular outcomes: An analysis of the cric study. *J. Clin. Endocrinol. Metab.* **2020**, *105*, E1772–E1780. [CrossRef] [PubMed]
4. Reitsma, M.B.; Fullman, N.; Ng, M.; Salama, J.S.; Abajobir, A.; Abate, K.H.; Abbafati, C.; Abera, S.F.; Abraham, B.; Abyu, G.Y.; et al. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990–2015: A systematic analysis from the global burden of disease study 2015. *Lancet* **2017**, *389*, 1885–1906. [CrossRef]
5. Nathan, R.H.; Samuel, T.F.; Jason, L.O.; Jennifer, A.H.; O'Callaghan, C.A.; Daniel, S.L.; Hobbs, F.D.R. Global Prevalence of Chronic Kidney Disease—A Systematic Review and Meta-Analysis. *PLoS ONE* **2016**, *11*, e0158765. [CrossRef]
6. Zhong, J.; Yang, H.C.; Fogo, A.B. A perspective on chronic kidney disease progression. *Am. J. Physiol. Ren. Physiol.* **2017**, *312*, F375–F384. [CrossRef] [PubMed]
7. Tozawa, M.; Iseki, K.; Iseki, C.; Kinjo, K.; Ikemiya, Y.; Takishita, S. Blood pressure predicts risk of developing end-stage renal disease in men and women. *Hypertension* **2003**, *41*, 1341–1345. [CrossRef] [PubMed]
8. Bullen, A.L.; Katz, R.; Jotwani, V.; Garimella, P.S.; Lee, A.K.; Estrella, M.M.; Shlipak, M.G.; Ix, J.H. Biomarkers of Kidney Tubule Health, CKD Progression, and Acute Kidney Injury in SPRINT (Systolic Blood Pressure Intervention Trial) Participants. *Am. J. Kidney Dis.* **2021**, *78*, 361–368. [CrossRef]
9. Wu, M.Y.; Lo, W.C.; Chao, C.T.; Wu, M.S.; Chiang, C.K. Association between air pollutants and development of chronic kidney disease: A systematic review and meta-analysis. *Sci. Total Environ.* **2020**, *706*, 135522. [CrossRef] [PubMed]
10. Jung, J.; Park, J.Y.; Kim, Y.C.; Lee, H.; Kim, E.; Kim, Y.S.; Lee, J.P.; Kim, H. Effects of air pollution on mortality of patients with chronic kidney disease: A large observational cohort study. *Sci. Total Environ.* **2021**, *786*, 147471. [CrossRef] [PubMed]
11. Pichon-Riviere, A.; Alcaraz, A.; Palacios, A.; Rodríguez, B.; Reynales-Shigematsu, L.M.; Pinto, M.; Castillo-Riquelme, M.; Peña Torres, E.; Osorio, D.I.; Huayanay, L.; et al. The health and economic burden of smoking in 12 Latin American countries and the potential effect of increasing tobacco taxes: An economic modelling study. *Lancet Glob. Health* **2020**, *8*, e1282–e1294. [CrossRef]
12. Volti, G.L.; Polosa, R.; Caruso, M. Assessment of E-cigarette impact on smokers: The importance of experimental conditions relevant to human consumption. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E3073–E3074. [CrossRef] [PubMed]
13. Flor, L.S.; Reitsma, M.B.; Gupta, V.; Ng, M.; Gakidou, E. The effects of tobacco control policies on global smoking prevalence. *Nat. Med.* **2021**, *27*, 239–243. [CrossRef] [PubMed]
14. Nagasawa, Y.; Yamamoto, R.; Rakugi, H.; Isaka, Y. Cigarette smoking and chronic kidney diseases. *Hypertens. Res.* **2012**, *35*, 261–265. [CrossRef]
15. Xia, J.; Wang, L.; Ma, Z.; Zhong, L.; Wang, Y.; Gao, Y.; He, L.; Su, X. Cigarette smoking and chronic kidney disease in the general population: A systematic review and meta-analysis of prospective cohort studies. *Nephrol. Dial. Transplant.* **2017**, *32*, 475–487. [CrossRef]
16. Yamaguchi, M.; Ando, M.; Yamamoto, R.; Akiyama, S.; Kato, S.; Katsuno, T.; Kosugi, T.; Sato, W.; Tsuboi, N.; Yasuda, Y.; et al. Smoking is a risk factor for the progression of idiopathic membranous nephropathy. *PLoS ONE* **2014**, *9*, e100835. [CrossRef] [PubMed]
17. Feodoroff, M.; Harjutsalo, V.; Forsblom, C.; Thorn, L.; Wadén, J.; Tolonen, N.; Lithovius, R.; Groop, P.H. Smoking and progression of diabetic nephropathy in patients with type 1 diabetes. *Acta Diabetol.* **2016**, *53*, 525–533. [CrossRef]

18. Maddatu, J.; Anderson-Baucum, E.; Evans-Molina, C. Smoking and the risk of type 2 diabetes. *Transl. Res.* **2017**, *184*, 101–107. [CrossRef]

19. Jhee, J.H.; Joo, Y.S.; Kee, Y.K.; Jung, S.Y.; Park, S.; Yoon, C.Y.; Han, S.H.; Yoo, T.H.; Kang, S.W.; Park, J.T. Secondhand smoke and CKD. *Clin. J. Am. Soc. Nephrol.* **2019**, *14*, 515–522. [CrossRef] [PubMed]

20. Tsai, H.J.; Wu, P.Y.; Huang, J.C.; Chen, S.C. Environmental pollution and chronic kidney disease. *Int. J. Med. Sci.* **2021**, *18*, 1121–1129. [CrossRef] [PubMed]

21. Lin, X.; Xu, Y.; Pan, X.; Xu, J.; Ding, Y.; Sun, X.; Song, X.; Ren, Y.; Shan, P.F. Global, regional, and national burden and trend of diabetes in 195 countries and territories: An analysis from 1990 to 2025. *Sci. Rep.* **2020**, *10*, 1470. [CrossRef] [PubMed]

22. Yang, M.; Cheng, H.; Shen, C.; Liu, J.; Zhang, H.; Cao, J.; Ding, R. Effects of long-term exposure to air pollution on the incidence of type 2 diabetes mellitus: A meta-analysis of cohort studies. *Environ. Sci. Pollut. Res.* **2020**, *27*, 798–811. [CrossRef]

23. Kim, J.H.; Seo, D.C.; Kim, B.J.; Kang, J.G.; Lee, S.J.; Lee, S.H.; Kim, B.S.; Kang, J.H. Association between cigarette smoking and new-onset diabetes mellitus in 78,212 Koreans using self-reported questionnaire and urine cotinine. *Diabetes Metab. J.* **2019**, *43*, 426–435. [CrossRef] [PubMed]

24. Cho, S.H.; Jeong, S.H.; Shin, J.; Park, S.; Jang, S.I. Short-term smoking increases the risk of insulin resistance. *Sci. Rep.* **2022**, *12*, 3550. [CrossRef]

25. Braffett, B.H.; Rice, M.M.; Young, H.A.; Lachin, J.M. Mediation of the association of smoking and microvascular complications by glycemic control in type 1 diabetes. *PLoS ONE* **2019**, *14*, e0210367. [CrossRef]

26. Campagna, D.; Alamo, A.; Di Pino, A.; Russo, C.; Calogero, A.E.; Purrello, F.; Polosa, R. Smoking and diabetes: Dangerous liaisons and confusing relationships. *Diabetol. Metab. Syndr.* **2019**, *11*, 85. [CrossRef] [PubMed]

