Mechanisms of microplastics on gastrointestinal injury and liver metabolism disorder (Review)

LI ZHOU[1*], LIDAN RAN[2*], YUFEN HE[1] and YAXI HUANG[1]

[1]Department of Gastroenterology and Hepatology, Chongqing University Central Hospital, Chongqing Emergency Medical Center, Chongqing 400014, P.R. China; [2]Department of Critical Care Medicine, Chongqing University Central Hospital, Chongqing Emergency Medical Center, Chongqing 400014, P.R. China

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Abstract. With the high production and use of plastic products, a large amount of microplastics (MPs) is generated by degradation, which causes environmental pollution. MPs are particles with a diameter <5 mm; further degradation of MPs produces nano-plastics (NPs), which could further increase the damage to cells when entering the human body. Therefore, the present review summarizes the effect of MP and NP deposition on the human gastrointestinal tract and the underlying injury mechanism of oxidative stress, inflammation and apoptosis, as well as the potential mechanism of glucose and liver lipid metabolism disorder. The present review provides a theoretical basis for research on the mechanisms of MPs in gastrointestinal injury and liver metabolism disorder. Further studies are needed for prevention and treatment of gastrointestinal diseases caused by MPs and NPs.

Contents

Correspondence to: Dr Yufen He or Dr Yaxi Huang, Department of Gastroenterology and Hepatology, Chongqing University Central Hospital, Chongqing Emergency Medical Center, 1 Health Road, Yuzhong, Chongqing 400014, P.R. China
E-mail: heyufen_emergency@163.com
E-mail: 381437582@qq.com

*Contributed equally

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1. Introduction

Plastics are widely used in modern society; every year ~320 tons of plastics are manufactured globally (1). Plastics are used in a wide range of applications, including packaging materials, construction, automotive parts, electronics, medical devices, textiles and consumer goods, due to their versatility, durability and cost-effectiveness. These plastic products are usually resistant to high temperature, acid, alkali and corrosion and have the benefit of convenience due to their lightweight nature, ease of manufacturing, versatility and cost-effectiveness in various applications. However, there is no efficient and feasible method for plastic degradation, which results in notable environmental issues. The most common plastic pollutants in the environment include polyethylene, polyvinyl chloride, polypropylene, polyethylene terephthalate and polystyrene (2). In the natural environment, these plastics are rarely completely degraded by microbiological activity, radiation and mechanical stress, leading to disintegration and fragmentation of larger plastic items into smaller particles; transfer and diffusion are more likely to occur, resulting in microplastic (MP) pollution of the environment.

Plastic particles are divided into MPs with diameter <5 mm and nano-plastics (NPs) with diameter <1 μm. MPs are found in a range of environmental domains, including air, fresh water, soil and oceans (3). MPs are released in numerous ways, for example as microfibers from textiles during washing and from synthetic textiles, personal care products, synthetic rubber tire erosion and industrial production. After a series of environmental processes such as decomposition and migration, they enter animals and plants, and enter the human body via inhalation, ingestion and skin contact (4). Ingestion of MPs or plastic derivatives such as chemical additives can cause a variety of toxicological effects, including growth inhibition, metabolic disorder, inflammatory response, reproductive problems and mortality (5,6).

Studies have found MPs and NPs are present in human blood, placenta and feces (7-9). The ingestion of MPs is a prevalent route of exposure, with MPs being detected in food and beverages such as seafood, drinking water and beer (4). Exposure models in mice have shown that MPs and NPs accumulate in the stomach, intestine, liver and other organs (10,11). Due to the high corrosion resistance of MPs and NPs entering into the digestive tract, digestive fluid changes the surface

roughness and particle size of MPs and NPs, making them more stable in the lining of the digestive tract and more prone to adsorption of toxic substances (12). The barriers within the tissues do not prevent invasion of MPs and NPs. After MPs and NPs enter the body, small plastic particles can cross the epithelial barrier of the digestive system (13-15) and enter the lymphatic and blood circulation. For example, NPs with a size of 0.1-10 μm cross the blood-brain barrier and the placenta (16-18). Ingested MPs and NPs with a particle size >150 μm pass through the intestinal epithelial cells with difficulty, resulting in ~90% of MPs being excreted through feces, with the rest having a localized effect outside the intestinal epithelial cell membranes. When nanosized plastic particles with diameter <150 μm come into contact with the villi of the small intestine, they pass through the small intestinal epithelial cells (19), enter the lymphatic system (20) and bloodstream (21), and reach the portal vein through the capillaries and are spread throughout the body (22-24). NPs with diameter <150 and >10 μm reach other organs and cell membranes (17), while those with a size of <5 μm are absorbed by lymphocytes (19). Smaller nanoparticles diffuse into the bloodstream via bypass of intercellular tight junctions (25). Mucus secreted by the intestinal epithelial cup cells promotes bypass diffusion of the nanoparticles (19). Larger nanoparticles (diameter, 50-200 nm) tend to cross intestinal epithelial cells by endocytosis; 40 nm diameter may be the optimal size for non-phagocytic uptake (26), while 200 nm may be the optimal size for crossing the blood-brain barrier (27). *In vivo* studies have found that intestinal cells internalize nanoscale particulate matter using different endocytosis mechanisms; additionally phagocytes can internalize them through phagocytosis (28), whereas non-phagocytes internalize smaller nanoparticles with the help of lattice proteins or cell-membrane-invasion-mediated endocytosis (25), in which actin serves an important role (29). In addition, energy-dependent pathways serve a key role in the mechanisms of endocytosis in intestinal epithelial cells (29). NPs smaller than 3 μm can be internalized into non-phagocytic cells via non-specific endocytosis (29), while the maximum particle size available for endocytosis increases to 5 μm (19), facilitated by the abundant M cells in the intestinal Peyer's patches (21) and aided by the intestinal mucosal membranes (30,31). The strong electrostatic interaction between positively charged particles and the plasma membrane increases surface tension, which subsequently reduces the membrane's elasticity (32), facilitating NPs internalization and their entry into the bloodstream. In addition to NPs absorbed by the digestive tract, inhaled MPs and NPs remain in the lungs or enter the circulatory system through capillaries; particles with a size of <2.5 μm enter the circulation or penetrate the alveoli (33). NPs that enter the circulation (diameter, ~100 nm) are surrounded by serum albumin (34), forming a multilayered serum albumin crown, which may help the NPs evade immune surveillance, increase their time in the circulatory system and help the particles reach secondary organs and accumulate in the liver, kidneys and intestines (34). The binding of serum albumin to NPs leads to changes in the secondary structure of the protein (35), which increases cytotoxicity of the plastic particles.

