microplastics

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Review

Micro- and Nanoplastics and Liver Disease: Mechanistic Insights, Experimental Evidence, and Pathways to Hepatic Inflammation, Fibrosis, and Carcinogenesis

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Abstract

Micro–nanoplastics (MNPs) have emerged as a critical environmental pollutant with significant potential implications for the development of liver disease. These MNPs can accumulate in the liver, initiating a series of detrimental biological responses. One of the main mechanisms is the initiation of oxidative stress, which is marked by overproduction of reactive oxygen species harming cellular structures. This oxidative damage is closely linked to hepatic inflammation, where immune responses are triggered, exacerbating tissue injury and disrupting normal liver function. As a result, hepatic metabolism, detoxification, and immune regulation become compromised due to persistent MNPs exposure. Although in vitro and vivo models effectively show direct cellular toxicity, oxidative stress, and metabolic disruption, direct evidence from human studies is mostly confined to tissue detection and cross-sectional correlations. As a result, advanced pathological outcomes like the progression of hepatic fibrosis and the development of cancer are considered mechanistic hypotheses grounded in biological plausibility rather than confirmed human causation.

Keywords: micro nano plastics; gut liver axis; gut microbiome; hepatocellular carcinoma; metabolic dysfunction-associated steatotic liver disease

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Academic Editor: Yao Zheng

Received: 27 September 2026
Revised: 30 October 2026
Accepted: 7 November 2026
Published: 12 November 2026

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1. Introduction

Microplastics (MPs) are typically characterized as plastic particles ranging from approximately 1 µm to 5 mm in size, though certain definitions extend the lower limit to 0.1 µm. In contrast, pr (NPs) are generally defined as particles smaller than 1 µm, or 1000 nm, with some analytical definitions encompassing sizes from 1 nm to 1000 nm. Particle size is a critical factor influencing both the mode of cellular entry and the degree of penetration and intracellular accumulation. NPs smaller than 100 nm have been observed to traverse biological barriers more efficiently, resulting in increased intracellular uptake. For instance, polystyrene NPs measuring 50 nm have demonstrated superior skin penetration and greater intracellular accumulation in human keratinocyte models compared to larger particles of

100 and 200 nm. These smaller particles also elicited more pronounced oxidative stress and sustained autophagy responses, indicating significant intracellular effects [1]. In intestinal models, 50 nm particles exhibited distinct translocation behaviors compared to particles of 100 and 500 nm, underscoring the size-dependent pattern of cellular internalization across various cell types [2].

Due to widespread plastic pollution, micro–nanoplastics (MNPs) are encountered in diverse environments, including oceans, soils, the atmosphere, and within biological organisms ranging from aquatic species to humans. Their pervasive presence leads to inevitable exposure primarily through ingestion and, to a lesser extent, via inhalation or dermal contact, albeit resulting in the accumulation of MNPs, but in particular NPs, given the size and ease of translocation, in virtually all human organs, including the liver [3].

The liver, as a key metabolic and detoxifying organ, is particularly vulnerable to MNPs-induced damage. Experimental studies in animal models have demonstrated that exposure to different types of MNPs, including polystyrene and polyvinyl chloride (PVC), can provoke oxidative stress and result in functional impairment in hepatic tissue. For instance, co-exposure of PVC MNPs with cadmium in female Muscovy ducks induced oxidative stress and disrupted glycolipid metabolism in the liver, leading to metabolic dysfunction-associated steatotic liver disease (MASLD)-like pathology characterized by lipid deposition, fibrosis, and hepatocyte apoptosis [4]. This metabolic disruption involves molecular pathways such as phosphoenolpyruvate carboxykinase 1 (PCK1) deficiency and activation of the PI3K/AKT signaling axis contributing to hepatocyte dysfunction and death [4]. At the cellular and molecular level, MNPs can induce oxidative stress, inflammation, and metabolic dysregulation within the liver, potentially through interactions with metabolic regulatory pathways and generation of reactive oxygen species. Occupational studies have particularly highlighted the hepatotoxicity of PVC microplastics, linking chronic exposure to increased risks of liver diseases, including carcinomas such as angiosarcomas and hepatocellular carcinomas [5]. It is important to distinguish historical occupational data regarding gaseous vinyl chloride monomer—which has an established link to hepatic angiosarcoma—from modern environmental concerns regarding particulate PVC microplastics as the two represent distinct chemical and physical exposures that should not be conflated. These unique potentials for promoting liver carcinogenicity associated with PVC contrast with the relatively limited evidence for other MNP types, underlining the necessity for further focused research [5].

