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Review

Impact of Traditional Cigarette Smoking on Liver Structure and Function

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Abstract

Background: Cigarette smoking exposes the human body to a complex mixture of toxic and carcinogenic compounds that can exert widespread biological effects across different organ systems. From addictive responses and consequence maladaptive neuroendocrine responses, cigarette smoke delivers a variety of reactive oxygen species, polycyclic aromatic hydrocarbons, nitrosamines, and heavy metals that collectively contribute to oxidative stress, inflammation, endothelial dysfunction, and metabolic disruption. The liver, as the primary organ responsible for xenobiotic metabolism, plays a central role in processing these harmful substances and is therefore uniquely susceptible to their effects. This narrative review will aim to provide an overview of the current evidence of cigarette smoking effects on hepatic structure and function and discuss clinical implications. **Methods:** This narrative review synthesizes evidence from in vitro studies, animal models, and human clinical research examining the effects of cigarette smoking on liver biology. Mechanistic pathways of injury, metabolic and vascular alterations, and clinical consequences for liver disease were considered. **Results:** Smoking influences hepatic function both directly—through biotransformation pathways generating reactive intermediates—and indirectly via vascular impairment, immune modulation, hormonal alterations, and changes in lipid and glucose metabolism. Emerging evidence indicates that cigarette smoking contributes to hepatic steatosis, accelerates fibrosis progression, worsens outcomes in viral and alcohol-related liver disease, and increases the risk of hepatocellular carcinoma. **Conclusions:** Cigarette smoking exerts multifaceted deleterious effects on the liver. Recognition of smoking as a modifiable risk factor for liver-related morbidity underscores the importance of smoking cessation in patients with or at risk for liver disease and highlights implications for research and clinical practice.

Keywords: tobacco smoking; cigarette smoking; hepatic metabolism; oxidative stress; animal study; human study; steatosis; fibrosis

1. Introduction

Tobacco smoking remains one of the most pervasive and modifiable risk factors for premature mortality worldwide and is a major contributor to an extensive range of diseases, most notably cardiopulmonary disorders and cancer [1–4]. Although global smoking prevalence has declined over

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the recent decades, many regions continue to report substantial rates of tobacco use, with some countries experiencing increasing rates of tobacco use [5,6]. The evolving landscape of nicotine consumption, characterized by the increasing use of electronic nicotine delivery systems (ENDS), including e-cigarettes and other vaping devices, may be perpetuating nicotine dependence at the population level. A considerable proportion of individuals engage in dual use, combining conventional combustible tobacco with ENDS, a pattern that appears to reinforce habitual smoking behaviors and sustain long-term nicotine addiction. Emerging evidence further suggests that dual use may attenuate the perceived urgency to quit, thereby undermining cessation efforts and complicating population-level tobacco control strategies. Moreover, the concurrent exposure to nicotine from multiple sources may potentiate neurobiological pathways involved in dependence, raising concerns about a sustained or even amplified addiction burden within the population [7,8].

While the majority of research on tobacco's harms has focused on cardiovascular, pulmonary, and oncological consequences, the liver — the body's central xenobiotic-metabolizing organ — is uniquely vulnerable to tobacco-derived toxicants such as nicotine, polycyclic aromatic hydrocarbons (PAH), nitrosamines, aldehydes, and reactive oxygen species. Yet until recently, the hepatic consequences of smoking received comparatively limited attention. Emerging evidence now suggests that smoking is associated with increased risk of metabolic-associated fatty liver disease (MASLD) and metabolic-associated steatohepatitis (MASH), fibrosis progression, and higher incidence of hepatocellular carcinoma (HCC) [9,10].

Tobacco smoke is a complex aerosol containing over 7,000 chemical compounds, partitioned into a gaseous phase—including carbon monoxide (CO), hydrogen cyanide (HCN), volatile organic compounds (VOCs), and carbonyls such as formaldehyde and acrolein—and a particulate phase carrying hydrophobic, low-volatility chemicals such as nicotine, PAHs, tobacco-specific nitrosamines (TSNA), phenols, and heavy metals [11,12]. Many of these compounds are rapidly absorbed across the pulmonary alveolar-capillary membrane due to their small size and lipophilicity, entering the systemic circulation and distributing extensively, including to the liver.

Nicotine, the primary psychoactive constituent of tobacco, is absorbed via the lungs and, to a lesser extent, buccal and gastric mucosa. At physiological pH (~7.4), roughly 31% of nicotine is unionized, facilitating passive diffusion across cell membranes, with minimal plasma protein binding (<5%), enabling free tissue penetration. Distribution studies indicate high accumulation in the liver, kidney, spleen, and lungs, reflecting high perfusion and the liver's central role in metabolism [9–13]. Nicotine also crosses the placenta, concentrates in gastric juice, saliva, and breast milk, highlighting its systemic and foetal bioavailability.

In the liver, nicotine undergoes extensive phase I metabolism, primarily via CYP2A6, which oxidizes nicotine to a reactive nicotine Δ1′(5′)-iminium ion. This intermediate is further oxidized by aldehyde oxidase to cotinine, the predominant human metabolite (~70–80%), which, although less pharmacologically active than nicotine, retains modulatory effects on hepatic metabolism and vascular tone. Minor pathways include nicotine N-oxide formation via flavin-containing monooxygenases (FMO), glucuronidation via UDP-glucuronosyltransferases (UGTs), and formation of nornicotine, with most metabolites excreted renally. The reactive iminium ion can form covalent adducts with nucleophilic sites on proteins and DNA, contributing to hepatocellular stress, oxidative injury, and potentially mutagenesis [14,15].

CYP2A6 activity varies with sex, age, and genetics. Female livers express significantly higher CYP2A6 mRNA and protein, and women metabolize nicotine and cotinine more rapidly than men [13,14,16–19]. Estrogen induces CYP2A6, and oral contraceptive use or pregnancy may further accelerate metabolism, leading to higher nicotine turnover and cumulative metabolic stress [16–19]. Age-related decreases in hepatic blood flow and enzyme activity slow nicotine clearance in older adults (>65 years), increasing exposure duration and risk of hepatocellular injury [20]. Common genetic variants (e.g., CYP2A6*2, *4, *9, *12) reduce or abolish nicotine metabolism, prolonging systemic exposure to reactive metabolites and enhancing oxidative stress and liver injury risk [21,22].