Although only a small percentage of NPs penetrate the epithelial barrier of alveolar and gastrointestinal tracts, and transfer into secondary tissues and organs (9), this low rate of internalization may have considerable consequences due to long-term exposure of humans to plastic particles and the potential of accumulation; harmful effects include oxidative stress, local inflammation, cellular apoptosis and alteration of intestinal flora (36-39). An *in vivo* study showed that following MP ingestion by mice, interaction between *Helicobacter pylori* and MPs in the stomach promoted the rapid colonization of *H. pylori* in the epithelial cells of the gastric mucosa (10); proliferation of this pathogenic bacterium leads to stomach inflammation in the mice. In several *in vivo* studies, MPs were found to cause intestinal flora disorders in mice, with an increase in number of conditionally pathogenic bacteria, accompanied by intestinal inflammation (40-42). The effects of NPs on the liver mainly include disruption of glycolipid metabolism, with an increase in glucose and diabetes mellitus in NP-exposed mice (43) and a decrease in hepatic fat, triglycerides and total cholesterol (44). An *in vitro* study has found that NPs enter cells and lead to injury effects (45). Co-culture of human gastric mucosal epithelial cells with NPs results in decreased proliferation and increased apoptosis (46). NPs cause oxidative stress in human intestinal cells (47).

To the best of our knowledge, there are no studies investigating whether MPs and NPs pass through the food chain to the human body; however, *in vitro* and *ex vivo* studies reveal the adverse effects of MPs and NPs in the human body (4,8,9). Investigating the mechanism of injury effects of MPs and NPs is key for understanding the impact of MPs and NPs on health, as well as for prevention and treatment of MP- and NP-induced health problems.

The present review discusses the mechanisms by which MPs and NPs damage the human gastrointestinal tract and liver and limitations of existing research and suggests future research directions to provide a scientific foundation for investigation of the effects and mechanisms of MPs and NPs on the human body.

2. Literature search

A comprehensive online search using PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), the Cochrane Library (https://www.cochranelibrary.com/) and the International Clinical Trials Registry Platform (https://clinicaltrials.gov/) was performed from their inception to January 2024 with the following MeSH and EMTREE keywords: 'Micro-plastics', 'nano-plastics', 'gastrointestinal disease', 'liver/hepatic metabolism', 'MPs', 'NPs' and 'digestive diseases'. All published studies associated with MPs and/or NPs, gastrointestinal disease or liver metabolism were included. Studies were excluded if they did not focus on MPs and/or NPs in the context of gastrointestinal diseases or liver metabolism, or if they were not published in peer-reviewed journals. Two independent investigators conducted the literature searches and eligibility assessment, and discrepancies were resolved by consensus and consultation with a third reviewer.

3. Mechanism of oxidative stress, inflammation and apoptosis in the gastrointestinal tract

MPs and NPs enter cells through endocytosis mechanisms or become adsorbed and accumulate on the surface of

gastrointestinal tissue, causing oxidative stress, inflammation and apoptosis (Tables I and II). Therefore, it is important to investigate the mechanism underlying injury effects of MPs and NPs on the gastrointestinal tract to provide a scientific basis for prevention and treatment of gastrointestinal diseases caused by MPs and NPs.