Emerging evidence suggests that a broader spectrum of plastic-associated toxicants are capable of disrupting liver function across multiple stages of disease [6]. Emerging evidence further suggests that exposure to biodegradable starch-based MNPs may also infiltrate the liver and cause microstructural lesions, oxidative stress, and disturbances in lipid and glucose metabolism, contributing to systemic metabolic dysregulation [7]. Collectively, these findings indicate that MNPs contamination represents an environmental health hazard to the liver, with effects ranging from biochemical and histopathological changes to the development of chronic liver conditions.

It is also important to distinguish between established experimental findings, correlational clinical observations, and proposed mechanistic pathways regarding micro- and nanoplastics (MNPs). While robust experimental models demonstrate direct cellular toxicity, oxidative stress, and metabolic disruption, direct human evidence remains largely limited to tissue detection and cross-sectional associations. Consequently, advanced pathological endpoints such as hepatic fibrosis progression and carcinogenesis represent mechanistic hypotheses supported by biological plausibility rather than established human causality.

While previous reviews have primarily cataloged general aquatic or rodent toxicity endpoints, the present work uniquely advances the field by synthesizing the multi-organ

intersection of the gut–liver axis, hepatokine-mediated metabolic cross-talk (linking hepatic stress to peripheral insulin resistance), and the critical distinction between experimental high-dose models and the complex confounding realities of human cirrhotic retention.

This study seeks to examine recent research on the impact of MNPs on the primary pathways through which they enter the human body. It explores the interconnected mechanisms, including oxidative stress, hepatocyte energy redistribution, immune responses, and inflammation. Furthermore, the study briefly examines the disruption of the microbiome and gut–liver axis and their association with clinical conditions such as metabolic dysfunction-associated fatty liver disease, steatohepatitis, liver fibrosis, and cirrhosis. The discussion also encompasses mechanistic plausibility, environmental and experimental evidence, and direct evidence in human liver disease. Finally, potential future research directions on this emerging topic are considered, along with the identification of current research challenges and the proposal of possible solutions.

2. Methods

A comprehensive literature search was conducted across PubMed, Embase, and Web of Science databases for peer-reviewed articles published up to 2026. Search terms included combinations of "microplastics", "nanoplastics", "liver", "hepatic fibrosis", "hepatocellular carcinoma", and "gut-liver axis". Articles lacking peer review or focusing exclusively on macro-plastics were excluded. While foundational animal models and clinical literature cited throughout this review historically utilized the legacy term non-alcoholic fatty liver disease (NAFLD), we consistently apply the updated consensus nomenclature of metabolic dysfunction-associated steatotic liver disease (MASLD) to align with modern metabolic hepatology guidelines while accurately interpreting the criteria used in original source studies.

3. Mechanisms of MNPs Entry and Bioaccumulation Within Hepatic Tissue

MNP particles, upon environmental exposure, are ingested by numerous organisms and can subsequently translocate from the gastrointestinal (GI) tract into various tissues, including hepatic tissue. The mechanism of such internalization into cells is primarily via cellular uptake, which is notably enhanced by the formation of an "eco-corona"—a layer of biomolecules that adsorb onto the MNPs surface during environmental exposure (Figure 1).

This eco-corona promotes significant cellular internalization of MNPs by macrophages, suggesting that internalization is a key route by which these particles enter tissues where they may exert toxic effects [8]. In aquatic organisms such as fish, MNPs initially bioaccumulate in the guts and gills and then spread through the circulatory system, eventually bioaccumulating in other organs, including the liver. This systemic distribution has been found to disrupt several physiological processes. In hepatic tissue specifically, MNPs exposure can cause oxidative injury due to an imbalance in reactive oxygen species (ROS) generation and antioxidant defenses, leading to oxidative stress [9]. Additionally, polystyrene MNPs exposure in juvenile brackish water fish has been directly observed to cause bioaccumulation in the liver, as well as in other tissues such as the GI tract, gills, spleen, muscle, and brain [10]. This accumulation correlates with biochemical markers indicating liver stress including elevated serum liver enzymes and oxidative stress markers (malondialdehyde and protein carbonyl content), along with down-regulation of hepatic antioxidant gene expression such as NRF2, principal regulator of the body's antioxidant response and tumor suppressor gene p53 [10]. Stress-related cortisol levels and heat shock protein (HSP70) gene expression are upregulated, indicating cellular stress responses in the liver. Moreover, MNPs exposure alters genes related to metabolism and detoxification pathways including IGF1

and CYP1A in hepatic tissue [10]. Mechanistically, the toxic effects of MNPs on the liver involve oxidative stress, inflammation, apoptosis, and interference with cellular metabolism and signaling pathways. These effects ultimately lead to inflammatory responses and can induce apoptotic cell death pathways within hepatic tissue, further compromising liver integrity and function [11]. Moreover, the size, dose, duration of exposure, and surface characteristics of MNPs influence their bioaccumulation and toxicity in the liver. Smaller particle size and environmentally altered surface chemistry (through eco-corona formation) enhance cellular uptake and thus bioaccumulation. In addition, MNPs frequently interact with other pollutants, such as heavy metals, which can absorb onto their surfaces, enhancing toxic effects due to combined exposures and increased bioaccumulation potential [12].