27. Rogers, J.M. Smoking and pregnancy: Epigenetics and developmental origins of the metabolic syndrome. *Birth Defects Res.* **2019**, *111*, 1259–1269. [CrossRef]

28. Carey, R.M.; Wright, J.T.; Taler, S.J.; Whelton, P.K. Guideline-Driven Management of Hypertension: An Evidence-Based Update. *Circ. Res.* **2021**, *128*, 827–846. [CrossRef]

29. Miller, C.R.; Shi, H.; Li, D.; Goniewicz, M.L. Cross-sectional associations of smoking and e-cigarette use with self-reported diagnosed hypertension: Findings from wave 3 of the population assessment of tobacco and health study. *Toxics* **2021**, *9*, 52. [CrossRef]

30. Rhee, M.Y.; Na, S.H.; Kim, Y.K.; Lee, M.M.; Kim, H.Y. Acute Effects of Cigarette Smoking on Arterial Stiffness and Blood Pressure in Male Smokers With Hypertension. *Am. J. Hypertens.* **2007**, *20*, 637–641. [CrossRef] [PubMed]

31. Talukder, M.A.H.; Johnson, W.M.; Varadharaj, S.; Lian, J.; Kearns, P.N.; El-Mahdy, M.A.; Liu, X.; Zweier, J.L. Chronic cigarette smoking causes hypertension, increased oxidative stress, impaired NO bioavailability, endothelial dysfunction, and cardiac remodeling in mice. *Am. J. Physiol. Heart Circ. Physiol.* **2011**, *300*, 388–396. [CrossRef] [PubMed]

32. Harwani, S.C.; Ratcliff, J.; Sutterwala, F.S.; Ballas, Z.K.; Meyerholz, D.K.; Chapleau, M.W.; Abboud, F.M. Nicotine Mediates CD161a+ Renal Macrophage Infiltration and Premature Hypertension in the Spontaneously Hypertensive Rat. *Circ. Res.* **2016**, *119*, 1101–1115. [CrossRef]

33. Mendelson, J.H.; Sholar, M.B.; Goletiani, N.; Siegel, A.J.; Mello, N.K. Effects of low- and high-nicotine cigarette smoking on mood states and the HPA axis in men. *Neuropsychopharmacology* **2005**, *30*, 1751–1763. [CrossRef] [PubMed]

34. Kelly, J.T.; Su, G.; Zhang, L.; Qin, X.; Marshall, S.; González-Ortiz, A.; Clase, C.M.; Campbell, K.L.; Xu, H.; Carrero, J.J. Modifiable lifestyle factors for primary prevention of CKD: A systematic review and meta-analysis. *J. Am. Soc. Nephrol.* **2021**, *32*, 239–253. [CrossRef]

35. Molino, A.R.; Jerry-Fluker, J.; Atkinson, M.A.; Furth, S.L.; Warady, B.A.; Ng, D.K. Alcohol, cigarette, e-cigarette and marijuana use among adolescents and young adults with chronic kidney disease in North America. *Ann. Epidemiol.* **2021**, *59*, 56–63. [CrossRef] [PubMed]

36. Oberg, B.P.; McMenamin, E.; Lucas, F.L.; McMonagle, E.; Morrow, J.; Ikizler, T.A.; Himmelfarb, J. Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. *Kidney Int.* **2004**, *65*, 1009–1016. [CrossRef] [PubMed]

37. Sureshbabu, A.; Ryter, S.W.; Choi, M.E. Oxidative stress and autophagy: Crucial modulators of kidney injury. *Redox Biol.* **2015**, *4*, 208–214. [CrossRef] [PubMed]

38. Stabbert, R.; Dempsey, R.; Diekmann, J.; Euchenhofer, C.; Hagemeister, T.; Haussmann, H.J.; Knorr, A.; Mueller, B.P.; Pospisil, P.; Reininghaus, W.; et al. Studies on the contributions of smoke constituents, individually and in mixtures, in a range of in vitro bioactivity assays. *Toxicol. In Vitro* **2017**, *42*, 222–246. [CrossRef]

39. Scharf, P.; Broering, M.F.; da Rocha, G.H.O.; Farsky, S.H.P. Cellular and molecular mechanisms of environmental pollutants on hematopoiesis. *Int. J. Mol. Sci.* **2020**, *21*, 6996. [CrossRef] [PubMed]

40. Heluany, C.S.; Scharf, P.; Schneider, A.H.; Donate, P.B.; dos Reis Pedreira Filho, W.; de Oliveira, T.F.; Cunha, F.Q.; Farsky, S.H.P. Toxic mechanisms of cigarette smoke and heat-not-burn tobacco vapor inhalation on rheumatoid arthritis. *Sci. Total Environ.* **2022**, *809*, 151097. [CrossRef]

41. Scharf, P.; da Rocha, G.H.O.; Sandri, S.; Heluany, C.S.; Pedreira Filho, W.R.; Farsky, S.H.P. Immunotoxic mechanisms of cigarette smoke and heat-not-burn tobacco vapor on Jurkat T cell functions. *Environ. Pollut.* **2021**, *268*, 115863. [CrossRef] [PubMed]

42. Yankey, B.N.A.; Strasser, S.; Okosun, I.S. A cross-sectional analysis of the association between marijuana and cigarette smoking with metabolic syndrome among adults in the United States. *Diabetes Metab. Syndr. Clin. Res. Rev.* **2016**, *10*, S89–S95. [CrossRef]

43. Jayes, L.; Haslam, P.L.; Gratziou, C.G.; Powell, P.; Britton, J.; Vardavas, C.; Jimenez-Ruiz, C.; Leonardi-Bee, J.; Dautzenberg, B.; Lundbäck, B.; et al. SmokeHaz: Systematic Reviews and Meta-analyses of the Effects of Smoking on Respiratory Health. *Chest* **2016**, *150*, 164–179. [CrossRef]

44. Chaffee, B.W.; Couch, E.T.; Vora, M.V.; Holliday, R.S. Oral and periodontal implications of tobacco and nicotine products. *Periodontol. 2000* **2021**, *87*, 241–253. [CrossRef] [PubMed]

45. Marques, P.; Piqueras, L.; Sanz, M.J. An updated overview of e-cigarette impact on human health. *Respir. Res.* **2021**, *22*, 151. [CrossRef] [PubMed]

46. Orellana-Barrios, M.A.; Payne, D.; Mulkey, Z.; Nugent, K. Electronic cigarettes—A narrative review for clinicians. *Am. J. Med.* **2015**, *128*, 674–681. [CrossRef] [PubMed]

47. Rowell, T.R.; Tarran, R. Will chronic e-cigarette use cause lung disease? *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2015**, *309*, L1398–L1409. [CrossRef]

48. Williams, M.; Talbot, P. Design features in multiple generations of electronic cigarette atomizers. *Int. J. Environ. Res. Public Health* **2019**, *16*, 2904. [CrossRef]

49. Shi, H.; Leventhal, A.M.; Wen, Q.; Ossip, D.J.; Li, D. Sex Differences in the Association of E-cigarette and Cigarette Use and Dual Use with Self-reported Hypertension Incidence in US Adults. *Nicotine Tob. Res. Off. J. Soc. Res. Nicotine Tob.* **2022**, *21*, ntac170. [CrossRef]

50. Dimitriadis, K.; Narkiewicz, K.; Leontsinis, I.; Konstantinidis, D.; Mihas, C.; Andrikou, I.; Thomopoulos, C.; Tousoulis, D.; Tsioufis, K. Acute Effects of Electronic and Tobacco Cigarette Smoking on Sympathetic Nerve Activity and Blood Pressure in Humans. *Int. J. Environ. Res. Public Health* **2022**, *19*, 3237. [CrossRef]