Reactive oxygen species (ROS) in cells induce generation of oxidative stress. Cells possess an antioxidant defense system that maintains intracellular ROS levels and protects biomolecules from free radical damage (48,49). Increased ROS and oxidative stress in cells are associated with antioxidant system imbalance and disease (50). *In vitro* and *in vivo* studies have shown that MPs and NPs increase intracellular ROS levels (16,31). The direct stimulatory effect of exogenous particles increases intracellular ROS production (51). However, MPs and NPs inhibit production of antioxidant enzyme transcription factors or decrease activity of antioxidant enzymes, which in turn inhibits ROS metabolism and increases mitochondrial membrane potential resulting in an increase in mitochondrial permeability and ROS production, thus increasing mitochondrial ROS production; this increases transfer of ROS produced in mitochondria to the cytoplasm (52). Superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) are key biomarkers for measuring the degree of oxidative stress. Polystyrene NPs can lead to increased levels of peroxidative biomarkers and markedly decreased SOD, CAT activity and GSH in the duodenum of mice (53,54); *in vitro* experiment using human normal colonic mucosal epithelial cells has revealed that ROS levels in NP-treated cells are increased compared with those in untreated cells (53). Therefore, MPs and NPs directly promote ROS production or indirectly inhibit ROS metabolism by inhibiting antioxidant enzyme activity and GSH production, leading to an increase in ROS (Fig. 1). As MPs and NPs interact with the cellular microenvironment, increased ROS settle on the surface of MPs and NPs, leading to oxidative stress in the cell, which induces localized inflammation in the gut if MPs and NPs are unable to cross the cellular membrane (55); if the particles are small enough to cross the intestinal epithelium, ROS toxicity on the surface of particles is enhanced, mediating a stress response in cells (56).

Underlying mechanisms of inflammation. Following ingestion, MPs and NPs accumulate in the gastrointestinal tract. Mechanical damage or stimulation induced by MPs and NPs causes inflammation in the gastrointestinal tract (10,40) due to release of proinflammatory cytokines (10) or imbalance of intestinal flora, causing an increase in conditionally pathogenic bacteria and resulting in immune imbalance and an increase in lipopolysaccharide content (42,57).

MPs and NPs induce proinflammatory cytokine release via direct stimulation of proinflammatory cytokine production. An *in vivo* study revealed that elevated IL-6 and TNF-α promote gastric injury and inflammation (10). *In vitro* studies reveal that expression of proinflammatory genes such as IL-1β, -6 and -8 is increased in MP- and NP-treated gastric and small intestinal epithelial cells, resulting in increased release of proinflammatory cytokines (15,58). Another mechanism involves oxidative stress promoting inflammation by activating transcription factors such as NF-κB, p53, peroxisome proliferator-activated receptor (PPAR)-γ and nuclear factor erythroid 2-related factor 2 (59), which regulate the expression of inflammatory cytokines and thus increase release of proinflammatory cytokines (Fig. 1).

In vivo studies have shown that MPs and NPs lead to gastrointestinal tract injury in mice (9,15-17). MPs and NPs promote rapid colonization of *H. pylori* on the epithelial cell surface of the gastric mucosa, increase the efficiency with which NPs enter tissues and promote inflammation (10). MPs and NPs cause intestinal dysbiosis, a marked decrease in abundance of immune function-associated bacteria (42), an increase in the number of pathogenic bacterial colonies and a decrease in the number of $CD4^+$ T helper 17 and regulatory T cells, leading to an immune imbalance, as well as an increase in plasma lipopolysaccharides (57), which stimulate intestinal inflammation (41).

Potential mechanisms of apoptosis. Both endogenous and exogenous factors contribute to DNA damage, and NPs can cross the nuclear membrane, directly inducing DNA damage (52). In addition, oxidative stress caused by increased intracellular ROS levels due to MPs and NPs can lead to DNA damage. If DNA damage is not repaired rapidly, apoptosis is induced (59). Apoptosis induced by oxidative stress is observed in *in vitro* studies (15,60), accompanied by an increase in mitochondrial membrane potential (Fig. 1). A study using HaCaT cells found that under conditions simulating oxidative stress *in vitro*, an increase in intracellular expression of inverted formin-2 leads to ROS overload in mitochondria, which disrupts cellular redox balance, alters mitochondrial membrane potential, causes mitochondrial stress and inhibits the hypoxia inducible factor-1 signaling pathway to mediate apoptosis (61). Bax, a member of the Bcl-2 family, regulates the release of apoptosis-inducing factors and the permeability of the outer mitochondrial membrane, with its overexpression potentially triggering apoptosis (60). Increased expression of Bax increases permeability of the mitochondrial membrane, leading to the release of apoptosis-inducing factors from the mitochondria into the cytoplasm, activating cysteoaspartic enzymes and leading to apoptosis. N-terminal acetylation of Bax is involved in its mitochondrial targeting; increase in expression of the *Bax* gene leads to an increase in permeability of the mitochondrial membrane, which results in the release of ROS from the mitochondria; this leads to ROS accumulation in cells, triggering apoptosis (Fig. 1). In addition, the inflammatory response caused by MPs and NPs triggers apoptosis.

In summary, increased ROS production or decreased ROS metabolism leads to accumulation of intracellular ROS resulting in DNA damage and oxidative stress. Immune imbalance caused by gastrointestinal flora dysbiosis and increased expression of inflammation-associated cytokines lead to inflammation. Oxidative stress and inflammation lead to apoptosis. MPs and NPs overexpress pro-apoptosis-related genes, directly leading to apoptosis (Fig. 1).

4. Mechanism of liver glucose and lipid metabolism disorder

The liver is a key detoxification organ in the human body. MPs and NPs accumulate on the surface of epithelial

Table I. Injury effects and mechanism of microplastics and nano-plastics *in vivo* in mice.