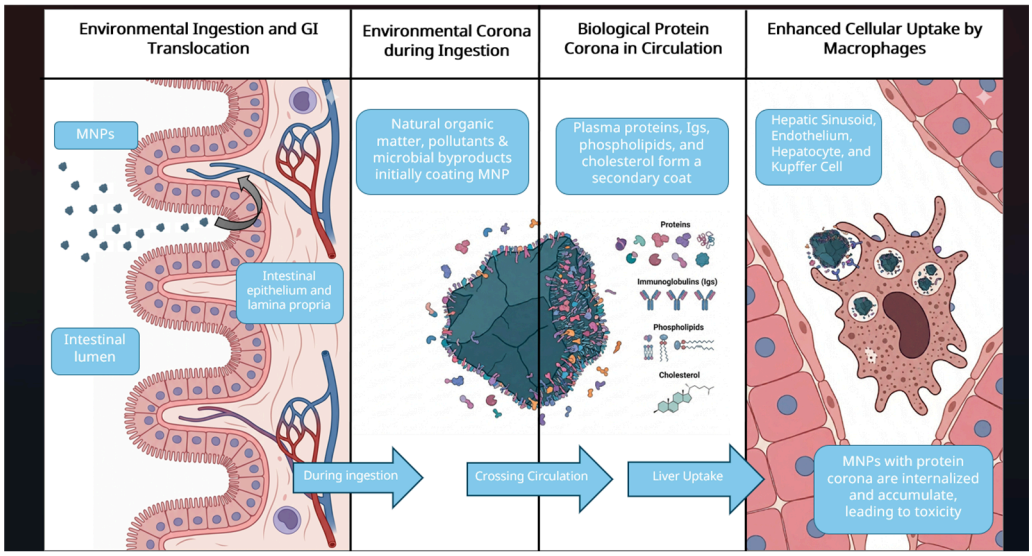

Figure 1. Mechanisms of environmental micro- and nanoplastic (MNP) ingestion, eco-corona formation, and hepatic internalization. Ingested environmental MNPs cross the intestinal lumen into the epithelium and lamina propria to enter systemic circulation. During ingestion, the MNP particle is coated with an initial eco-corona consisting of ambient environmental macromolecules, pollutants, organic matter, or microbial byproducts. During transit into circulation, these particles adsorb a secondary surface layer (including plasma proteins, immunoglobulins, phospholipids, and cholesterol), forming a secondary "eco-corona" coating that alters their surface properties. This biomolecule corona significantly enhances the cellular internalization and bioaccumulation of MNPs by resident macrophages (Kupffer cells), endothelial cells, and hepatocytes within the hepatic sinusoid, establishing a major route for localized tissue accumulation and subsequent toxicological impact.

4. Structural and Functional Effects on the Liver

One key study investigating the effects of polystyrene MNPs on juvenile crucian carp (*Carassius auratus*) showed clear pathological damage to liver tissue cells. The extent of liver cell damage correlated positively with the concentration of MNPs, demonstrating a dose-dependent relationship. Higher MNPs concentrations led to lower antioxidant enzyme activities, including catalase (CAT), glutathione S-transferase (GST), and superoxide dismutase (SOD), which are critical for mitigating oxidative stress. This enzymatic decline coincided with increased oxidative damage and cellular injury in the liver, confirming that MNPs compromise liver cell integrity and function at multiple molecular and cellular levels [13]. A broader review focusing on hepatic metabolic dysregulation highlighted that MNPs damage liver tissue structure, induce hepatocellular death, and disrupt lipid metabolism. These liver impairments appear influenced by factors such as particle size and exposure duration. Despite establishing these associations, the review emphasized that the precise mechanisms of MNPs-induced liver injury and their long-term effects

remain incompletely understood, necessitating further research [14]. In addition to direct cellular damage, MNPs exposure has also been linked to epigenetic modifications in liver tissue. A multigenerational study on fathead minnows (*Pimephales promelas*) revealed that MNPs exposure induced differential DNA methylation patterns in the liver, with these epigenomic changes partially persisting across generations [15]. Many of the affected genes were involved in metabolic pathways and hormonal regulation, indicating that MNPs contamination could have enduring and heritable effects on liver function and overall organism health [15]. Animal studies investigating perinatal exposure have shown that MNPs cross placental barriers and accumulate in neonatal and fetal tissues, including the liver. This early-life exposure leads to hepatic inflammation and lipid dysregulation in offspring, with potential long-term consequences for metabolic health. Oxidative stress and inflammatory mechanisms were recurrent themes in these animal models, linking MNPs exposure during critical developmental windows with impaired immune and metabolic programming. These findings underline the vulnerability of the developing liver to MNPs toxicity and suggest risk for persistent hepatic dysfunction later in life [16].