51. Zhang, Z.; Jiao, Z.; Blaha, M.J.; Osei, A.; Sidhaye, V.; Ramanathan, M.J.; Biswal, S. The Association Between E-Cigarette Use and Prediabetes: Results From the Behavioral Risk Factor Surveillance System, 2016-2018. *Am. J. Prev. Med.* **2022**, *62*, 872–877. [CrossRef] [PubMed]

52. Kim, S.H.; Park, M.; Kim, G.R.; Joo, H.J.; Jang, S.-I. Association of Mixed Use of Electronic and Conventional Cigarettes and Exposure to Secondhand Smoke With Prediabetes. *J. Clin. Endocrinol. Metab.* **2022**, *107*, e44–e56. [CrossRef] [PubMed]

53. Liu, H.; Kotova, T.I.; Timko, M.P. Increased leaf nicotine content by targeting transcription factor gene expression in commercial flue-cured tobacco (*Nicotiana tabacum* L.). *Genes* **2019**, *10*, 930. [CrossRef] [PubMed]

54. Kolli, A.R.; Kuczaj, A.K.; Martin, F.; Hayes, A.W.; Peitsch, M.C.; Hoeng, J. Bridging inhaled aerosol dosimetry to physiologically based pharmacokinetic modeling for toxicological assessment: Nicotine delivery systems and beyond. *Crit. Rev. Toxicol.* **2019**, *49*, 725–741. [CrossRef]

55. Pérez-Rubio, G.; López-Flores, L.A.; Cupertino, A.P.; Cartujano-Barrera, F.; Reynales-Shigematsu, L.M.; Ramírez, M.; Ellerbeck, E.F.; Rodríguez-Bolaños, R.; Falfan-Valencia, R. Genetic variants in smoking-related genes in two smoking cessation programs: A cross-sectional study. *Int. J. Environ. Res. Public Health* **2021**, *18*, 6597. [CrossRef] [PubMed]

56. Gotti, C.; Clementi, F. Neuronal nicotinic receptors: From structure to pathology. *Prog. Neurobiol.* **2004**, *74*, 363–396. [CrossRef] [PubMed]

57. De Jonge, W.J.; Ulloa, L. The alpha7 nicotinic acetylcholine receptor as a pharmacological target for inflammation. *Br. J. Pharmacol.* **2007**, *151*, 915–929. [CrossRef]

58. Fujii, T.; Mashimo, M.; Moriwaki, Y.; Misawa, H.; Ono, S.; Horiguchi, K.; Kawashima, K. Physiological functions of the cholinergic system in immune cells. *J. Pharmacol. Sci.* **2017**, *134*, 1–21. [CrossRef]

59. Fujii, T.; Mashimo, M.; Moriwaki, Y.; Misawa, H.; Ono, S.; Horiguchi, K.; Kawashima, K. Expression and function of the cholinergic system in immune cells. *Front. Immunol.* **2017**, *8*, 1085. [CrossRef]

60. Quick, M.W.; Lester, R.A.J. Desensitization of neuronal nicotinic receptors. *J. Neurobiol.* **2002**, *53*, 457–478. [CrossRef] [PubMed]

61. Changeux, J.P. Allostery and the monod-wyman-changeux model after 50 years. *Annu. Rev. Biophys.* **2012**, *41*, 103–133. [CrossRef] [PubMed]

62. Karlin, A. Ion channel structure: Emerging structure of the Nicotinic Acetylcholine receptors. *Nat. Rev. Neurosci.* **2002**, *3*, 102–114. [CrossRef] [PubMed]

63. Somm, E.; Guérardel, A.; Maouche, K.; Toulotte, A.; Veyrat-Durebex, C.; Rohner-Jeanrenaud, F.; Maskos, U.; Hüppi, P.S.; Schwitzgebel, V.M. Concomitant alpha7 and beta2 nicotinic AChR subunit deficiency leads to impaired energy homeostasis and increased physical activity in mice. *Mol. Genet. Metab.* **2014**, *112*, 64–72. [CrossRef] [PubMed]

64. Gotti, C.; Moretti, M.; Gaimarri, A.; Zanardi, A.; Clementi, F.; Zoli, M. Heterogeneity and complexity of native brain nicotinic receptors. *Biochem. Pharmacol.* **2007**, *74*, 1102–1111. [CrossRef] [PubMed]

65. Picciotto, M.R.; Higley, M.J.; Mineur, Y.S. Acetylcholine as a Neuromodulator: Cholinergic Signaling Shapes Nervous System Function and Behavior. *Neuron* **2012**, *76*, 116–129. [CrossRef] [PubMed]

66. Shao, X.M.; Feldman, J.L. Central cholinergic regulation of respiration: Nicotinic receptors. *Acta Pharmacol. Sin.* **2009**, *30*, 761–770. [CrossRef]

67. Mansvelder, H.D.; Keath, J.R.; Mcgehee, D.S. Synaptic Mechanisms Underlie Nicotine-Induced Excitability of Brain Reward Areas types in the nucleus by the presence of a prominent. *Neuron* **2002**, *33*, 905–919. [CrossRef]

68. Cuny, H.; Yu, R.; Tae, H.S.; Kompella, S.N.; Adams, D.J. α-Conotoxins active at α3-containing nicotinic acetylcholine receptors and their molecular determinants for selective inhibition. *Br. J. Pharmacol.* **2018**, *175*, 1855–1868. [CrossRef] [PubMed]

69. Eom, S.; Kim, C.; Yeom, H.D.; Lee, J.; Lee, S.; Baek, Y.B.; Na, J.; Park, S.I.; Kim, G.Y.; Lee, C.M.; et al. Molecular regulation of α3β4 nicotinic acetylcholine receptors by lupeol in cardiovascular system. *Int. J. Mol. Sci.* **2020**, *21*, 4329. [CrossRef] [PubMed]

70. Nordenstam, F. Prenatal nicotine exposure was associated with long-term impact on the cardiovascular system and regulation—Review. *Acta Paediatr. Int. J. Paediatr.* **2021**, *110*, 2536–2544. [CrossRef] [PubMed]

71. El-Mas, M.M.; El-gowilly, S.M.; Fouda, M.A.; Saad, E.I. Role of adenosine A2A receptor signaling in the nicotine-evoked attenuation of reflex cardiac sympathetic control. *Toxicol. Appl. Pharmacol.* **2011**, *254*, 229–237. [CrossRef]

72. Albillos, A.; McIntosh, J.M. Human nicotinic receptors in chromaffin cells: Characterization and pharmacology. *Pflugers Arch. Eur. J. Physiol.* **2018**, *470*, 21–27. [CrossRef] [PubMed]

73. Wang, Y.; Wang, J.; Yang, R.; Wang, P.; Porche, R.; Kim, S.; Lutfy, K.; Liu, L.; Friedman, T.C.; Jiang, M.; et al. Decreased 11β-Hydroxysteroid Dehydrogenase Type 2 Expression in the Kidney May Contribute to Nicotine/Smoking-Induced Blood Pressure Elevation in Mice. *Hypertension* **2021**, *77*, 1940–1952. [CrossRef]

74. Coelho, F.O.; Jorge, L.B.; de Bragança Viciana, A.C.; Sanches, T.R.; dos Santos, F.; Helou, C.M.B.; Irigoyen, M.C.; Kuro-o, M.; Andrade, L. Chronic nicotine exposure reduces klotho expression and triggers different renal and hemodynamic responses in klotho-haploinsufficient mice. *Am. J. Physiol. Ren. Physiol.* **2018**, *314*, F992–F998. [CrossRef]