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Mechanistically, tobacco constituents induce oxidative stress, mitochondrial dysfunction, and inflammatory activation in the liver. CYP-mediated metabolism generates reactive oxygen species (ROS) and depletes glutathione (GSH), promoting lipid peroxidation and hepatocellular damage. Nicotine and aldehydes activate Kupffer cells, stimulating secretion of pro-inflammatory cytokines such as tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), which in turn activate hepatic stellate cells, driving fibrosis over time. Tobacco exposure also disrupts hepatic energy homeostasis by inhibiting AMP-activated protein kinase (AMPK), decreasing fatty acid oxidation, and upregulating sterol regulatory element-binding protein 1c (SREBP-1c), promoting de novo lipogenesis and hepatic fat accumulation. Collectively, these molecular alterations underlie the progression of MASLD, MASH, fibrosis, and ultimately, increased susceptibility to HCC [10,21–25].

Despite these mechanistic insights, research on the hepatic effects of tobacco remains fragmented. Most evidence focuses on epidemiological associations with liver disease, with fewer studies elucidating precise molecular pathways, sex- and age-specific differences, or the impact of exposure timing (e.g., prenatal, early adulthood).

Given the persistence of nicotine addiction worldwide, the ongoing diversification of nicotine delivery modalities and the substantial global burden of chronic liver disease, a focused narrative review integrating mechanistic, clinical and epidemiological evidence is warranted. This review will address the full continuum of tobacco-related exposures, including combustible cigarettes, waterpipe smoking, electronic nicotine delivery systems and third-hand smoke, and synthesize data from human studies, animal models and in vitro experimental systems. In addition, it will critically evaluate hepatic outcomes across multiple biological levels, from molecular and biochemical alterations to histopathological features and clinically meaningful endpoints.

2. Materials and Methods

This narrative review synthesizes mechanistic, clinical, and epidemiological evidence on the hepatic consequences of tobacco smoking and related nicotine exposures. In order to conduct this narrative review, a comprehensive literature search was conducted. Three electronic databases were searched from their inception to December 1, 2025: PubMed (Medline), Scopus and Web of Science. Additional targeted searches were performed using Google Scholar to identify relevant grey literature and recent preprints when appropriate.

2.1. Search Strategy

Search terms were combined using Boolean operators and included combinations of exposure terms, including “tobacco smoking”, “cigarette smoke” and “nicotine”, liver-related terms “liver”, “hepatocyte”, “MASLD”, “alcoholic liver disease”, “cirrhosis” and “hepatocellular carcinoma” as well as mechanistic terms such as “oxidative stress”, “Kupffer cell”, “cytochrome P450”, “metabolism”, “immune response” and “pathophysiology”. Reference lists of key articles were manually screened to identify additional relevant studies.

2.2. Eligibility Criteria

Studies were included if they investigated tobacco smoking and reported liver-related outcomes, including molecular, biochemical, histological or clinical endpoints. All studies involving human subjects, animal models or in vitro hepatic systems were included. Studies that did not report data on hepatic function and disease were excluded. This narrative review included original research articles and secondary research that examined the hepatic consequences of traditional tobacco smoking. Eligible study designs comprised randomized controlled trials, non-randomized interventional studies, cohort studies, case–control studies, cross-sectional studies, and systematic reviews or meta-analyses that reported liver-related outcomes in human subjects. Experimental animal studies were included when they provided mechanistic insight into smoking-related hepatic injury. The following types of publications were excluded: case reports, case series, editorials, letters

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to the editor, commentaries, conference abstracts, expert opinions, and narrative reviews that did not present original data or systematic methodology. Only studies published in the English language were considered eligible. Articles for which only the abstract was available, without access to the full text, were excluded from the review. There were no restrictions regarding publication year; however, studies had to specifically evaluate traditional combustible tobacco smoking. Studies focusing exclusively on electronic cigarettes, heated tobacco products, or other non-combustible nicotine delivery systems were excluded.The Materials and Methods should be described with sufficient details to allow others to replicate and build on the published results. Please note that the publication of your manuscript implicates that you must make all materials, data, computer code, and protocols associated with the publication available to readers. Please disclose at the submission stage any restrictions on the availability of materials or information. New methods and protocols should be described in detail while well-established methods can be briefly described and appropriately cited.

Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication.

Interventionary studies involving animals or humans, and other studies that require ethical approval, must list the authority that provided approval and the corresponding ethical approval code.

In this section, where applicable, authors are required to disclose details of how generative artificial intelligence (GenAI) has been used in this paper (e.g., to generate text, data, or graphics, or to assist in study design, data collection, analysis, or interpretation). The use of GenAI for superficial text editing (e.g., grammar, spelling, punctuation, and formatting) does not need to be declared.

3. Results

3.1. In Vitro Studies

Several in vitro studies have provided evidence that tobacco smoke exerts direct hepatotoxic effects through multiple cellular mechanisms, including disruption of hepatic drug transporter function, impairment of cellular energy metabolism, and induction of reactive oxygen species (ROS) production [26–30]. The list of studies included is summarized in Table 1. Sayyed et al. (2016) demonstrated that exposure of human hepatocytes to tobacco smoke led to downregulation of hepatic drug transporters, resulting in impaired xenobiotic metabolism and clearance [26].

Lucendo-Villarin et al. (2017) reported sex-dependent effects in human hepatoblasts derived from pluripotent stem cells. While ATP production was relatively preserved in female-derived hepatoblasts, caspase activation was more than twofold higher compared to male counterparts, indicating enhanced susceptibility to apoptosis in females under tobacco smoke exposure [27].

Yamamoto et al. (2022) highlighted the role of oxidative stress, showing that tobacco smoke induced micronucleus formation, cytotoxicity, and ROS production in hepatocyte cultures. These effects were dose-dependent and modulated by intracellular antioxidant levels, including glutathione (GSH), N-acetylcysteine (NAC), and buthionine sulfoximine (BSO) [28].

Ma et al. (2020) combined in vivo and in vitro approaches, showing that second-hand smoke exposure increased serum lipid levels in mice and reduced low lipoprotein (LDL) receptor expression in HepG2 hepatocytes, linking smoke exposure to alterations in lipid metabolism [29]. Finally, Bovard et al. (2022) used 3D cultured hepatocytes and liver spheroids to demonstrate that tobacco smoke exposure modifies liver cytochrome P450 activity in a dose-dependent manner, further confirming the direct impact of smoke on hepatic enzymatic function [30].This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

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Table 1. In vitro studies.