MNPs may also contribute to human liver diseases such as metabolic dysfunction-associated steatotic liver disease (MASLD). Evidence from laboratory animal models shows that chronic MNPs exposure can trigger inflammation, immunological disturbances, endocrine disruption, and altered lipid and energy metabolism, all of which are key pathological features of MASLD [17]. Moreover, MNPs and their chemical additives may act as "obesogens," compounds that exacerbate fat accumulation and fibrosis in liver tissue. Obesogens are chemicals that directly or indirectly promote increased fat storage and obesity by disrupting multiple metabolic and hormonal signaling pathways, often from early developmental stages, which can predispose individuals to lifelong susceptibility to obesity and metabolic syndrome. These compounds, including environmental endocrine-disrupting chemicals (EDCs), may alter adipocyte size, phenotype, hormone levels, and metabolic activity, contributing to systemic metabolic dysregulation [17,18]. Some obesogens have been shown to trigger epigenetic changes that sustain fat accumulation over time [17]. This eventually contributes to obesity and related pathologies. While human exposure to MNPs is confirmed by their presence in various biological samples, the direct causal relationship with MASLD requires further investigation [19]. A summary of the current reports on this topic is provided (Table 1).

Table 1. Summary of major experimental animal models, human tissue findings, particle characteristics, and key methodological limitations.

Study/Model	Polymer Type & Size	Exposure Dose	Key Hepatic Findings	Limitations/Notes
Chen et al. (2024) (Duck model)	Polyvinyl chloride (PVC) MNPs	Co-exposure with cadmium	Glycolipid accumulation, MASLD-like pathology, PCK1 deficiency, PI3K/AKT activation.	Animal model; reflects heavy metal co-exposure.
Li et al. (2025) (Crucian carp)	Polystyrene (PS) MNPs	Dose-dependent concentrations	Decreased antioxidant enzymes (CAT, GST, SOD); increased oxidative injury.	Aquatic model; high experimental dosing.
Horvatits et al. (2022) (Human tissue)	Multiple polymers (PP, PET)	End-stage liver disease tissue	Significantly higher MNP concentrations in explanted cirrhotic livers vs. controls.	Small sample size; cross-sectional design (cannot prove reverse causality).

5. Health Consequences Potentially Related to MNPs-Induced Liver Injury

The liver's role as a central metabolic organ involves intricate regulation of systemic glucose and lipid homeostasis through hepatokines—hormone-like proteins secreted by hepatocytes—which mediate inter-organ crosstalk affecting insulin sensitivity and whole-body metabolism. In MASLD, the altered secretory profile of hepatokines contributes significantly to insulin resistance and metabolic dysfunction in peripheral tissues, bridging a complex pathological relationship between hepatic steatosis and systemic metabolic diseases such as type 2 diabetes mellitus (T2DM) [20,21]. Metabolically, MASLD pathogenesis involves both lipid and glucose dysregulation. Transcriptional dysregulation in hepatocytes under chronic nutrient excess promotes lipogenesis and gluconeogenesis, exacerbating lipid accumulation and impairing glucose homeostasis. Nuclear receptors, including liver X receptors (LXRs), play pivotal roles in modulating hepatic lipid metabolism, fatty acid oxidation, inflammation, and immune responses. Dysregulated LXR signaling in MASLD contributes to triglyceride and cholesterol buildup, mitochondrial deterioration, and heightened inflammatory states. Targeting these pathways holds therapeutic promise but also requires nuanced understanding due to cell type-specific receptor functions [22,23]. Insulin resistance arises from hepatic lipid overload, particularly due to accumulation of lipid intermediates like diacylglycerols, which activate protein kinase C epsilon (PKCε), disturbing insulin signaling within the liver and fostering systemic glucose intolerance. While general paradigms of MASLD emphasize lipid overload and diacylglycerol-mediated PKCε activation, emerging toxicological data indicate that MNPs actively drive these exact enzymatic and metabolic perturbations. Specifically, experimental models demonstrate that MNP internalization induces severe mitochondrial dysfunction and reactive oxygen species overproduction, which directly impair hepatocyte insulin signaling cascades (such as the PI3K/AKT pathway) and suppress key metabolic regulators like PCK1 [4]. By instigating this localized hepatocellular stress, MNP bioaccumulation shifts the hepatic secretory output—upregulating diabetogenic hepatokines while suppressing protective factors—thereby directly translating MNP-induced lipotoxicity into systemic insulin resistance and metabolic dysfunction mirroring clinical MASLD [4]. This hepatic insulin resistance is central to the bidirectional relationship between MASLD and T2DM, where liver dysfunction exacerbates peripheral insulin resistance and vice versa, thereby accelerating disease progression [21].