75. Kuro-o, M.; Matsumura, Y.; Arawa, H.; Kawaguchi, H.; Suga, T.; Utsugi, T.; Ohyama, Y.; Kurabayashi, M.; Kaname, T.; Kume, E.; et al. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. *Chemtracts* **1999**, *12*, 703–707. [CrossRef]

76. Hu, M.C.; Shi, M.; Zhang, J.; Quiñones, H.; Kuro-O, M.; Moe, O.W. Klotho deficiency is an early biomarker of renal ischemia-reperfusion injury and its replacement is protective. *Kidney Int.* **2010**, *78*, 1240–1251. [CrossRef] [PubMed]

77. Zou, Q.; Leung, S.W.S.; Vanhoutte, P.M. Activation of nicotinic receptors can contribute to endothelium-dependent relaxations to acetylcholine in the rat aorta. *J. Pharmacol. Exp. Ther.* **2012**, *341*, 756–763. [CrossRef]

78. Fu, X.; Zong, T.; Yang, P.; Li, L.; Wang, S.; Wang, Z.; Li, M.; Li, X.; Zou, Y.; Zhang, Y.; et al. Nicotine: Regulatory roles and mechanisms in atherosclerosis progression. *Food Chem. Toxicol.* **2021**, *151*, 112154. [CrossRef] [PubMed]

79. Liu, C.; Zhou, M.S.; Li, Y.; Wang, A.; Chadipiralla, K.; Tian, R.; Raij, L. Oral nicotine aggravates endothelial dysfunction and vascular inflammation in diet-induced obese rats: Role of macrophage TNFα. *PLoS ONE* **2017**, *12*, e0188439. [CrossRef] [PubMed]

80. Oakes, J.M.; Fuchs, R.M.; Gardner, J.D.; Lazartigues, E.; Yue, X. Nicotine and the renin-angiotensin system. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2018**, *315*, R895–R906. [CrossRef]

81. Cora, N.; Ghandour, J.; Marie Pollard, C.; Lynn Desimine, V.; Elaine Ferraino, K.; Marie Pereyra, J.; Valiente, R.; Lymperopoulos, A. Nicotine-induced adrenal beta-arrestin1 upregulation mediates tobacco-related hyperaldosteronism leading to cardiac dysfunction. *World J. Cardiol.* **2020**, *12*, 192–202. [CrossRef]

82. Laustiola, K.E.; Lassila, R.; Kaprio, J.; Koskenvuo, M. Decreased β-adrenergic receptor density and catecholamine response in male cigarette smokers. A study of monozygotic twin pairs discordant for smoking. *Circulation* **1988**, *78*, 1234–1240. [CrossRef] [PubMed]

83. Rohleder, N.; Kirschbaum, C. The hypothalamic-pituitary-adrenal (HPA) axis in habitual smokers. *Int. J. Psychophysiol.* **2006**, *59*, 236–243. [CrossRef]

84. Vu, C.U.; Siddiqui, J.A.; Wadensweiler, P.; Gayen, J.R.; Avolio, E.; Bandyopadhyay, G.K.; Biswas, N.; Chi, N.W.; O'Connor, D.T.; Mahata, S.K. Nicotinic acetylcholine receptors in glucose homeostasis: The acute hyperglycemic and chronic insulin-sensitive effects of nicotine suggest dual opposing roles of the receptors in male mice. *Endocrinology* **2014**, *155*, 3793–3805. [CrossRef]

85. Kuo, T.; McQueen, A.; Chen, T.-C.; Wang, J.-C. Regulation of Glucose Homeostasis by Glucocorticoids. In *Glucocorticoid Signaling: From Molecules to Mice to Man*; Wang, J.-C., Harris, C., Eds.; Springer: New York, NY, USA, 2015; pp. 99–126; ISBN 978-1-4939-2895-8.

86. Lee, H.W.; Yang, S.H.; Kim, J.Y.; Kim, H. The role of the medial habenula cholinergic system in addiction and emotion-associated behaviors. *Front. Psychiatry* **2019**, *10*, 100. [CrossRef]

87. Kimura, T.; Obata, A.; Shimoda, M.; Okauchi, S.; Hirukawa, H.; Kohara, K.; Kinoshita, T.; Nogami, Y.; Nakanishi, S.; Mune, T.; et al. Decreased glucagon-like peptide 1 receptor expression in endothelial and smooth muscle cells in diabetic db/db mice: TCF7L2 is a possible regulator of the vascular glucagon-like peptide 1 receptor. *Diabetes Vasc. Dis. Res.* **2017**, *14*, 540–548. [CrossRef]

88. Duncan, A.; Heyer, M.P.; Ishikawa, M.; Caligiuri, S.P.B.; Liu, X.; Chen, Z.; Vittoria Micioni Di Bonaventura, M.; Elayouby, K.S.; Ables, J.L.; Howe, W.M.; et al. Habenular TCF7L2 links nicotine addiction to diabetes. *Nature* **2019**, *574*, 372–377. [CrossRef]

89. Chen, X.; Zhang, W.; Gao, Y.F.; Su, X.Q.; Zhai, Z.H. Senescence-like changes induced by expression of p21Waf1/Cip1 in NIH3T3 cell line. *Cell Res.* **2002**, *12*, 229–233. [CrossRef] [PubMed]

90. Sun, L.; Wang, X.; Gu, T.; Hu, B.; Luo, J.; Qin, Y.; Wan, C. Nicotine triggers islet β cell senescence to facilitate the progression of type 2 diabetes. *Toxicology* **2020**, *441*, 152502. [CrossRef] [PubMed]

91. Lan, X.; Lederman, R.; Eng, J.M.; Shoshtari, S.S.M.; Saleem, M.A.; Malhotra, A.; Singhal, P.C. Nicotine induces podocyte apoptosis through increasing oxidative stress. *PLoS ONE* **2016**, *11*, e0167071. [CrossRef]

92. Lan, K.; Zhang, G.; Liu, L.; Guo, Z.; Luo, X.; Guan, H.; Yu, Q.; Liu, E. Electronic cigarette exposure on insulin sensitivity of ApoE gene knockout mice. *Tob. Induc. Dis.* **2020**, *18*, 3–8. [CrossRef]

93. Xu, H.; Wang, Q.; Sun, Q.; Qin, Y.; Han, A.; Cao, Y.; Yang, Q.; Yang, P.; Lu, J.; Liu, Q.; et al. In type 2 diabetes induced by cigarette smoking, activation of p38 MAPK is involved in pancreatic β-cell apoptosis. *Environ. Sci. Pollut. Res.* **2018**, *25*, 9817–9827. [CrossRef] [PubMed]

94. Yoshikawa, H.; Hellström-Lindahl, E.; Grill, V. Evidence for functional nicotinic receptors on pancreatic β cells. *Metabolism* **2005**, *54*, 247–254. [CrossRef] [PubMed]

95. Somm, E. Nicotinic cholinergic signaling in adipose tissue and pancreatic islets biology: Revisited function and therapeutic perspectives. *Arch. Immunol. Ther. Exp.* **2014**, *62*, 87–101. [CrossRef]

96. Marrero, M.B.; Lucas, R.; Salet, C.; Hauser, T.A.; Mazurov, A.; Lippiello, P.M.; Bencherif, M. An α7 nicotinic acetylcholine receptor-selective agonist reduces weight gain and metabolic changes in a mouse model of diabetes. *J. Pharmacol. Exp. Ther.* **2010**, *332*, 173–180. [CrossRef]