Organ	Mouse strain	Microplastic		Exposure route	Dosage	Biomarker	Effect	Mechanism	(Refs.)
		Type	Size, μm						
Stomach	Balb/c	PE	10-150	Intragastric administration (3 times, 1 week)	100 μg/ml	IL6, MPO and TNF-α	Rapid colonization of *Helicobacter pylori* in gastric mucosal epithelial cells, gastric injury and inflammation	Increased expression of myeloperoxidase, IL-6 and TNF-α	(10)
Liver, colon, ileum and cecum	ICR	PS	5	Water consumption for ~6 weeks	100, 1,000 μg/l	TG, PYR, TCH, GLU, HDL-C, LDL-C, CPT1, CPT2	Disorder of lipid metabolism, intestinal shielding dysfunction	Changes in intestinal flora	(11)
Colon and duodenum	C57BL/6	PE	10-150	Consumption of MP-enriched feed for 5 weeks	6, 60, 600 μg/day	IL-1α, G-CSF, IL-2, IL-5, IL-6, IL-9, IP-10 and RANTES	Intestinal inflammation	Upregulation of IL-1α, *TLR4*, *AP-1* and *IRF5*, changes in intestinal flora, immune imbalance	(40)
Colon	C57BL/6	PS	5	Water consumption for 28 days	500 μg/day	TNF-α, IL-1β and IL-6	Impaired intestinal barrier and intestinal inflammation, increased intestinal pathogenic bacteria, interference with intestinal microbial metabolism	Immune imbalance, changes in intestinal flora, upregulation of inflammatory factors (TNF-α, IL-1β and IFN-γ)	(41)
Intestines and cecum	CD-1	PE	45-53	Oral gavage daily for 30 days	5.24×10^4 particles/day	DAO, D-Lac	Increased intestinal permeability, intestinal inflammation, metabolic disorder	Changes in composition of intestinal flora, decreased abundance of bacteria associated with energy metabolism and immune function; downregulation of genes associated with oxidative stress, immune response and lipid metabolism	(42)
Liver and intestine	ICR	PS	1	Water consumption for 1-2 weeks	55 μg/d	CAT, SOD, GSH-Px	Insulin resistance, diabetes mellitus	Metabolic crosstalk of gut-liver axis	(43)

Table I. Continued.

Organ	Mouse strain	Microplastic		Exposure route	Dosage	Biomarker	Effect	Mechanism	(Refs.)
		Type	Size, μm						
Liver, colon, ileum	ICR	PS	5	Water consumption for 6 weeks	100, 1,000 μg/l	TG, TCH, PYR, TBA, CFTR and NKCC1	Decreased secretion of intestinal mucus, damage to intestinal barrier function, dysbiosis of the gut microbiome and metabolic disorder	NR	(44)
Liver and cecum	ICR	PS	0.5 and 50	Water consumption for 5 weeks	100, 1,000 μg/l	TG, TCH, GLU, TBA	Decreased liver weight, secretion of intestinal mucus, TG and TCH levels and hepatic lipid disorder	Changes in intestinal flora, decreased mRNA levels of genes involved in the synthesis of fats and TG in the liver	(63)
Liver	C57BL/6J	PS	0.5	Water consumption for 28 days	0.5 mg/day	AST, ALB, ALT, TBIL	Affect the liver immune microenvironment, hepatic inflammation	Increased immune infiltration of NK cells and macrophages and decreased immune infiltration of B cells, increased expression of ALT and aspartate aminotransferase, activation of the NF-κB signaling pathway	(85)
Intestine and colon	C57/B6	PS	5	Water consumption for 28 days	0.2 mg/kg	ZO-1, claudin-1-3	Intestinal barrier dysfunction, increased opportunistic pathogens and decreased tight junction promoting functional microorganisms	Downregulation of tight junction protein expression, changes in intestinal flora	(86)

PS, polystyrene; PE, polyethylene; ROS, reactive oxide species; ASL, argininosuccinate lyase; ALT, alanine aminotransferase; TNF-α, tumor necrosis factor α; TG, triglyceride; PYR, pyruvate; TCH, total cholesterol; GLU, glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CPT1, hepatic carnitine palmityl transferase 1; DAO, diamine oxidase; D-Lac, D-lactate; TBA, total bile acid; CFTR, cystic fibrosis transmembrane conductance regulator; NKCC1, Na-K-2Cl co-transporter 1; CAT, catalase; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; TBIL, total bilirubin; NR, not reported.

Table II. Injury effects and mechanism of microplastics and nano-plastics in human cells.