Authors / Year/Reference No	Study Model	Exposure Type	Measurements / Endpoints	Outcomes (liver-related)
Sayyed et al., 2016 [26]	In vitro (human hepatocytes)	Tobacco smoke exposure	Drug transporter activity and gene expression	Downregulation of hepatic drug transporters; impaired xenobiotic metabolism and clearance
Lucendo-Villarin et al., 2017 [27]	In vitro (human hepatoblasts derived from pluripotent stem cells)	Tobacco smoke exposure	ATP levels, secretory function, caspase activation	Sex-dependent reductions in ATP, metabolic and secretory activity; females showed twofold higher caspase activations, but reduced ATP depletion
Yamamoto et al., 2022 [28]	In vitro (hepatocyte culture)	Tobacco smoke exposure	Micronucleus induction, cytotoxicity, ROS production, GSH modulation	Dose-dependent effects modulated by antioxidant levels of GSH, NAC, BSO
Ma et al., 2020 [29]	In vivo (adult mouse models) and in vitro (HepG2 hepatocyte culture)	Second-hand smoke exposure	Serum lipid measurements, liver LDL receptor expression analysis	Increased serum lipid levels; downregulation of HepG2 LDL receptor expression
Bovard et al., 2022 [30]	In vitro (3D cultured hepatocytes & liver spheroids)	Tobacco smoke exposure	Liver cytochrome enzyme activity	Smoking alters liver CYP activity in a dose-dependent manner

Legends: ATP – adenosine triphosphate, BSO – buthionine sulfoximine, CYP – cytochrome P450, GSH – glutathione, HepG2 – human hepatocellular carcinoma cell line, LDL – low-density lipoprotein, NAC – N-acetylcysteine, ROS – reactive oxygen species.

3.2. Animal Studies

Most preclinical studies investigating the effects of tobacco smoke on liver health have been conducted using rodent models, primarily mice and rats [31–46]. A total of 15 animal studies were included in this review, with key details summarized in Table 2. The studies included reported on diverse aspects of hepatic function, ranging from histological changes to metabolic and epigenetic alterations, under varying conditions of tobacco exposure, including direct inhalation, second-hand smoke, prenatal exposure, and exposure to specific tobacco constituents such as nicotine or nitrosamines.

Several studies consistently demonstrated that tobacco smoke exposure adversely affects liver structure and function. Zabala et al. reported that rats exposed to tobacco-specific nitrosamines exhibited increased ethanol-induced liver damage, including enhanced inflammation and insulin and insulin-like growth factor (IGF) resistance [31]. Similarly, Li et al. observed impaired glucose metabolism and reduced hepatic glycogen synthesis in rats exposed to second-hand smoke [32]. Also, early life exposure to tobacco smoke also had long-term metabolic consequences. Soares et al. and Li et al. showed that postnatal or maternal exposure during gestation led to hepatic lipid accumulation, steatosis, oxidative stress, and glucose intolerance in offspring, with some effects being sex-specific [33,34].

Prenatal and paternal exposures were found to influence hepatic metabolism through epigenetic mechanisms. Lkhagvadorj et al. reported that prenatal exposure to tobacco smoke enhances nicotine metabolism in offspring [35]. Liu et al. demonstrated that paternal smoking induces alterations in sperm DNA methylation, potentially predisposing progeny to long-term hepatic dysfunction [40]. Similarly, Zeng et al. reported organ- and sex-specific changes in hepatic IGF1 promoter methylation following prenatal exposure, suggesting persistent alterations in growth and metabolic programming [37].

In adult models, exposure to second-hand or direct cigarette smoke induced hepatic steatosis, inflammation, fibrosis, and dysregulated lipid metabolism. Tommasi et al. and Ma et al. observed

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increased fat accumulation, collagen deposition, and downregulation of LDL receptor expression [29,36]. Additional studies confirmed these findings, showing oxidative stress, inflammatory signalling, and metabolic dysregulation as common features of tobacco-induced liver injury [38–42]. Notably, interventions such as antioxidant or lycopene supplementation partially mitigated some of these detrimental effects [39,42].

Emerging evidence also implicates tobacco smoke in gut-liver axis perturbations. Meng et al. found that chronic smoke exposure altered gut microbiota and liver gene regulation, whereas Pan et al. linked tobacco-induced upregulation of hepatic nicotinic acetylcholine receptors to inflammatory stress [43,44]. In a murine model of α-galactosylceramide–induced fulminant hepatitis, Pavlovic et al. found that mesenchymal stem cells cultured in cigarette smoke–exposed medium acquired a pro-inflammatory phenotype with reduced production of hepatoprotective and immunosuppressive cytokines and were unable to attenuate liver injury or suppress inflammatory immune cell infiltration, in contrast to control MSCs cultured in non-smoke-exposed medium [45]. Nemmar et al. demonstrated that water pipe smoke caused hepatic degeneration, lipid peroxidation, immune cell infiltration, and elevated liver enzymes, underscoring the hepatotoxic potential of various forms of tobacco use [46].

Table 2. Animal studies.

Authors / Year / Refrence No	Study Model	Exposure Type	Measurements / Endpoints	Outcomes (liver-related)
Zabala et al., 2015 [31]	In vivo (rat; standard-fed and alcohol-fed)	Saline or intraperitoneal injection of tobacco specific nitrosamine (NNK)	Liver histology, fibrosis, ER disruption	Ethanol-fed and smoke-exposed rats have increased rates of ALD pathogenesis, including insulin and IGF resistance and inflammation
Li et al., 2018 [32]	In vivo (rat models)	Second-hand tobacco smoke exposure	Serum glucose, haemoglobin A1c level, insulin secretion, hepatic glycogen synthesis	Glucose metabolic alterations, liver glycogen synthesis suppressed
Soares et al., 2018 [33]	In vivo (rat)	Early postnatal tobacco smoke exposure (during lactation)	Hormonal assays (corticosterone, ACTH), liver and visceral adipose tissue, obesity markers	Postnatal smoke exposure induced abdominal obesity, induced liver lipogenesis and vitamin-D related-enzymes; more pronounced in male offspring
Li et al., 2019 [34]	In vivo (maternal exposure in mice; offspring studied)	Second-hand tobacco smoke exposure during gestation and lactation	Glucose tolerance testing, liver histology, mitochondrial oxidative stress markers, biogenesis assays	Maternal tobacco exposure in pregnancy increases risk of hepatic steatosis, oxidative stress and glucose intolerance
Lkhagvadorj et al., 2020 [35]	In vivo (maternal exposure in mice; livers of offspring studied)	Prenatal tobacco smoke exposure	Hepatic CYP2A5 mRNA, promoter methylation, enzyme activity, cotinine levels	Higher hepatic nicotine metabolism in prenatally exposed offspring; potential predisposition to nicotine dependence later in life
Tommasi et al., 2020 [36]	In vivo (mouse; standard-fed and high-fat-diet fed)	Second-hand tobacco smoke exposure	Gene expression analysis, histological findings,, glycogen deposition	Significant hepatic fat accumulation, lobular inflammation infiltrates, collagen deposition and loss of glycogen
Zeng et al., 2020 [37]	In vivo (mice exposed to prenatal smoke)	Prenatal tobacco smoke exposure	IGF1 promoter methylation rates in liver, lung across foetal, neonatal and adult	Organ- and sex-specific alterations in liver IGF1 promoter methylation; potential long-term