In the context of MNPs exposure, specific mechanistic studies were not provided in the current context—such environmental pollutants could plausibly contribute to hepatic metabolic dysregulation by mechanisms akin to those observed in MASLD. For example, MNPs might induce oxidative stress, disrupt mitochondrial function, and elicit inflammatory responses within hepatocytes, thereby triggering lipid accumulation, altered hepatokine secretion, and insulin resistance (Figure 2).

These perturbations would manifest as disrupted lipid and glucose homeostasis consistent with fatty liver disease phenotypes seen in MASLD. The pathophysiology of MASLD underscores six key lipid metabolism disturbances: increased hepatic fatty acid uptake and synthesis, diminished fatty acid oxidation, and dysregulated cholesterol and bile acid metabolism, all of which contribute to hepatic steatosis and metabolic impairment [24].

Furthermore, metabolic dysfunction in the liver can synergize with systemic metabolic alterations including gut microbiota dysbiosis and immune activation, fueling lipotoxicity and chronic inflammation that exacerbate hepatic injury and progression toward fibrotic liver disease and cirrhosis. These mechanisms emphasize the multifactorial nature of fatty liver disease and its close interplay with altered lipid and glucose homeostasis [25]. Notably,

a retrospective study reported findings of six different MNPs polymers in hepatic tissue of cirrhotic patients but in none without underlying liver disease [26].