Cell	Microplastic		Dosage, μg/ml	Duration of exposure	Biomarkers	Effects	Mechanism	(Refs.)
	Type	Size						
Human colon adenocarcinoma Caco-2, HT29-MTX	PS	25 and 100 nm	0-200; 0.01-100	4 h	LDH, ROS	Decreased cell viability, oxidative stress, inflammation, mitochondrial apoptosis	Upregulation of HSP70, HO1 and IL- 1β, increased mitochondrial membrane potential	(15,52)
Liver organoids H1 ES	PS	1 μm	0.25-25	48 h	LDH, ATP, CYP3A4 activity, COL1A1, IL-6, ALT, AST, TG, GSH, GST, SOD	Disrupted function of metabolic enzymes, increased lipid accumulation, ROS production, oxidative stress and inflammatory response, hepatotoxicity	Increased release of ASL and ALT, gene expression associated with disrupt liver function, expression of *HNF4A*, *CYP2EI*, *IL-6* and *COL1AI*	(39)
Human gastric mucosal epithelial GES-1	PS	NR	100	24 h	RhoA, Rac1, F-actin, Rab5, RAB7, LAMP1, LC3B II	Decreased cell proliferation rate, increased apoptosis	NR	(46)
Human colon adenocarcinoma Caco-2	PS	50 nm	100	24 h; 8 weeks	ROS, HO1, GSTP1, HSP70, SOD2	Oxidative stress	*HO1* and *SOD 2* transcript levels were significantly increased	(47)
Human gastric adenocarcinoma CRL1739	PS	100, 44 nm	0.1-100	1 h	c-Myc, ERK-1, Ki67, CCNE1, CCND1, p38, p53, IL8, IL6, IL-1β, TGF-β1, NF-κB1, HPTR1	Decreased cell viability and morphology and inflammation	Upregulation of IL-6 and IL-8	(58)
Human gastric carcinoma AGS	PS	60 and 500 nm	0.1-100	24 h	ROS, apoptotic protein	Decreased cell viability; increased apoptosis or necrosis	Disruption of cell membrane integrity, upregulation of *Bax*, increased expression of Caspase-3 and Caspase-8	(60)

PS, polystyrene; ROS, reactive oxide species; ASL, argininosuccinate lyase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ROS, reactive oxygen species; AST, aspartate amino transferase; TG, total triglyceride; GSH, glutathione; NR, not reported; CCN, cysteine-rich angiogenic protein 61; HPTR, hydroxyphenylpyruvate reductase; RhoA, Ras homolog family member A; Rac, Ras-related C3 botulinum toxin substrate 1; Rab, Ras-related protein Rab; LAMP, lysosome-associated membrane protein; LC3B, microtubule-associated protein 1 light chain 3 beta; HSP, heat shock protein; HO1, heme oxygenase 1; GSTP, glutathione S-transferase pi; SOD, superoxide dismutase; CYP, cytochrome P450; COL, collagen; HNF, hepatocyte nuclear factor.