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			stages; mRNA expression	effects on hepatic growth and metabolic programming
Ma et al., 2020 [29]	In vivo (adult mouse models) and in vitro (HepG2 hepatocyte cultues)	Second-hand tobaccosmoke exposure	Serum lipid measurements, liver LDL receptor expression analysis	Increased serum lipid levels; downregulation of HepG2 LDLreceptor expression
Fouda et al., 2021 [38]	In vivo (mouse; low-fat chow-fed and high-fat-chow-fed)	Second-hand tobacco smoke exposure	Nitrotyrisine levels, liver histology, inflammation	High-fat diet alone lead to steatosis, but not injury. Concomitant use of tobacco induced liver injury, inflammation and fibrosis
Rocha et al., 2021 [39]	In vivo (mouse models)	Long-term tobacco smoke exposure with or without lycopene administration	Liver histology, oxidative stress markers, inflammatory signalling, collagen deposition	Tobacco smoke exposure induces hepatic damage, oxidative stress, inflammation and collagen; lycopene ameliorates these effects
Liu et al., 2022 [40]	In vivo (paternal exposure to tobacco smoke; offspring livers studied)	Tobacco smoke exposure	Paternal spermatozoa methylation, progeny liver histology	Smoking increases global methylation of sperm DNA and alterations in inherited genes that may perturb long-term liver metabolic function
Ge et al., 2022 [41]	In vivo (rat models)	Tobacco smoke exposure	Plasma cholesterol levels, trimethylamine oxide (TMAO) content, liver lipid gene regulation	Increased serum cholesterol and TMAO content, upregulation of HMG-CoA reductase
Torres et al., 2021 [42]	In vivo (male mouse models)	Tobacco smoke exposure with and without antioxidant treatment	Metabolomics analysis, lipid mapping	Metabolite alteration, oxidative stress, hepatic steatosis; partial protection with antioxidant treatment
Meng et al., 2022 [43]	In vivo (mouse livers, gut microbiota analysis)	Tobacco smoke exposure	Liver gene regulation and microbiota balance	Reduced body weight, blood lipids and food-intake, gut dysbiosys
Pan et al., 2023 [44]	In vivo (mouse with diet-induced MASH)	Tobacco smoke exposure	Nicotinic acetylcholine receptor (nAChR) induction	Tobacco increases nAchR expression and promotes inflammatory stress
Pavlovic et al., 2023 [45]	In vivo (murine model of fulminant hepatitis)	Mesenchymal cells cultured in tobacco smoke-exposed medium	Liver histology, cytokine profile, immune cell infiltration	Reduced immunosuppression and hepatoprotection
Nemmar et al., 2024 [46]	In vivo (mouse models)	Waterpipe smoke exposure	Liver morphology and function	Immune cell infiltration, vacuolar hepatic degeneration, lipid peroxidation, increased plasma ALT & AST, as well as pro-inflammatory cytokine release

Legends: ACTH – adrenocorticotropic hormone, ALD – alcohol-associated liver disease, ER – endoplasmatic reticulum, HepG2 – human hepatocellular carcinoma cell line, HMG-CoA – 3-hydroxy-3-methylglutaryl-coenzyme A, IGF1 – insulin-like growth factor 1, LDL – low-density lipoprotein, mRNA – messenger ribonucleic acid, NNK -4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; tobacco-specific nitrosamine, TMAO- trymethylamine N-oxide.

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3.3. Human Clinical and Epidemiological Studies

A growing body of clinical and epidemiological evidence highlights the adverse effects of tobacco use on liver health in humans [47–74]. These studies span observational cohorts, retrospective analyses, case-control genetic studies, proteomics, and systematic reviews, and collectively examine both direct and indirect effects of tobacco exposure on liver structure, function, and disease progression (Table 3).

Several studies have linked tobacco use to the onset and progression of MASLD. Okamoto et al. and Zhang et al. demonstrated that cigarette smoking independently increases MASLD risk, with synergistic effects observed when certain genetic polymorphisms are present [50,53,56]. Smoking has also been associated with more severe liver fibrosis in MASLD patients, as shown in cross-sectional and meta-analytic studies [54,57,64]. Notably, retrospective and prospective analyses indicate that smoking cessation may reduce long-term MASLD risk, although short-term weight gain may transiently influence disease markers [68,69,72].

Maternal smoking exerts detectable effects on foetal liver development. Drake et al., Filis et al., and Walker et al. found that in utero exposure to tobacco smoke alters nutrient metabolism, protein expression, and fatty-acid transporter transcripts, which could predispose offspring to metabolic dysregulation [49,51,59]. Mentholated cigarette use in young adults was also shown to slow nicotine metabolism, highlighting pharmacokinetic differences that may modulate hepatic risk [52].

Tobacco use further impacts liver function through metabolic, enzymatic, and inflammatory pathways. Studies report elevations in liver enzymes alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT), C-reactive protein, and dyslipidemia in smokers, often compounded by other risk factors such as alcohol or high BMI [60,65,66]. CYP1A2 activity, a key hepatic metabolic enzyme, is reduced in chronic smokers but transiently induced in acute second-hand smoke exposure, suggesting complex modulatory effects on xenobiotic metabolism [63].

In the context of liver transplantation, smoking—both by donors and recipients—was associated with adverse outcomes, including increased risk of early thrombosis, graft failure, and reduced overall survival [47,55,62,74]. Tobacco exposure also appears to elevate the risk of liver cancer and autoimmune liver disease, particularly primary biliary cirrhosis (PBC), with ever-smokers showing a threefold higher risk of advanced fibrosis compared to non-smokers [47,58,64].