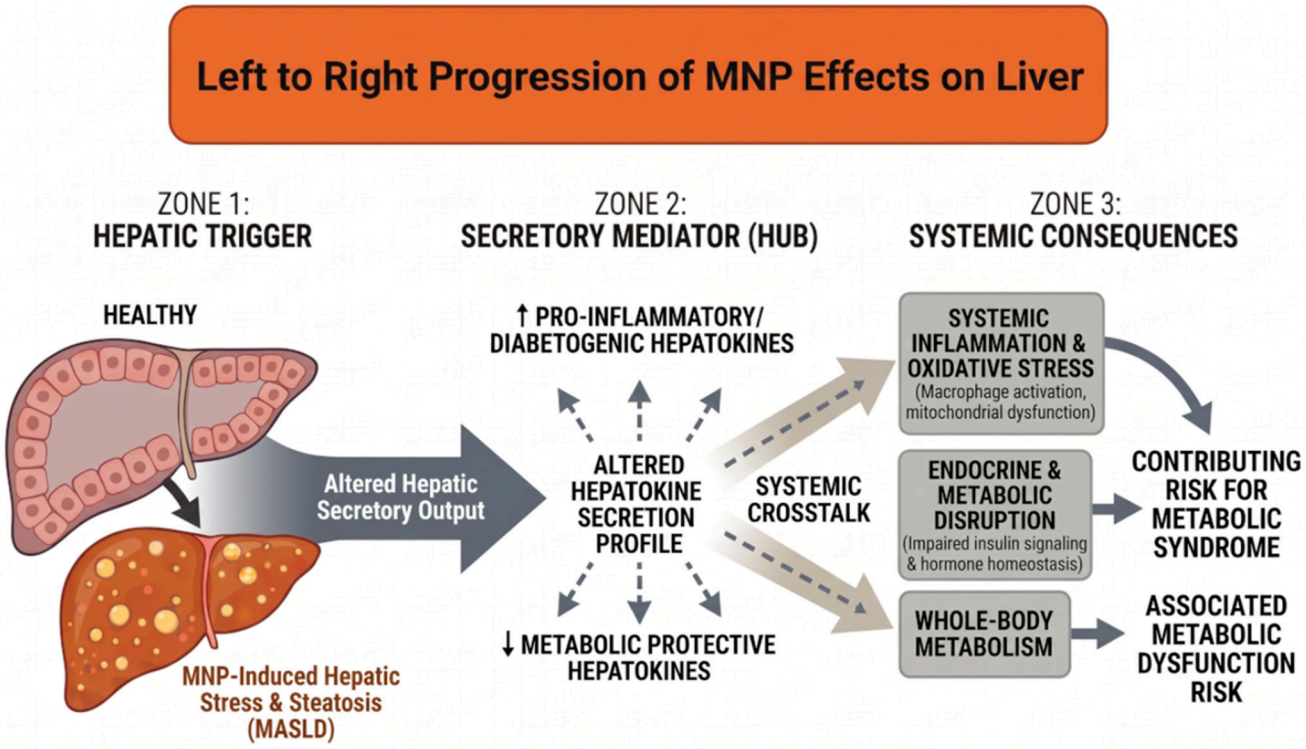

Figure 2. Pathological schematic of MNP-induced hepatic stress and downstream systemic metabolic dysfunction. Progression from left to right illustrates three distinct pathological phases driven by microplastic exposure: an initial hepatic trigger (Zone 1), where MNPs transition a healthy liver into a state of chronic stress and steatosis (MASLD); a secretory mediator hub (Zone 2), characterized by an altered hepatic secretory output that upregulates pro-inflammatory/diabetogenic hepatokines while downregulating metabolically protective hepatokines; and subsequent systemic consequences (Zone 3), characterized by low-grade chronic systemic inflammation (e.g., macrophage activation, pro-inflammatory cytokine release), oxidative stress and mitochondrial dysfunction in metabolic tissues (liver, adipose tissue, skeletal muscle), and endocrine disruption (interference with insulin signaling pathways or metabolic hormone homeostasis). This altered hepatokine profile drives detrimental systemic crosstalk, impairing insulin sensitivity and inducing peripheral insulin resistance in skeletal muscle and adipose tissue, which increases the risk of metabolic dysfunction and metabolic syndrome.

In summary, hepatic metabolic dysregulation in fatty liver disease involves a complex network of altered lipid uptake, synthesis, oxidation, and export along with disturbed glucose metabolism and insulin resistance. While direct evidence linking MNPs exposure to these mechanisms is not explicitly described, the hallmark features of MASLD pathogenesis—including mitochondrial dysfunction, oxidative stress, inflammatory activation, and nuclear receptor dysregulation—offer plausible pathways through which MNPs could contribute to hepatic lipid and glucose homeostasis disruption. Understanding these molecular and metabolic derangements remains crucial for developing targeted therapies to address hepatic metabolic diseases associated with environmental and nutritional insults.

6. Gut Microbiome and Gut–Liver Axis

MNPs have been shown to adversely affect the gut microbiome and contribute to disruptions in the gut–liver axis, impacting liver function and systemic health. Research in mice demonstrates that exposure to MNPs induces liver inflammation marked by elevated pro-inflammatory cytokines such as IL-6 and TNF-α, as well as disturbances in lipid metabolism.

Concurrently, it causes dysbiosis in the gut microbiota, impairing colon health by inducing defects in the ciliary structure and abnormal mucus secretion, thereby compromising the intestinal barrier integrity [24,25]. These disruptions facilitate the translocation of microbial components and metabolites from the gut to the liver, exacerbating liver inflammation and dysfunction through the gut–liver axis, a bidirectional communication pathway essential for maintaining liver and intestinal homeostasis [27,28] (Figure 3).

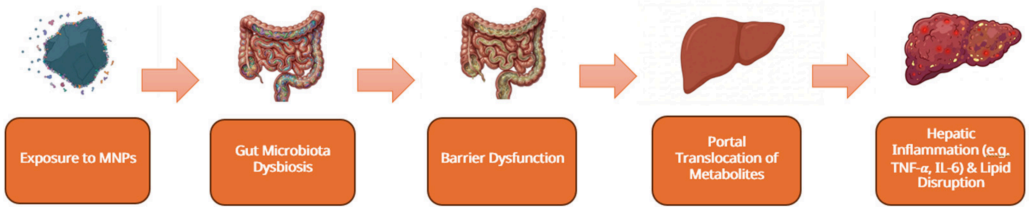

Figure 3. Polystyrene microplastic (PS-MP) exposure disrupts bidirectional communication along the gut–liver axis. In contrast to baseline intestinal and hepatic homeostasis, ingestion of and exposure to PS-MPs induces parallel disruptions in both organs. Within the gastrointestinal tract, MNPs drive severe gut microbiota dysbiosis and intestinal barrier dysfunction. This compromised barrier facilitates the translocation of harmful microbial components and metabolites through the portal system into the liver, which—coupled with direct hepatic plastic exposure—triggers elevated pro-inflammatory markers (e.g., TNF-α, IL-6) and drives severe hepatic lipid metabolism dysregulation.

The gut microbiota plays a pivotal role in modulating liver health by producing a variety of metabolites such as short-chain fatty acids (SCFAs), bile acids, and microbial cell wall components (e.g., lipopolysaccharides and lipoteichoic acid) that influence liver immune responses. Disrupted gut microbial communities alter these metabolites, contributing to chronic inflammation, impaired metabolism, and liver disease pathogenesis, including liver cancer. For instance, microbial dysbiosis can increase the exposure of the liver to inflammatory bacterial products through the portal vein, leading to sustained immune activation and metabolic imbalance within hepatic tissues. This connection highlights the significance of the gut microbiome in liver disease progression and the maintenance of liver homeostasis [27,29,30]. Probiotics, such as *Lactobacillus rhamnosus* GG (LGG), have been investigated as potential modulators to mitigate the harmful effects of MNPs on the gut–liver axis. This probiotics administration has been found to partially restore gut microbiota balance disrupted by PS-microplastics, improve gut barrier function, and alleviate liver inflammation and lipid metabolic disturbances induced by microplastic exposure. Mechanistically, LGG modulates bile acid metabolism by regulating key liver enzymes involved in bile acid synthesis (e.g., Cyp7a1 and Cyp7b1), which may contribute to its protective effect on liver function. These findings suggest that maintaining gut homeostasis through microbiota-targeted therapies can counteract environmental pollutant-induced toxicities along the gut–liver axis [28]. While preclinical murine models demonstrate that probiotic administration—such as *Lactobacillus rhamnosus* GG—can partially restore gut microbiota balance and alleviate MNPs-induced hepatic inflammation, these findings remain strictly experimental; probiotic supplementation has not been evaluated or established as a validated clinical intervention for MNPs mitigation in humans.