97. Ishibashi, T.; Morita, S.; Kishimoto, S.; Uraki, S.; Takeshima, K.; Furukawa, Y.; Inaba, H.; Ariyasu, H.; Iwakura, H.; Furuta, H.; et al. Nicotinic acetylcholine receptor signaling regulates inositol-requiring enzyme 1α activation to protect β-cells against terminal unfolded protein response under irremediable endoplasmic reticulum stress. *J. Diabetes Investig.* **2020**, *11*, 801–813. [CrossRef] [PubMed]

98. Fan, J.; Zhang, W.X.; Rao, Y.S.; Xue, J.L.; Wang, F.F.; Zhang, L.; Yan, Y.E. Perinatal nicotine exposure increases obesity susceptibility in adult male rat offspring by altering early adipogenesis. *Endocrinology* **2016**, *157*, 4276–4286. [CrossRef] [PubMed]

99. Nemoto, T.; Ando, H.; Nagao, M.; Kakinuma, Y.; Sugihara, H. Prenatal Nicotine Exposure Induces Low Birthweight and Hyperinsulinemia in Male Rats. *Front. Endocrinol.* **2021**, *12*, 688. [CrossRef]

100. Pietrobon, C.B.; Lisboa, P.C.; Bertasso, I.M.; Peixoto, T.C.; Soares, P.N.; de Oliveira, E.; Rabelo, K.; de Carvalho, J.J.; Manhães, A.C.; de Moura, E.G. Pancreatic steatosis in adult rats induced by nicotine exposure during breastfeeding. *Endocrine* **2021**, *72*, 104–115. [CrossRef] [PubMed]

101. Xu, D.; Xia, L.P.; Zhang, B.J.; Shen, L.; Lei, Y.Y.; Liu, L.; Zhang, L.; Magdalou, J.; Wang, H. Prenatal nicotine exposure enhances the susceptibility to metabolic syndrome in adult offspring rats fed high-fat diet via alteration of HPA axis-associated neuroendocrine metabolic programming. *Acta Pharmacol. Sin.* **2013**, *34*, 1526–1534. [CrossRef]

102. Miranda, R.A.; Gaspar de Moura, E.; Lisboa, P.C. Tobacco smoking during breastfeeding increases the risk of developing metabolic syndrome in adulthood: Lessons from experimental models. *Food Chem. Toxicol.* **2020**, *144*, 111623. [CrossRef]

103. Raez-Villanueva, S.; Debnath, A.; Hardy, D.B.; Holloway, A.C. Prenatal nicotine exposure leads to decreased histone H3 lysine 9 (H3K9) methylation and increased p66shc expression in the neonatal pancreas. *J. Dev. Orig. Health Dis.* **2022**, *13*, 156–160. [CrossRef] [PubMed]

104. Huang, S.J.; Chen, S.; Lin, Y.; Yang, H.Y.; Ran, J.; Yan, F.F.; Huang, M.; Liu, X.L.; Hong, L.C.; Zhang, X.D.; et al. Maternal nicotine exposure aggravates metabolic associated fatty liver disease via PI3K/Akt signaling in adult offspring mice. *Liver Int.* **2021**, *41*, 1867–1878. [CrossRef]

105. Kohjima, M.; Higuchi, N.; Kato, M.; Kotoh, K.; Yoshimoto, T.; Fujino, T.; Yada, M.; Yada, R.; Harada, N.; Enjoji, M.; et al. SREBP-1c, regulated by the insulin and AMPK signaling pathways, plays a role in nonalcoholic fatty liver disease. *Int. J. Mol. Med.* **2008**, *21*, 507–511. [CrossRef] [PubMed]

106. Yeboah, M.M.; Xue, X.; Duan, B.; Ochani, M.; Tracey, K.J.; Susin, M.; Metz, C.N. Cholinergic agonists attenuate renal ischemia-reperfusion injury in rats. *Kidney Int.* **2008**, *74*, 62–69. [CrossRef]

107. Yeboah, M.M.; Xue, X.; Javdan, M.; Susin, M.; Metz, C.N. Nicotinic acetylcholine receptor expression and regulation in the rat kidney after ischemia-reperfusion injury. *Am. J. Physiol. Ren. Physiol.* **2008**, *295*, 654–661. [CrossRef] [PubMed]

108. Sadis, C.; Teske, G.; Stokman, G.; Kubjak, C.; Claessen, N.; Moore, F.; Loi, P.; Diallo, B.; Barvais, L.; Goldman, M.; et al. Nicotine protects kidney from renal ischemia/reperfusion injury through the cholinergic anti-inflammatory pathway. *PLoS ONE* **2007**, *2*, e469. [CrossRef]

109. Arany, I.; Fülöp, T.; Dixit, M. Chronic nicotine exposure reduces antioxidant function of simvastatin in renal proximal tubule cells. *In Vivo* **2018**, *32*, 1033–1037. [CrossRef]

110. Rangarajan, S.; Rezonzew, G.; Chumley, P.; Fatima, H.; Golovko, M.Y.; Feng, W.; Hua, P.; Jaimes, E.A. COX-2-derived prostaglandins as mediators of the deleterious effects of nicotine in chronic kidney disease. *Am. J. Physiol. Ren. Physiol.* **2020**, *312*, F475–F485. [CrossRef] [PubMed]

111. Raikwar, N.; Braverman, C.; Snyder, P.M.; Fenton, R.A.; Meyerholz, D.K.; Abboud, F.M.; Harwani, S.C. Renal denervation and CD161a immune ablation prevent cholinergic hypertension and renal sodium retention. *Am. J. Physiol. Heart Circ. Physiol.* **2019**, *317*, H517–H530. [CrossRef]

112. Arany, I.; Grifoni, S.; Clark, J.S.; Csongradi, E.; Maric, C.; Juncos, L.A. Chronic nicotine exposure exacerbates acute renal ischemic injury. *Am. J. Physiol. Ren. Physiol.* **2011**, *301*, 125–133. [CrossRef] [PubMed]

113. Arany, I.; Reed, D.K.; Grifoni, S.C.; Chandrashekar, K.; Booz, G.W.; Juncos, L.A. A novel U-STAT3-dependent mechanism mediates the deleterious effects of chronic nicotine exposure on renal injury. *Am. J. Physiol. Ren. Physiol.* **2012**, *302*. [CrossRef]

114. Zheng, C.M.; Lee, Y.H.; Chiu, I.J.; Chiu, Y.J.; Sung, L.C.; Hsu, Y.H.; Chiu, H.W. Nicotine causes nephrotoxicity through the induction of nlrp6 inflammasome and alpha7 nicotinic acetylcholine receptor. *Toxics* **2020**, *8*, 92. [CrossRef] [PubMed]

115. Loeffler, I.; Wolf, G. Epithelial-to-mesenchymal transition in diabetic nephropathy: Fact or fiction? *Cells* **2015**, *4*, 631–652. [CrossRef]

116. Lan, X.; Wen, H.; Aslam, R.; Shoshtari, S.S.M.; Mishra, A.; Kumar, V.; Wang, H.; Wu, G.; Luo, H.; Malhotra, A.; et al. Nicotine enhances mesangial cell proliferation and fibronectin production in high glucose milieu via activation of Wnt/β-catenin pathway. *Biosci. Rep.* **2018**, *38*, BSR20180100. [CrossRef] [PubMed]