Additional studies underscore the dose-dependent nature of tobacco's hepatic effects. Both initiation at an early age and cumulative exposure correlate with increased fibrosis and MASLD severity, while smoking cessation generally attenuates these risks [71–73]. Nicotine-specific exposure has also been linked to gallstone formation, highlighting a broader hepatobiliary impact beyond steatotic disease [70].

Table 3. Human studies.

Authors / Year/Reference No	Study Model	Exposure Type	Measurements / Endpoints	Outcomes (liver-related)
Heide et al., 2009 [47]	Retrospective cohort study	Current, previous and never-smokers	Long-term post-transplant outcomes	Smoking may increase the risk of liver cancer
Zein et al., 2011 [48]	Multicenter cohort study	Consumption of alcohol and/or tobacco smoke in MASLD patients	Liver biopsy findings	Smoking history associated with advanced liver fibrosis; more pronounced in use of both substances
Drake et al., 2015 [49]	Retrospective analysis (human foetal liver samples)	Maternal tobacco smoking	Nutrient and metabolic markers (vitamin B12, plasma homocysteine, cobalt levels), gene expression	Reduced foetal liver B12, reduced sex-related metabolic differences
Zhang et al., 2015 [50]	Case-control genetic association study	Smoking and genetic polymorphisms of GPx-1 and resistin gene promoters in MASLD and healthy population	MASLD outcome	Smoking independently increases risk of MASLD; risk increased with certain gene variants

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Filis et al., 2015 [51]	Proteomics study (foetal liver samples)	Maternal tobacco smoking	Protein expression in utero	Increased expression of proteins linked to necrosis and cancer pathways, disrupted glucose metabolism
Fagan et al., 2016 [52]	Observational study	Menthol and non-menthol tobacco smoke exposure	Nicotine metabolite ratio, CO, cotinine and nicotine levels	Menthol smokers had slower nicotine metabolism
Zhang et al., 2016 [53]	Case-control genetic association study	Tobacco smoking in MASLD patients and healthy controls	MASLD susceptibility and severity	Smoking and gene polymorphisms exert both independent and synergistic risk of MASLD
Munsterman et al., 2017 [54]	Cross-sectional study	Current, previous and never-smokers	Fibrosis severity, overall histological disease activity	Smoking is associated with more severe liver fibrosis in MASLD patients, but not overall histological disease activity
Li et al., 2017 [55]	Retrospective cohort and meta analysis	Current, previous and never-smokers	Early & late post-transplant complications	No significant association between smoking and hepatic thrombosis, biliary complications; long term effects on CVD and de-novo malignancies
Okamoto et al., 2018 [56]	Longitudinal cohort study	Tobacco smoking in nondrinkers	MASLD onset	Smoking increases risk of MASLD; dose-dependent effect
Ou et al., 2019 [57]	Cross-sectional study	MASLD patients with or without smoking history	FibroScan measurement of liver stiffness (LS)	Significantly higher LS values in smokers compared to non-smokers
Wijarnpreecha et al., 2019 [58]	Systematic Review and Meta-Analysis	Current, previous and never smokers	Risk of PBC, pooled odds ratio	Smoking increases the risk of PBC
Walker et al., 2019 [59]	Cross-sectional study (human foetal liver study)	Maternal smoking	Nutrient transporter transcripts in placenta and liver	Reduced hepatic fatty-acid transporter transcripts
Nivukoski et al., 2019 [60]	Cross-sectional study	Smoking history	Liver enzymes, C-reactive protein levels, lipid profile, lifestyle risk score	Increased GGT, ALT, CRP, dyslipidemia; effects most pronounced in men with highest number of risk factors
Takenaka et al., 2020 [61]	Retrospective study	Smoking history	Ultrasonography findings	Smoking associated with prevalence and severity of MASLD, particularly in males; smoking cessation improved MASLD
Li et al., 2020 [62]	Observational cohort study	Donor smoking history in liver transplantations	Early post-transplant thrombosis, patient and graft survival	Donor smoking more than doubled the risk of early post-transplant thrombosis; increased mortality and graft failure
Garduno et al., 2021 [63]	Cross-sectional study	Current, previous and never-smokers	CYP1A2 activity, liver function tests,	Smoking reduces CYP1A2 activity; CYP1A2 activity increased in acute second-hand smoke exposure in never smokers
Wijarnpreecha et al., 2021 [64]	Systematic Review and Meta analysis	Current, previous and never-smokers	Presence of liver fibrosis in PBC patients; odds ratio extracted or calculated from cross-	Ever-smokers with PBC had 3x risk of advanced liver fibrosis compared to non-smokers

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			sectional data and pooled analysis using inverse-variance method	
Bijani et al., 2022 [65]	Cohort study	Tobacco, alcohol and opium cosumption	Liver function tests (LFT)	Both alcohol and tobacco consumption increased LFT; inhaled, but not oral opium increased LFT
Mehling et al., 2022 [66]	Prospective cohort	Smoking history, alcohol and coffee consumption	Liver enzyme levels	Synergistic effects of smoking and alcohol on liver function; coffee mitigate this effect
Jang et al., 2023 [67]	Cross-sectional study	Current, previous and never-smokers	MASLD liver fat score	Smoking may contribute to MASLD
Jeong et al,. 2023 [68]	Retrospective cohort (epidemiological) study	Current, previous, relapsed and never-smokers	Fatty liver index, liver enzyme levels, BMI changes	Weight monitoring post-smoking cessation may mitigate MASLD risk
Zhang et al., 2023 [69]	Systematic Review and Meta analysis	Smoking history	MASLD prevalence	Smoking cessation may transiently increase MASLD risk
Kim et al., 2024 [70]	Cohort study	Tobacco smoke exposure	Abdominal ultrasound findings of gallstones, urinary cotinine	Cotinine-verified smokers have increased risk of gallstones
Li et al., 2025 [71]	Cross-sectional study	Tobacco smoking history	Liver fibrosis detected via transient elastography	Smoking history and early initiation associated with higher fibrosis risk in MASLD, even after cessation
Joe et al., 2025 [72]	Cross-sectional study	Current, previous and never-smokers	Abdominal ultrasound	Risk of MASLD in tobacco users is dose-dependent; smoking cessation decreases risk of MASLD
Ma et al., 2025 [73]	Mendelian randomization study	Tobacco smoking	MASLD severity	Smoking increases MASLD risk; significantly affected by BMI
Cecil et al., 2025 [74]	Prospective cohort study	Current, previous and never-smokers	Overall survival in candidates for liver transplantation	Smoking worsens prognosis in advanced liver disease, even accounting for transplantation

Legends: ALT – alanine aminotransferase, CO – carbon monoxide, CRP – C-reactive protein, CVD – cardiovascular disease, GGT – gamma-glutamyl transferase, GPx1 – glutathione peroxidase-1, LFT – liver function tests, LS – liver stiffness, MASLD – metabolic dysfunction-associated steatotic liver disease, PBC – primary biliary chirrosis.