In addition to MNPs exposure, gut microbiota dysbiosis and compromised intestinal barrier integrity, often resulting from dietary factors, can lead to endotoxemia via increased permeability of lipopolysaccharides and other bacterial components into circulation through the portal vein, further activating hepatic inflammation and metabolic disturbances [24,28]. This mechanism underscores how alterations in the gut microbial ecosystem can trigger systemic effects on distal organs such as the liver, emphasizing the importance of interventions aimed at preserving or restoring gut microbial balance and barrier integrity to prevent liver

disease progression [27,31]. Overall, MNPs negatively impact the gut microbiome by causing dysbiosis and impairing gut barrier function, which leads to the translocation of harmful microbial metabolites and components to the liver through the gut–liver axis. This process drives hepatic inflammation and metabolic disturbances, contributing to liver toxicity and disease development. Approaches such as probiotic supplementation that restore gut microbial homeostasis and enhance intestinal barrier integrity represent promising strategies to mitigate the adverse effects of MNPs on the gut–liver axis and liver health [27,28].

7. Carcinogenic Effects Linked to Persistent Liver Cell Damage and Inflammatory Processes

Due to their ubiquity in the environment, MNPs are practically unavoidable and are inevitably taken up via ingestion, inhalation, and topically from skin contact [32]. The continued exposure to and bioaccumulation of MNPs has led to their identification in blood, many organs, joints, and even placenta and amniotic fluid, where they can cause detrimental direct and indirect effects [33–35]. In the liver, direct effects consist of increased oxidative stress; inflammation, evidenced by increased inflammatory markers (interleukins, NF-KB, and proinflammatory cytokines); mitochondrial dysfunction; hepatic stellate cell activation; and immunotoxicity. At the cellular level, MNP-induced generation of reactive oxygen species (ROS) triggers Kupffer cell activation and the release of profibrotic cytokines (such as TGF-β), which subsequently stimulate hepatic stellate cell (HSC) transdifferentiation into myofibroblast-like cells, driving excessive extracellular matrix (ECM) accumulation and fibrogenesis. While ROS-mediated oxidative DNA damage is experimentally documented, direct genotoxic hepatic carcinogenesis independent of established fibrosis remains a theoretical hypothesis requiring longitudinal verification.

Additionally, disruption of bile acid metabolism leads to a buildup of toxic bile acids and the ensuing hepatitis and liver damage, modified gene expression, and disruption of cell signaling pathways [35–37]. Ultimately, hepatocellular and parenchymal damage occurs, as well as disruption of the liver's metabolic systems leading to overall liver dysfunction [36]. Hepatic cancer is therefore a concern, given the increased risk of hepatocellular carcinoma (HCC) associated with the conditions induced by MNPs. For healthy individuals without pre-existing liver disease, MNP-induced HCC is hypothesized by some models to potentially occur through direct genotoxic mechanisms such as ROS generation; however, demonstrating in vivo mutagenicity, clonal expansion, and direct hepatocarcinogenesis attributable to MNPs remains a critical evidence gap that requires longitudinal investigation [37]. This supports biologic plausibility, not definitive causation. Conversely, for patients with established hepatic fibrosis or cirrhosis, MNPs exposure may act synergistically to accelerate HCC development through different, amplified mechanisms. Although biologically plausible, the evidence comes from mechanistic and not prospective human studies [35]. Environmental and exposure evidence shows that humans are chronically exposed to MNPs via diet, water, and inhalation; that particles can translocate from gut and lung into the circulation; and that MNPs have now been detected and semi-quantified in human liver tissue, with indications that hepatic burdens have risen over the last decade [38,39]. A broader systematic review of MNPs in human tissues summarizes autopsy and surgical studies that detect MNPs in liver, kidney, brain, and placenta and collates experimental and epidemiological evidence linking MNPs exposure to oxidative stress, inflammation, and altered lipid and energy metabolism, reinforcing biological plausibility of hepatic effects in exposed humans [40]. Direct evidence in human liver disease, however, remains limited: current clinical data are largely cross-sectional or small series demonstrating the presence of MNPs in explanted or biopsied livers and reporting associations with steatosis, inflammation, or fibrosis, but without longitudinal exposure data, dose–response relationships, or intervention studies needed