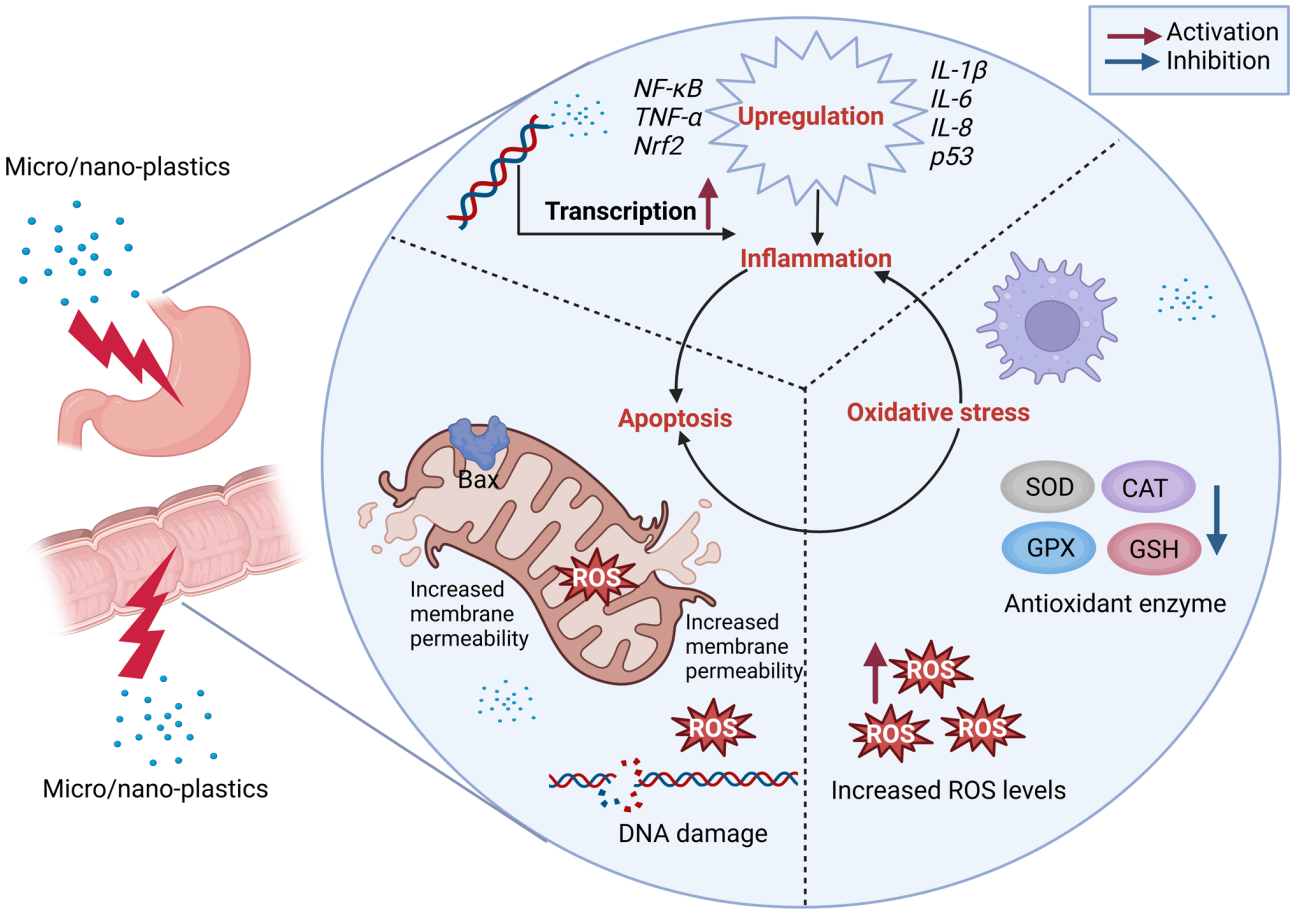

Figure 1. Oxidative stress, inflammation and apoptosis in the gastrointestinal tract. Microplastics and nano-plastics directly stimulate cells to produce ROS, while regulating the cellular antioxidant system to inhibit ROS metabolism, leading to a surge in levels of ROS and inducing oxidative stress. Microplastics and nano-plastics can directly stimulate cells to produce inflammatory cytokines or induce an inflammatory response through oxidative stress. These responses lead to apoptosis. TNF-α, tumor necrosis factor α; ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, catalase; GPX, glutathione peroxidase; GSH, glutathione.

cells in the gastrointestinal tract following ingestion. NPs are absorbed by epithelial cells and they then enter the lymphatic and blood circulation, arriving at the liver through the portal vein (62). Study has also found that NPs disturb the glucose-lipid metabolism of liver tissues (63), and similar toxic effects have been detected in an *in vitro* study of human liver-like organs. Toxic effects of NPs were also found in *in vitro* human liver-like organs (6). Previous biochemical and transcriptomics studies have investigated the injury mechanism of NPs causing disruption of glyco-lipid metabolism in liver tissue (11,43,57) and found that NPs affect glycolipid metabolism at both biochemical and transcriptional levels. NPs cause injury due to effects on intermediate glycolipid metabolism at the biochemical level and production of key rate-limiting enzymes in glycolipid metabolism at the transcriptional level.

Effect of NPs on production of intermediate metabolites for glycolipid metabolism. NPs affect glycolipid metabolism by influencing the production of intermediate metabolites. Pyruvate is a key intermediate metabolite in the glycolytic pathway and creates a notable association between glucose and lipid metabolism (64). Its increased production may be due to elevated levels of pyruvate kinase (PK) and phosphoenolpyruvate carboxykinase (64,65), which may promote the conversion of glucose to lipid metabolism and lead to increased production of fatty acids. Elevated levels of glucose and cholesterol in the liver may increase risk of type II diabetes, hyperlipidemia and fatty liver disease (64). A study revealed that biochemical levels of important factors and catalytic enzymes (Aldh9a1a, Aldh2b, Ehhadh and Echs1) involved in regulation of glucose metabolism in liver tissues are altered after the ingestion of NPs (65). The expression of carbohydrate regulatory element-binding protein (ChREBP) (63), which prevents the conversion of glucose to acetyl coenzyme A by inhibiting production of PK and ATP-citrate lyase (ACL) in the liver cells of mice following ingestion of NPs, is considerably reduced, resulting in a marked decrease in glucose metabolism. By inhibiting production of PK and ACL, ChREBP prevents conversion of glucose to acetyl coenzyme A, leading to the accumulation of glycogen in the liver and increasing the risk of type II diabetes (66). In addition, decrease in ChREBP synthesis also leads to a decrease in the synthesis of palmitic-5-hydroxystearic acid, which has been shown to increase insulin sensitivity in adipose tissue (67) and insulin secretion through activation of G protein-coupled receptor 40 (68); decrease in the expression of ChREBP as