4. Impact of Smoking on Metabolic Dysfunction-Associated Liver Disease (MASLD)

Tobacco smoking, primarily via nicotine, exerts significant effects on liver metabolism, contributing to the development and progression of MASLD. Multiple mechanistic and epidemiological studies highlight the role of nicotine in promoting insulin resistance, dyslipidaemia, and oxidative stress, key drivers of hepatic steatosis and progression toward steatohepatitis [36,41]. Nicotine directly impairs insulin signalling in hepatocytes and peripheral tissues, promoting hyperglycaemia and compensatory hyperinsulinemia [32,63]. Concurrently, nicotine alters lipid metabolism by increasing hepatic lipogenesis, reducing fatty acid oxidation, and promoting dyslipidaemia, with elevated serum triglycerides and LDL cholesterol [29,41]. This metabolic milieu promotes excessive lipid deposition within hepatocytes, thereby creating a permissive environment for the development of MASLD. Cigarette smoking not only contributes to the initiation of hepatic steatosis but also accelerates its transition toward MASH. Mechanistic evidence indicates that

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nicotine-induced oxidative stress, mitochondrial dysfunction and gut-derived endotoxaemia interact with underlying metabolic derangements to amplify hepatocellular injury and inflammatory signalling [23,43]. Clinical cohorts report that smokers with MASLD are more likely to develop ballooning degeneration, lobular inflammation, and fibrosis, consistent with a higher MASH burden [38,75]. The deleterious effects of smoking on MASLD are exacerbated by obesity and metabolic syndrome. Nicotine amplifies insulin resistance and dyslipidaemia in overweight individuals, increasing hepatic fat deposition and inflammatory signalling [76–80]. These interactions suggest that smoking acts as a disease modifier, worsening outcomes in patients with pre-existing metabolic risk factors.

5. Smoking and Alcoholic Liver Disease (ALD): Synergistic Effects

Tobacco smoking and alcohol consumption frequently co-occur, and use of one often increases the intake of the other [81,82]. Epidemiological studies show that combined exposure is associated with higher liver enzyme levels, increased steatosis, and faster progression to fibrosis compared with either exposure alone [83].

Both alcohol and nicotine induce liver injury via oxidative stress, mitochondrial dysfunction, and lipid accumulation [36,84]. Nicotine also promotes hepatic fat deposition and collagen accumulation through CYP2A5-mediated pathways [22,85]. Animal studies demonstrate that nicotine enhances ethanol-induced steatosis and collagen deposition, even without increasing inflammation, suggesting a direct pro-fibrotic effect [86].

In hypercholesterolemic mouse models, combined exposure to ethanol and tobacco smoke results in markedly greater hepatic steatosis and tissue hypoxia compared with either insult alone [87,88]. Clinically, individuals with alcohol-associated liver disease who smoke exhibit significantly elevated serum AST, ALT and GGT levels, more advanced stages of hepatic fibrosis and poorer long-term clinical outcomes than nonsmokers with comparable alcohol consumption [59,83,89].

While nicotine itself contributes to steatosis and fibrosis, other compounds in cigarette smoke, including aldehydes and polycyclic aromatic hydrocarbons, amplify oxidative stress and hepatocellular damage [22,35,84]. Findings from mouse models indicate that while nicotine alone can promote hepatic lipid accumulation, exposure to whole cigarette smoke elicits substantially greater inflammatory activation and hepatocellular injury, reflecting the additive toxicity of smoke-derived constituents beyond nicotine [22,84,90].

6. Smoking and Viral Hepatitis (HBV, HCV)

Multiple clinical studies show that cigarette smoking accelerates fibrosis progression in chronic viral hepatitis. In patients with HCV, Hézode et al. demonstrated significantly more advanced fibrosis, necroinflammatory activity, and steatosis in smokers compared with non-smokers, independent of alcohol intake and metabolic factors [91]. Mallat et al. identify smoking as a major environmental factor accelerating chronic HCV progression by intensifying oxidative stress and hepatic stellate cell activation [92]. Some investigators have reported that smoking exacerbates histological liver injury in both HCV- and HBV-infected individuals, although the evidence supporting this association in HBV appears comparatively limited [2,93].

In chronic HCV infection, smoking is markedly overrepresented, and qualitative research shows that patients frequently use cigarettes to cope with the psychological burden of diagnosis and treatment, highlighting a high-risk behavioural phenotype rather than a purely biological effect [94]. Early biopsy-based studies reported more severe necrosis and inflammation and fibrosis in HCV smokers, while mechanistic reviews have proposed that smoke-induced oxidative stress and stellate-cell activation may accelerate fibrogenesis [91–93]. Wang et al. demonstrated that smoking increases HCC risk through measurable immunovirological pathways, including sustained elevations in HBV viral load, higher ALT, impairment of NK-cell frequency and function, and reduced interferon-γ

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production—indicating that nicotine and smoke constituents may directly weaken antiviral immunity [95].

The most robust epidemiological data come from a 2023 meta-analysis, which showed a striking synergistic effect between smoking and HBV or HCV infection on hepatocellular carcinoma, and even higher risk in HBV/HCV coinfection [96]. Despite these convergent signals for carcinogenesis, evidence that smoking consistently accelerates fibrosis progression remains inconsistent, likely due to confounding by alcohol, metabolic factors, and socioeconomic variables. Importantly, the impact of smoking on antiviral treatment response remains poorly characterized, representing a major gap in the literature. Overall, the available data suggest that smoking acts as a cofactor that worsens immunologic control of HBV, may aggravate histological injury in HCV, and significantly amplifies HCC risk across both infections, but high-quality prospective studies are urgently needed to clarify its role in fibrosis progression and treatment outcomes.