117. Dai, C.; Stolz, D.B.; Kiss, L.P.; Monga, S.P.; Holzman, L.B.; Liu, Y. Wnt/β-catenin signaling promotes podocyte dysfunction and albuminuria. *J. Am. Soc. Nephrol.* **2009**, *20*, 1997–2008. [CrossRef]

118. Guo, Q.; Zhong, W.; Duan, A.; Sun, G.; Cui, W.; Zhuang, X.; Liu, L. Protective or deleterious role of Wnt/beta-catenin signaling in diabetic nephropathy: An unresolved issue. *Pharmacol. Res.* **2019**, *144*, 151–157. [CrossRef]

119. Jaimes, E.A.; Zhou, M.S.; Siddiqui, M.; Rezonzew, G.; Tian, R.; Seshan, S.V.; Muwonge, A.N.; Wong, N.J.; Azeloglu, E.U.; Fornoni, A.; et al. Nicotine, smoking, podocytes, and diabetic nephropathy. *Am. J. Physiol. Ren. Physiol.* **2021**, *320*, F442–F453. [CrossRef] [PubMed]

120. Golli, N.E.; Jrad-Lamine, A.; Neffati, H.; Dkhili, H.; Rahali, D.; Dallagi, Y.; El May, M.V.; El Fazaa, S. Impact of e-cigarette refill liquid exposure on rat kidney. *Regul. Toxicol. Pharmacol.* **2016**, *77*, 109–116. [CrossRef]

121. Erythropel, H.C.; Jabba, S.V.; Dewinter, T.M.; Mendizabal, M.; Anastas, P.T.; Jordt, S.E.; Zimmerman, J.B. Formation of flavorant-propylene Glycol Adducts with Novel Toxicological Properties in Chemically Unstable E-Cigarette Liquids. *Nicotine Tob. Res.* **2019**, *21*, 1248–1258. [CrossRef]

122. Phillips, B.; Titz, B.; Kogel, U.; Sharma, D.; Leroy, P.; Xiang, Y.; Vuillaume, G.; Lebrun, S.; Sciuscio, D.; Ho, J.; et al. Toxicity of the main electronic cigarette components, propylene glycol, glycerin, and nicotine, in Sprague-Dawley rats in a 90-day OECD inhalation study complemented by molecular endpoints. *Food Chem. Toxicol.* **2017**, *109*, 315–332. [CrossRef] [PubMed]

123. Azimi, P.; Keshavarz, Z.; Luna, M.L.; Cedeno Laurent, J.G.; Vallarino, J.; Christiani, D.C.; Allen, J.G. An unrecognized hazard in E-cigarette vapor: Preliminary quantification of methylglyoxal formation from propylene glycol in E-cigarettes. *Int. J. Environ. Res. Public Health* **2021**, *18*, 385. [CrossRef]

124. Chang, S.N.; Haroon, M.; Dey, D.K.; Kang, S.C. Rhabdomyolysis-induced acute kidney injury and concomitant apoptosis induction via ROS-mediated ER stress is efficaciously counteracted by epigallocatechin gallate. *J. Nutr. Biochem.* **2022**, *23*, 109134. [CrossRef]

125. Kosmider, L.; Sobczak, A.; Fik, M.; Knysak, J.; Zaciera, M.; Kurek, J.; Goniewicz, M.L. Carbonyl compounds in electronic cigarette vapors: Effects of nicotine solvent and battery output voltage. *Nicotine Tob. Res.* **2014**, *16*, 1319–1326. [CrossRef]

126. Flora, J.W.; Wilkinson, C.T.; Wilkinson, J.W.; Lipowicz, P.J.; Skapars, J.A.; Anderson, A.; Miller, J.H. Method for the determination of carbonyl compounds in E-cigarette aerosols. *J. Chromatogr. Sci.* **2017**, *55*, 142–148. [CrossRef]

127. Ooi, B.G.; Dutta, D.; Kazipeta, K.; Chong, N.S. Influence of the E-Cigarette Emission Profile by the Ratio of Glycerol to Propylene Glycol in E-Liquid Composition. *ACS Omega* **2019**, *4*, 13338–13348. [CrossRef] [PubMed]

128. Conklin, D.J.; Haberzettl, P.; Jagatheesan, G.; Kong, M.; Hoyle, G.W. Role of TRPA1 in acute cardiopulmonary toxicity of inhaled acrolein. *Toxicol. Appl. Pharmacol.* **2017**, *324*, 61–72. [CrossRef]

129. Henning, R.J.; Johnson, G.T.; Coyle, J.P.; Harbison, R.D. Acrolein Can Cause Cardiovascular Disease: A Review. *Cardiovasc. Toxicol.* **2017**, *17*, 227–236. [CrossRef] [PubMed]

130. Andrè, E.; Campi, B.; Materazzi, S.; Trevisani, M.; Amadesi, S.; Massi, D.; Creminon, C.; Vaksman, N.; Nassini, R.; Civelli, M.; et al. Cigarette smoke-induced neurogenic inflammation is mediated by α,β-unsaturated aldehydes and the TRPA1 receptor in rodents. *J. Clin. Investig.* **2008**, *118*, 2574–2582. [CrossRef]

131. Li, L.; Jiang, L.; Geng, C.; Cao, J.; Zhong, L. The role of oxidative stress in acrolein-induced DNA damage in HepG2 cells. *Free Radic. Res.* **2008**, *42*, 354–361. [CrossRef]

132. Vikman, P.; Xu, C.B.; Edvinsson, L. Lipid-soluble cigarette smoking particles induce expression of inflammatory and extracellularmatrix-related genes in rat cerebral arteries. *Vasc. Health Risk Manag.* **2009**, *5*, 333–341. [CrossRef]

133. Moghe, A.; Ghare, S.; Lamoreau, B.; Mohammad, M.; Barve, S.; McClain, C.; Joshi-Barve, S. Molecular mechanisms of acrolein toxicity: Relevance to human disease. *Toxicol. Sci.* **2015**, *143*, 242–255. [CrossRef]

134. Perez, C.M.; Hazari, M.S.; Ledbetter, A.D.; Haykal-Coates, N.; Carll, A.P.; Cascio, W.E.; Winsett, D.W.; Costa, D.L.; Farraj, A.K. Acrolein inhalation alters arterial blood gases and triggers carotid body-mediated cardiovascular responses in hypertensive rats. *Inhal. Toxicol.* **2015**, *27*, 54–63. [CrossRef] [PubMed]

135. Daimon, M.; Sugiyama, K.; Kameda, W.; Saitoh, T.; Oizumi, T.; Hirata, A.; Yamaguchi, H.; Ohnuma, H.; Igarashi, M.; Kato, T. Increased urinary levels of pentosidine, pyrraline and acrolein adduct in type 2 diabetes. *Endocr. J.* **2003**, *50*, 61–67. [CrossRef] [PubMed]

136. Feroe, A.G.; Attanasio, R.; Scinicariello, F. Acrolein metabolites, diabetes and insulin resistance. *Environ. Res.* **2016**, *148*, 1–6. [CrossRef] [PubMed]

137. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Formaldehyde, 2-butoxyethanol and 1-tert-butoxypropan-2-ol. *IARC Monogr. Eval. Carcinog. Risks Hum.* **2006**, *88*, 1–478.