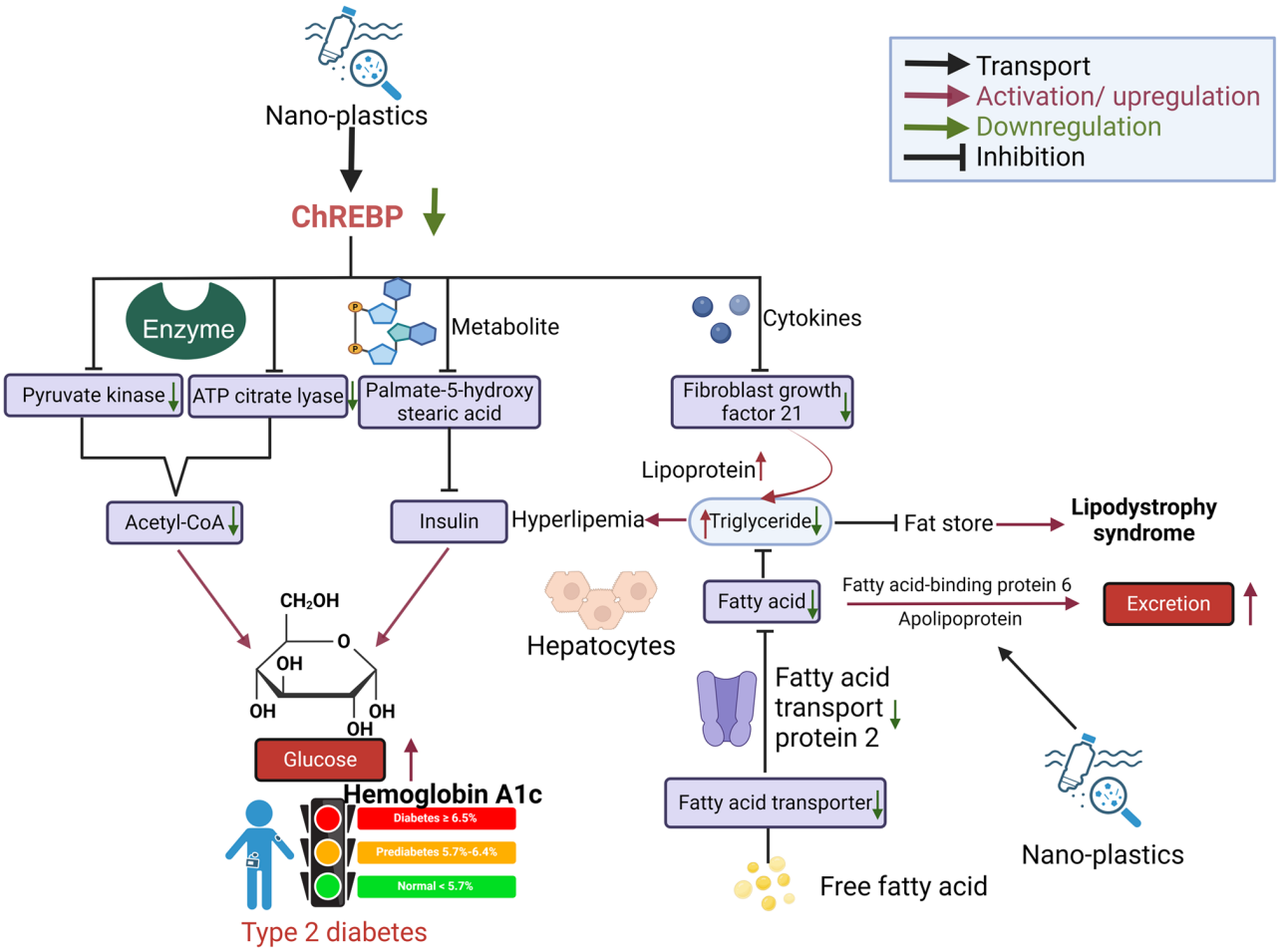

Figure 2. Effect of nano-plastics on glucose and lipid metabolism. At the biochemical level, nano-plastics inhibit synthesis of ChREBP and production of pyruvate kinase, ATP citrate lyase and palmitic acid-5-hydroxystearic acid, which inhibits synthesis of acetyl-CoA. This leads to insulin resistance and increase in the glucose content and risk of type II diabetes. Decreased synthesis of ChREBP can also inhibit the synthesis of fibroblast factor 21 and decomposition of lipoproteins, thereby increasing the content of triglyceride in plasma, leading to hyperlipidemia. Nano-plastics inhibit the synthesis of fatty acid transporter and fatty acid transporter 2, activate synthesis of apolipoprotein and fatty acid binding protein 6, decrease synthesis of fatty acid and increase export of fatty acid in hepatocytes. This results in the reduction of fat storage and increases the risk of lipodystrophy syndrome. ChREBP, carbohydrate regulatory element-binding protein.

a direct result of NPs indirectly inhibits insulin sensitivity and secretion. Therefore, NPs indirectly inhibit insulin sensitivity and secretion and hinder the glycolysis pathway leading to glucose metabolism disorders (69). NPs can increase the activities of lactate dehydrogenase and citrate synthase (CS), the key enzymes participating in glycolysis and gluconeogenesis (69). This leads to glucose metabolism disorder (Fig. 2), but the specific mechanism of the influence of NPs on enzyme activities is unclear (70).

In terms of lipid metabolism, NPs decrease expression of ChREBP, leading to a decrease in fibroblast growth factor 21 (FGF21) synthesis in hepatocytes, which inhibits the role of FGF21 in decreasing plasma triglycerides by increasing catabolism of lipoproteins in adipose tissue. Thus, plasma triglycerides build up, leading to an increased risk of hyperlipidemia in humans (71,72). Free fatty acids from the blood enter hepatocytes to synthesize fatty acids in liver tissues. However, a study revealed that synthesis of fatty acid transporter (FAT) protein 2 and FAT was reduced after NP treatment of hepatocytes (63), preventing transport of fatty acids from the blood to the liver, indirectly impeding synthesis of fatty acids in the liver. Another study revealed that the synthesis of ApoE and fatty acid-binding protein 6 was decreased after treatment of hepatocytes with NPs (73), and the synthesis of fatty acids in the liver is indirectly impeded. Therefore, the decreased levels of fatty acids in the liver leads to insufficient synthesis of triglycerides, which indirectly affects storage of fat. The lack of fat storage may lead to lipodystrophy syndrome (73). Lipodystrophy syndrome is a metabolic disorder that leads to metabolic complications similar to those observed in obese patients, such as those with insulin resistance, diabetes mellitus, hepatic steatosis and dyslipidemia (74).