7. Smoking and Hepatocellular Carcinoma (HCC)

Epidemiological data consistently identify smoking as an independent and clinically meaningful risk factor for HCC. In a large prospective cohort of patients with MASLD, active smokers demonstrated significantly higher incidence of HCC compared with non-smokers, even after adjustment for metabolic comorbidities, body mass index (BMI), and fibrosis severity [83]. Population-based evidence from the Singapore Chinese Health Study similarly showed that current smokers had a substantially increased risk of HCC, with a clear dose–response relationship according to number of cigarettes and years smoked [97].

High-level syntheses confirm this pattern: an umbrella review of systematic reviews and meta-analyses reported smoking as a consistent, moderate-strength carcinogenic risk factor for HCC, with pooled effect sizes generally in the range of 1.3–2.0 after adjustment for alcohol and viral hepatitis [98].

The risk becomes substantially amplified when smoking co-occurs with HBV or HCV infection. A recent meta-analysis of >22,000 participants found supra-additive interactions, where smoking combined with HBV or HCV infection exponentially increased the risk for developing HCC [96]. HBV-infected smokers exhibit higher viral loads, persistent ALT elevation, impaired NK-cell function, and reduced interferon-γ levels—immunological changes that contribute directly to hepatic oncogenesis [95]. The interaction with alcohol is also clinically meaningful: alcohol promotes oxidative stress and acetaldehyde-mediated DNA damage, while smoking introduces nitrosamines and PAH, creating a multihit environment that accelerates mutagenesis in hepatocytes. In MASLD, smoking enhances insulin resistance, promotes lipotoxicity, accelerates fibrosis progression, and increases HCC risk even in the absence of cirrhosis—supporting its role as a disease modifier.

The carcinogenic mechanisms underlying smoking-related HCC involve several well-characterized pathways. Tobacco smoke contains nitrosamines (e.g., NNK), PAH, benzene, and heavy metals, all of which induce DNA adduct formation, oxidative DNA damage (8-oxo-dG), and mutational signatures affecting tumour suppressors such as TP53—a mechanism supported by genomic studies in smoking-related cancers. Chronic exposure alters hepatic methylation patterns, disrupts DNA repair pathways, and induces epigenetic modifications that facilitate malignant transformation [99].

Nicotine itself is not a classical carcinogen, but it promotes hepatocarcinogenesis indirectly through activation of nicotinic acetylcholine receptors (nAChRs), enhancement of angiogenesis (VEGF upregulation),anti-apoptotic signalling (Akt, MAPK pathways) and immunomodulation that weakens anti-tumour surveillance. However, nicotine's contribution is minor compared with the directly carcinogenic compounds in smoke [11]. Studies comparing tobacco vs. nicotine-alone exposures consistently show that nicotine facilitates tumour progression but does not initiate carcinogenesis by itself.

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8. Alterations in Liver Enzymes (ALT, AST, GGT) Among Smokers

Cigarette smoking is associated with modest but consistent elevations in liver enzymes, including ALT, AST and GGT. Population-based analyses, such as the Tromsø Study, demonstrated higher mean GGT levels among current smokers compared with never-smokers, independent of alcohol intake, age, and BMI [100]. Similarly, a large cohort study reported both independent and supra-additive effects of smoking, alcohol, and metabolic syndrome on ALT, AST, and GGT, highlighting that smoking contributes to hepatic enzyme elevations even in the absence of excessive alcohol consumption [101].

GGT is particularly sensitive to smoking, likely due to its role in glutathione metabolism and oxidative stress defence. Tobacco smoke induces reactive oxygen species (ROS) and xenobiotic-metabolizing enzymes, increasing hepatic oxidative burden and triggering compensatory upregulation of GGT. Mechanistically, nicotine and other smoke constituents enhance cytochrome P450 activity, promoting metabolic processing of xenobiotics and secondary oxidative stress, which can also mildly elevate ALT and AST. Preclinical models support this: in nicotine-administered mice, hepatocellular stress and lipid accumulation led to increased ALT and AST, whereas interventions reducing oxidative or metabolic load, such as corn silk extract, attenuated these elevations [102].

Importantly, several studies indicate that these enzyme elevations are at least partially reversible upon smoking cessation, suggesting that ongoing exposure maintains oxidative and metabolic stress on hepatocytes. Reduction in GGT, ALT, and AST after cessation may reflect decreased xenobiotic load, lower ROS production, and improved hepatic lipid metabolism.

9. Differences Between Nicotine-Containing Cigarettes and e-Cigarettes

Cigarette smoke and e-cigarette aerosol differ fundamentally in chemical composition. Traditional cigarette smoke contains thousands of chemicals, including tar, polycyclic aromatic hydrocarbons, nitrosamines, heavy metals, and reactive oxygen species, whereas e-cigarette aerosols primarily deliver nicotine, propylene glycol, glycerol, and flavouring compounds, with far fewer combustion products [2,11,103–107].

Nicotine itself exhibits hepatotoxic effects, promoting oxidative stress, lipid dysregulation, and mild hepatocellular injury. However, studies comparing nicotine-containing and nicotine-free e-cigarettes indicate that the additional toxins present in cigarette smoke amplify liver damage beyond the effects of nicotine alone. Notably, a preclinical study in mice under high-fat diet conditions found that e-vapour reduced fat mass, and only nicotine-containing e-vapour improved glucose tolerance; in chow-fed mice, e-vapour increased both blood and liver lipid content. These findings suggest that nicotine may exert both harmful and partly protective effects on liver metabolism depending on the metabolic context, but combustion products in cigarette smoke exacerbate hepatotoxicity [108].

Available data on e-cigarettes and liver outcomes remain limited and largely short-term, with evidence of oxidative stress, DNA damage, and mild liver enzyme elevations reported in studies [109,110]. While the long-term hepatotoxic potential of e-cigarettes is not yet fully known, these studies indicate that the focus of hepatotoxicity in both traditional and electronic cigarettes should remain on nicotine and its interaction with metabolic stressors, as well as the additive effects of other smoke or aerosol constituents in conventional tobacco. Available evidence on the hepatic effects of e-cigarettes remains limited and is derived predominantly from short-term experimental and observational studies, which consistently report increased oxidative stress, DNA damage, and mild elevations in liver enzymes [109,110]. Although the long-term hepatotoxic potential of e-cigarettes has yet to be fully characterized, current data suggest that nicotine, through its metabolic and inflammatory and oxidative pathways, constitutes a central driver of hepatic susceptibility. Moreover, the potential additive or synergistic effects of other aerosol constituents, including carbonyl compounds, metals, and ultrafine particles, highlight the need for caution when interpreting e-cigarettes as a harmless alternative to combustible tobacco. Overall, these findings underscore the

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importance of continued investigation into both nicotine-mediated toxicity and the broader chemical burden associated with electronic aerosol exposure.