138. Güleç, M.; Songur, A.; Sahin, S.; Ozen, O.A.; Sarsilmaz, M.; Akyol, O. Antioxidant enzyme activities and lipid peroxidation products in heart tissue of subacute and subchronic formaldehyde-exposed rats: A preliminary study. *Toxicol. Ind. Health* **2006**, *22*, 117–124. [CrossRef]

139. Tan, T.; Zhang, Y.; Luo, W.; Lv, J.; Han, C.; Hamlin, J.N.R.; Luo, H.; Li, H.; Wan, Y.; Yang, X.; et al. Formaldehyde induces diabetes-associated cognitive impairments. *FASEB J.* **2018**, *32*, 3669–3679. [CrossRef] [PubMed]

140. Vehkala, L.; Ukkola, O.; Kesäniemi, Y.A.; Kähönen, M.; Nieminen, M.S.; Salomaa, V.; Jula, A.; Hörkkö, S. Plasma iga antibody levels to malondialdehyde acetaldehyde-adducts are associated with inflammatory mediators, obesity and type 2 diabetes. *Ann. Med.* **2013**, *45*, 501–510. [CrossRef]

141. Zararsiz, I.; Kus, I.; Ogeturk, M.; Akpolat, N.; Kose, E.; Meydan, S.; Sarsilmaz, M. Melatonin prevents formaldehyde-induced neurotoxicity in prefrontal cortex of rats: An immunohistochemical and biochemical study. *Cell Biochem. Funct.* **2007**, *25*, 413–418. [CrossRef]

142. De Oliveira Ramos, C.; Nardeli, C.R.; Campos, K.K.D.; Pena, K.B.; Machado, D.F.; Bandeira, A.C.B.; de Paula Costa, G.; Talvani, A.; Bezerra, F.S. The exposure to formaldehyde causes renal dysfunction, inflammation and redox imbalance in rats. *Exp. Toxicol. Pathol.* **2017**, *69*, 367–372. [CrossRef] [PubMed]

143. Zhu, S.; Sun, J.Y.; Bonnevie, E.; Cummins, S.E.; Gamst, A.; Yin, L.; Lee, M. Four hundred and sixty brands of e-cigarettes and counting: Implications for product regulation. *Tob. Control* **2014**, *23*, 3–9. [CrossRef]

144. Barrington-Trimis, J.L.; Urman, R.; Leventhal, A.M.; Gauderman, W.J.; Cruz, T.B.; Gilreath, T.D.; Howland, S.; Unger, J.B.; Berhane, K.; Samet, J.M.; et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics* **2016**, *138*, 474–475. [CrossRef] [PubMed]

145. Friedman, A.S. A Difference-in-Differences Analysis of Youth Smoking and a Ban on Sales of Flavored Tobacco Products in San Francisco, California. *JAMA Pediatr.* **2021**, *175*, 863–865. [CrossRef] [PubMed]

146. Kaur, G.; Gaurav, A.; Lamb, T.; Perkins, M.; Muthumalage, T.; Rahman, I. Current Perspectives on Characteristics, Compositions, and Toxicological Effects of E-Cigarettes Containing Tobacco and Menthol/Mint Flavors. *Front. Physiol.* **2020**, *11*, 613948. [CrossRef] [PubMed]

147. Kabbani, N. Not so cool? Menthol's discovered actions on the nicotinic receptor and its implications for nicotine addiction. *Front. Pharmacol.* **2013**, *4*, 95. [CrossRef]

148. Kabbani, N.; Nordman, J.C.; Corgiat, B.A.; Veltri, D.P.; Shehu, A.; Seymour, V.A.; Adams, D.J. Are nicotinic acetylcholine receptors coupled to G proteins? *BioEssays* **2013**, *35*, 1025–1034. [CrossRef]

149. Henderson, B.J.; Wall, T.R.; Henley, B.M.; Kim, C.H.; Mckinney, S.; Lester, H.A. Menthol enhances nicotine reward-related behavior by potentiating nicotine-induced changes in nachr function, nachr upregulation, and DA neuron excitability. *Neuropsychopharmacology* **2017**, *42*, 2285–2291. [CrossRef] [PubMed]

150. Winters, B.R.; Kochar, T.K.; Clapp, P.W.; Jaspers, I.; Madden, M.C. Impact of E-Cigarette Liquid Flavoring Agents on Activity of Microsomal Recombinant CYP2A6, the Primary Nicotine-Metabolizing Enzyme. *Chem. Res. Toxicol.* **2020**, *33*, 1689–1697. [CrossRef] [PubMed]

151. Wu, C.K.; Wu, C.L.; Su, T.C.; Kou, Y.R.; Kor, C.T.; Lee, T.S.; Tarng, D.C. Renal tubular TRPA1 as a risk factor for recovery of renal function from acute tubular necrosis. *J. Clin. Med.* **2019**, *8*, 2187. [CrossRef]

152. Wu, C.K.; Wu, C.L.; Lee, T.S.; Kou, Y.R.; Tarng, D.C. Renal tubular epithelial trpa1 acts as an oxidative stress sensor to mediate ischemia-reperfusion-induced kidney injury through mapks/nf-κb signaling. *Int. J. Mol. Sci.* **2021**, *22*, 2309. [CrossRef] [PubMed]

153. Noël, J.C.; Rainer, D.; Gstir, R.; Rainer, M.; Bonn, G. Quantification of selected aroma compounds in e-cigarette products and toxicity evaluation in HUVEC/Tert2 cells. *Biomed. Chromatogr.* **2020**, *34*, e4761. [CrossRef] [PubMed]

154. Nystoriak, M.A.; Kilfoil, P.J.; Lorkiewicz, P.K.; Ramesh, B.; Kuehl, P.J.; McDonald, J.; Bhatnagar, A.; Conklin, D.J. Comparative effects of parent and heated cinnamaldehyde on the function of human iPSC-derived cardiac myocytes. *Toxicol. In Vitro* **2019**, *61*, 104648. [CrossRef] [PubMed]

155. Behar, R.Z.; Luo, W.; Lin, S.C.; Wang, Y.; Valle, J.; Pankow, J.F.; Talbot, P. Distribution, quantification and toxicity of cinnamaldehyde in electronic cigarette refill fluids and aerosols. *Tob. Control* **2016**, *25*, 94–102. [CrossRef] [PubMed]

156. McAdam, K.; Waters, G.; Moldoveanu, S.; Margham, J.; Cunningham, A.; Vas, C.; Porter, A.; Digard, H. Diacetyl and Other Ketones in e-Cigarette Aerosols: Some Important Sources and Contributing Factors. *Front. Chem.* **2021**, *9*, 742538. [CrossRef] [PubMed]

157. Allen, J.G.; Flanigan, S.S.; LeBlanc, M.; Vallarino, J.; MacNaughton, P.; Stewart, J.H.; Christiani, D.C. Response to "Comment on 'flavoring chemicals in e-cigarettes: Diacetyl, 2,3-pentanedione, and acetoin in a sample of 51 products, including fruit-, candy-, and cocktail- flavored e-cigarettes'". *Environ. Health Perspect.* **2016**, *124*, A102–A103. [CrossRef] [PubMed]

158. Rose, C.S. Early detection, clinical diagnosis, and management of lung disease from exposure to diacetyl. *Toxicology* **2017**, *388*, 9–14. [CrossRef]

159. Wallace, K.B. Future perspective of butter flavorings-related occupational lung disease. *Toxicology* **2017**, *388*, 7–8. [CrossRef]

160. Hubbs, A.F.; Cumpston, A.M.; Goldsmith, W.T.; Battelli, L.A.; Kashon, M.L.; Jackson, M.C.; Frazer, D.G.; Fedan, J.S.; Goravanahally, M.P.; Castranova, V.; et al. Respiratory and olfactory cytotoxicity of inhaled 2,3-pentanedione in sprague-dawley rats. *Am. J. Pathol.* **2012**, *181*, 829–844. [CrossRef]