to establish a causal role of MNPs in specific liver diseases. In a proof-of-concept case series, Horvatits et al. quantified MNPs in explanted livers from patients with cirrhosis versus controls and detected multiple polymer types with significantly higher concentrations in cirrhotic livers, providing the first direct demonstration that MP burdens are elevated in human end-stage liver disease [26]. However, these human findings must be interpreted with caution due to several critical methodological limitations. Published cohorts are currently limited by small sample sizes, potential background environmental contamination during sample processing, and the analytical challenges associated with accurately quantifying nanoplastics using spectroscopic techniques. An additional consideration is that of reverse causality, specifically, that advanced hepatic dysfunction, altered biliary clearance, or impaired reticuloendothelial filtering inherent to cirrhosis may secondarily promote particle retention within damaged parenchyma rather than MNPs acting as the primary initiating driver of pathology.

Although research on this topic is scarce thus far, available data indicate that MNPs can lead to modified gene expression, as well as carrying adsorbed heavy metals, such as cadmium (Cd), and other carcinogenic substances, including Phthalates and bisphenols, with them into cells [32]. Li et al. identified specific pathways by which MNPs and Cd lead to hepatotoxicity and tumorigenesis [41]. Cadmium was shown to induce the activation of the extracellular matrix and genes related to cell proliferation. MNPs by themselves were found to mainly regulate BAX and CASP8, genes involved in MASLD and inflammation. Together, they also demonstrated a detrimental synergistic effect when Cd was present with MNPs [41]. Huang et al. showed that the presence of MNPs significantly amplified hepatic injury during infectious conditions [36]. When evaluating hepatic pathology, it is critical to distinguish the intrinsic toxicological profile of pristine MNPs from their role as vectors for environmental co-contaminants; many reported synergistic or additive effects, such as exacerbated oxidative stress and lipid accumulation, are driven by co-exposure with heavy metals like cadmium rather than MNPs exposure alone. Overall, these results provide more detailed evidence for how MNPs influence tumorigenesis and potential avenues for management in the future.

8. Current Knowledge Gaps and Future Research Directions

While we utilize the umbrella term 'micro- and nanoplastics (MNPs)' to align with standard nomenclature and our previous work, a critical limitation in the current literature is that the vast majority of available in vivo and human evidence relies on micro-sized particles (predominantly polystyrene beads) rather than true NPs. Consequently, attributing generalized MNP toxicity across diverse sizes remains challenging. While current evidence has established strong associations between MNPs and liver disease, direct epidemiological links between the two remain limited. While in-vitro studies have shown that even brief exposure to MNPs can have hepatotoxic effects, future research should focus on identifying causal relationships through long-term and multigenerational studies at exposure levels that are relevant to both the environment and biology. In vivo studies in zebrafish and medaka fish models have demonstrated hepatotoxic effects induced by low-dose, short-term MNPs exposure as confirmed by metabolomic and histopathologic analysis [42,43]. Additionally, future research should also seek to close the gaps related to understanding the mechanisms underlying MNPs translocation into and sequestration within the liver. Although it is well documented that MNPs negatively impact gut stability through promotion of microbial dysbiosis and disruption of barrier integrity, thereby facilitating MNPs entry into liver, the precise cellular mechanisms governing these processes remain unknown. A critical limitation in translating experimental data to humans is the reliance on high-dose, acute animal and in vitro models using uniform polystyrene beads, which are conditions that

frequently exceed realistic, chronic, low-dose human environmental exposure to heterogeneous MNPs. Additional research and biological studies in humans are necessary to address the gap between animal and human evidence. This includes the development of validated methodologies for quantifying human MNPs, the establishment of prospective biosample cohorts, and the implementation of epidemiological adjustments for conventional liver disease risk factors with adequate statistical power. Efforts must focus on prevention, mitigation, and regulations to expedite recognition and early intervention towards these widespread pollutants—especially as it relates to liver health.

9. Conclusions

In summary, MNPs represent an emerging environmental health concern capable of bioaccumulating within hepatic tissue and disrupting metabolic homeostasis via oxidative stress, gut–liver axis dysfunction, and inflammatory cascades. Translating existing evidence is constrained by heavy reliance on high-dose experimental models and limited, cross-sectional human data that cannot yet establish definitive causality. Future research must prioritize establishing a standardized analytical methodology for tissue quantification, utilizing environmentally relevant exposure dosing, and conducting rigorous longitudinal prospective or case–controlled studies to define the true clinical impact of MNPs on human liver disease.

Funding: This research received no external funding.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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

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