10. Clinical Implications and Practice Recommendations

Assessment of smoking habits is crucial in hepatology practice, as cigarette use significantly influences disease progression and treatment outcomes across multiple liver conditions. In patients with metabolic dysfunction-associated steatotic liver disease (MASLD), smoking exacerbates insulin resistance, dyslipidaemia, and steatosis, contributing to faster progression toward MASH and fibrosis [83]. Among individuals with chronic hepatitis B or C, smoking is associated with higher viral loads, impaired immune responses, accelerated fibrosis, and increased risk of hepatocellular carcinoma [2,95]. In alcoholic liver disease (ALD), combined exposure to alcohol and tobacco amplifies hepatic steatosis, oxidative stress, and fibrogenesis, worsening clinical outcomes [2,23,86].

Given these findings, systematic evaluation of smoking status should be incorporated into all routine hepatology assessments. Clinicians should provide clear counselling on the additive and synergistic hepatotoxic, metabolic and oncologic consequences of tobacco use, emphasizing its influence on disease progression and treatment outcomes. The integration of structured smoking-cessation strategies—including behavioural counselling, evidence-based pharmacotherapy such as nicotine replacement therapy or varenicline, and regular follow-up, should be considered a standard component of hepatology care. Targeted cessation interventions delivered at key clinical junctures, such as the diagnosis of MASLD, HBV or HCV infection, or alcohol-associated liver disease, have the potential to improve clinical trajectories, reduce liver-related morbidity and lower the long-term risk of hepatocellular carcinoma [2,80].

11. Limitations of the Available Literature

Despite a growing body of evidence linking smoking to various liver diseases, several limitations of the available literature must be acknowledged. Most studies are observational and cross-sectional, with a paucity of longitudinal or randomized controlled trials, limiting the ability to infer causality [2,78]. Definitions of smoking exposure vary widely, ranging from self-reported current smoking to pack-years, and methodologies for assessing liver outcomes differ between cohorts, creating heterogeneity that complicates data synthesis [80]. Confounding factors, including alcohol consumption, metabolic syndrome, obesity, and concomitant medication use, are frequently present and not uniformly controlled for, which may bias associations between tobacco use and liver outcomes. Additionally, while animal models provide mechanistic insights, translational limitations exist: differences in nicotine metabolism, liver physiology, and dose exposure between rodents and humans restrict the direct applicability of preclinical findings to clinical. *Our recent systematic review of nicotine-free electronic cigarettes reported acute endothelial dysfunction and oxidative stress, alongside experimental evidence of mitochondrial injury and systemic inflammation [111]. Given the established role of oxidative stress and mitochondrial dysfunction in liver disease, these observations suggest a possible mechanistic link between nicotine-free aerosol exposure and hepatic pathophysiology [111].* These gaps highlight the need for more rigorous, standardized, and prospective research to clarify the causal pathways and quantify the true impact of smoking on liver disease progression.

12. Conclusion

Current evidence indicates that nicotine, independent of other toxic constituents of cigarette smoke, plays a substantive pathogenic role in the initiation and progression of multiple liver diseases, including alcohol-associated liver disease, metabolic dysfunction–associated steatotic liver disease, viral hepatitis and hepatocellular carcinoma. Nicotine promotes insulin resistance, dyslipidemia, oxidative stress and immune dysregulation, thereby exacerbating hepatocellular injury, inflammation and fibrogenesis. Clinically, tobacco use constitutes a major modifiable risk factor that can alter disease severity, impair therapeutic responses and contribute to adverse long-term

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outcomes in hepatology patients. Despite these insights, key knowledge gaps persist, including the scarcity of longitudinal and randomized controlled studies, inconsistent characterization of nicotine exposure and the limited translational relevance of existing preclinical models. Future research should prioritize delineating the direct hepatotoxic effects of nicotine from those of other combustion and aerosol-derived toxicants, clarifying dose–response relationships across diverse exposure modalities and evaluating the clinical effectiveness of structured smoking-cessation interventions embedded within standard hepatology care. Greater integration of mechanistic, biomarker-driven approaches with large-scale epidemiological studies will be essential to strengthen causal inference and refine risk stratification. Ultimately, a more comprehensive understanding of nicotine's impact on liver health will be critical for improving patient management, guiding public-health policy and informing the development of targeted preventive and therapeutic strategies.

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Abbreviations

The following abbreviations are used in this manuscript:

ACTH	Adrenocorticotropic hormone
ALD	Alcohol-associated liver disease
ALT	Alanine aminotransferase
AMP	Adenosine monophosphate
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BMI	Body mass index
BSO	Buthionine sulfoximine
CO	Carbon monoxide
CRP	C-reactive protein
CVD	Cardiovascular disease
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
ENDS	Electronic nicotine delivery system
ER	Endoplasmic reticulum
FMO	Flavin-containing monooxygenase
GGT	Gamma-glutamyl transferase
GPx-1	Glutathione peroxidase-1
GSH	Glutathione
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCN	Hydrogen cyanide
HCV	Hepatitis C virus
HepG2	Human hepatocellular carcinoma cell line
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
IGF	Insulin-like growth factor
IL-6	Interleukin-6
LDL	Low-density lipoprotein
LFT	Liver function tests
LS	Liver stiffness
MAPK	Mitogen-activated protein kinase
MASLD	Metabolic dysfunction-associated steatotic liver disease
MASH	Metabolic dysfunction-assocaited steatohepatitis
mRNA	Messenger ribonucleic acid

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NAC	N-acetylcysteine
nAChR	Nicotinic acetylcholine receptor
NNK	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone
PAH	Polycyclic aromatic hydrocarbons
PBC	Primary biliary cirrhosis
ROS	Reactive oxygen species
SREBP-1c	Sterol regulatory element binding protein 1c
TMAO	Trimethylamine oxide
TNF-α	Tumor-necrosis factor-α
TPM	Total particulate matter
TSNA	Tobacco-specific nitrosamines
UPD	Uridine diphosphate
VEGF	Vascular endothelial growth factor
VOC	Volatile organic compounds

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