161. Hubbs, A.F.; Fluharty, K.L.; Edwards, R.J.; Barnabei, J.L.; Grantham, J.T.; Palmer, S.M.; Kelly, F.; Sargent, L.M.; Reynolds, S.H.; Mercer, R.R.; et al. Accumulation of Ubiquitin and Sequestosome-1 Implicate Protein Damage in Diacetyl-Induced Cytotoxicity. *Am. J. Pathol.* **2016**, *186*, 2887–2908. [CrossRef]

162. Anders, M.W. Diacetyl and related flavorant α-Diketones: Biotransformation, cellular interactions, and respiratory-tract toxicity. *Toxicology* **2017**, *388*, 21–29. [CrossRef]

163. Nguyen, C.; Li, L.; Sen, C.A.; Ronquillo, E.; Zhu, Y. Fine and ultrafine particles concentrations in vape shops. *Atmos. Environ.* **2019**, *211*, 159–169. [CrossRef]

164. Phalmisani, J. Evaluation of Second-Hand Exposure to Electronic Cigarette Vaping under a Real Scenario: Measurements of Ultrafine Particle Number. *Toxics* **2019**, *7*, 59. [CrossRef]

165. Volesky, K.D.; Maki, A.; Scherf, C.; Watson, L.; Van Ryswyk, K.; Fraser, B.; Weichenthal, S.A.; Cassol, E.; Villeneuve, P.J. The influence of three e-cigarette models on indoor fine and ultrafine particulate matter concentrations under real-world conditions. *Environ. Pollut.* **2018**, *243*, 882–889. [CrossRef]

166. Li, L.; Lee, E.S.; Nguyen, C.; Zhu, Y. Effects of propylene glycol, vegetable glycerin, and nicotine on emissions and dynamics of electronic cigarette aerosols. *Aerosol Sci. Technol.* **2020**, *54*, 1270–1281. [CrossRef] [PubMed]

167. Protano, C.; Manigrasso, M.; Avino, P.; Vitali, M. Second-hand smoke generated by combustion and electronic smoking devices used in real scenarios: Ultrafine particle pollution and age-related dose assessment. *Environ. Int.* **2017**, *107*, 190–195. [CrossRef]

168. Fuoco, F.C.; Buonanno, G.; Stabile, L.; Vigo, P. Influential parameters on particle concentration and size distribution in the mainstream of e-cigarettes. *Environ. Pollut.* **2014**, *184*, 523–529. [CrossRef]

169. Floyd, E.L.; Queimado, L.; Wang, J.; Regens, J.L.; Johnson, D.L. Electronic cigarette power affects count concentration and particle size distribution of vaping aerosol. *PLoS ONE* **2018**, *13*, e0210147. [CrossRef] [PubMed]

170. Terzano, C.; Di Stefano, F.; Conti, V.; Graziani, E.; Petroianni, A. Air pollution ultrafine particles: Toxicity beyond the lung. *Eur. Rev. Med. Pharmacol. Sci.* **2010**, *14*, 809–821. [PubMed]

171. Yacobi, N.R.; Malmstadt, N.; Fazlollahi, F.; DeMaio, L.; Marchelletta, R.; Hamm-Alvarez, S.F.; Borok, Z.; Kim, K.J.; Crandall, E.D. Mechanisms of alveolar epithelial translocation of a defined population of nanoparticles. *Am. J. Respir. Cell Mol. Biol.* **2010**, *42*, 604–614. [CrossRef]

172. Möller, W.; Felten, K.; Sommerer, K.; Scheuch, G.; Meyer, G.; Meyer, P.; Häussinger, K.; Kreyling, W.G. Deposition, retention, and translocation of ultrafine particles from the central airways and lung periphery. *Am. J. Respir. Crit. Care Med.* **2008**, *177*, 426–432. [CrossRef] [PubMed]

173. Downward, G.S.; van Nunen, E.J.H.M.; Kerckhoffs, J.; Vineis, P.; Brunekreef, B.; Boer, J.M.A.; Messier, K.P.; Roy, A.; Verschuren, W.M.M.; van Der Schouw, Y.T.; et al. Long-term exposure to ultrafine particles and incidence of cardiovascular and cerebrovascular disease in a prospective study of a Dutch cohort. *Environ. Health Perspect.* **2018**, *126*, 127007. [CrossRef]

174. Moheimani, R.S.; Bhetraratana, M.; Yin, F.; Peters, K.M.; Gornbein, J.; Araujo, J.A.; Middlekauff, H.R. Increased cardiac sympathetic activity and oxidative stress in habitual electronic cigarette users: Implications for cardiovascular risk. *JAMA Cardiol.* **2017**, *2*, 278–285. [CrossRef] [PubMed]

175. Du, Y.; Navab, M.; Shen, M.; Hill, J.; Pakbin, P.; Sioutas, C.; Hsiai, T.K.; Li, R. Ambient ultrafine particles reduce endothelial nitric oxide production via S-glutathionylation of eNOS. *Biochem. Biophys. Res. Commun.* **2013**, *436*, 462–466. [CrossRef]

176. Bai, L.; Chen, H.; Hatzopoulou, M.; Jerrett, M.; Kwong, J.C.; Burnett, R.T.; Van Donkelaar, A.; Copes, R.; Martin, R.V.; Van Ryswyk, K.; et al. Exposure to ambient ultrafine particles and nitrogen dioxide and incident hypertension and diabetes. *Epidemiology* **2018**, *29*, 323–332. [CrossRef] [PubMed]

177. Lin, L.Z.; Gao, M.; Xiao, X.; Knibbs, L.D.; Morawska, L.; Dharmage, S.C.; Heinrich, J.; Jalaludin, B.; Lin, S.; Guo, Y.; et al. Ultrafine particles, blood pressure and adult hypertension: A population-based survey in Northeast China. *Environ. Res. Lett.* **2021**, *16*, 094041. [CrossRef]

178. Vora, R.; Zareba, W.; Utell, M.J.; Pietropaoli, A.P.; Chalupa, D.; Little, E.L.; Oakes, D.; Bausch, J.; Wiltshire, J.; Frampton, M.W. Inhalation of ultrafine carbon particles alters heart rate and heart rate variability in people with type 2 diabetes. *Part. Fibre Toxicol.* **2014**, *11*, 31. [CrossRef]

179. Peters, A.; Hampel, R.; Cyrys, J.; Breitner, S.; Geruschkat, U.; Kraus, U.; Zareba, W.; Schneider, A. Elevated particle number concentrations induce immediate changes in heart rate variability: A panel study in individuals with impaired glucose metabolism or diabetes. *Part. Fibre Toxicol.* **2015**, *12*, 7. [CrossRef] [PubMed]

180. Stewart, J.C.; Chalupa, D.C.; Devlin, R.B.; Frasier, L.M.; Huang, L.S.; Little, E.L.; Lee, S.M.; Phipps, R.P.; Pietropaoli, A.P.; Taubman, M.B.; et al. Vascular effects of ultrafine particles in persons with type 2 diabetes. *Environ. Health Perspect.* **2010**, *118*, 1692–1698. [CrossRef]

181. Sun, Y.; Song, X.; Han, Y.; Ji, Y.; Gao, S.; Shang, Y.; Lu, S.; Zhu, T.; Huang, W. Size-fractioned ultrafine particles and black carbon associated with autonomic dysfunction in subjects with diabetes or impaired glucose tolerance in Shanghai, China. *Part. Fibre Toxicol.* **2015**, *12*, 8. [CrossRef] [PubMed]