In summary, in glucose metabolism, NPs inhibit synthesis of ChREBP, impede the conversion of glucose to acetyl-coenzyme A and inhibit the sensitivity and secretion of insulin. Taken together, these lead to the accumulation of glucose causing disorders of glucose metabolism. In lipid metabolism, NPs inhibit the production of fatty acids and simultaneously facilitate the transport of fatty acids out of the cell, indirectly leading to a decrease in triglyceride content and fat storage (Fig. 2).

NPs affect production of intermediate metabolites for glycolipid metabolism at the transcription level. Studies have revealed that NPs can affect key rate-limiting enzymes involved in glucose metabolism, including hexokinase 1 (HK1), PK and CS. In a study, zebrafish were given polystyrene MPs and the liver tissue was extracted for transcriptome analysis; transcript levels of PK were markedly decreased in the experimental compared with those in the control group, while the transcript levels of PK1 markedly increased in the experimental group (65). HK1 is a member of the hexokinase family that catalyzes the conversion of glucose to fructose; increase of the HK1 transcript levels results in an increase in the synthesis of HK1 protein, which increases glucose conversion to fructose (74). Decreased levels of PK inhibit the conversion of fructose to pyruvate, leading to the accumulation of fructose; the accumulated fructose reaches the intestinal tract through the blood circulation and accumulates in the intestine, where it is used by the intestinal flora to produce acetate (74). The acetate reaches the liver through the portal vein and is converted into acetyl coenzyme A, which is used as a substrate for lipogenesis, resulting in an increase of adipogenesis (75). CS is a key enzyme in the tricarboxylic acid cycle, converting oxaloacetic to citric acid. Transcriptome analysis has revealed that MPs lead to a decrease in the transcription of CS, leading to a decrease in the synthesis of oleanic and α-ketoglutaric acid (76), which affects the tricarboxylic acid cycle and leads to disorders of glucose and lipid metabolism.

Influencing fatty acid synthesis and β-oxidation at the transcriptional level is another mechanism by which NPs affect lipid metabolism. Fatty acid synthesis and β-oxidation are key components of glycolipid metabolism (76). When studying the effects of NPs on hepatic lipid metabolism, key enzymes involved in fatty acid synthesis and β-oxidation, such as SLC27A, ACS and CPT1A, serve as important biomarkers (77). The transcript levels of the relevant genes are examined to investigate the effects of NPs on glycolipid metabolism pathways and the signaling pathways involved (78,79). Studies have shown that NPs promote fatty acid synthesis by promoting transcription of mRNAs for acetyl coenzyme A carboxylase 1, sterol regulatory element-binding protein 1α and fatty acid synthase (77). NPs inhibit fatty acid β-oxidation by suppressing the transcription of mRNAs for acetyl coenzyme A oxidase and cotinine palmitoyl transferase 1 oxidation of fatty acids (78). PPAR-α and -γ are ligand-activated receptors in the nuclear hormone receptor family that serve as transcriptional activator proteins to regulate expression of oxidative enzymes in peroxisomes, which contain a variety of oxidative enzymes involved in various types of metabolism, including β-oxidation of fatty acids, bile acids and cholesterol metabolism (80). NPs affect the PPAR signaling pathway by increasing the transcript levels of PPAR-α and -γ. Elevation of the transcript levels of PPAR-α leads to an increase in the amount of oxidative enzymes in peroxisomes, which promotes β-oxidation of fatty acids, bile acid and cholesterol metabolism (77). A marked increase in size and number of peroxisomes in the liver can lead to hepatic hypertrophy, hyperplasia and hepatocellular carcinoma (77). PPAR-γ is involved in the differentiation and maturation of adipocytes (81); increases of its transcriptional level promotes the synthesis of fats, contributing to disorders of lipid metabolism. Diacylglycerol acyltransferase (DGAT) is a key enzyme in the synthesis of triglycerides and lipid droplets in adipocytes; DDGAT serves an important role in the regulation of lipid metabolism (82). NPs inhibit mRNA transcription of DGAT, resulting in the reduction of the expression of DGAT, inhibition of the formation of lipid droplets and fatty acids and the reduction of lipid storage. DGAT2-deficient mice died soon after birth due to the severe reduction in energy metabolism substrates and impaired skin permeability barrier function (83). Therefore, inhibition of DGAT mRNA transcription by NPs not only affects lipid metabolism, but also causes damage to the skin permeability barrier function, which is harmful to human health.

In summary, after MPs and NPs enter the human body by ingestion, NPs reach the liver through the circulatory system and cause disorders in glucose and lipid metabolism of the liver including enlargement, hyperplasia, type II diabetes, hyperlipidemia and lipodystrophy syndrome and may contribute to occurrence of hepatocellular carcinoma.

5. Discussion

As MPs and NPs are widely located in the biosphere, their impact on human health is of concern. Studies have demonstrated that humans are continuously exposed to MPs and NPs by inhalation or ingestion (4-6). When MPs and NPs enter the human body, larger particles are eliminated in feces, while smaller particles are processed by gastric juices and intestinal mucus, accumulating in the gastrointestinal tract (84) where they are absorbed into the cells (16). Current research suggests that a small proportion of particles cross the lung and intestinal barriers and accumulate in tissues and organs. Particles with diameter <150 μm are able to travel from the intestinal lumen to the lymphatic and circulatory system, accumulating in tissues throughout the body, including the liver, kidney and brain, producing various toxic effects (62). MPs and NPs induce oxidative stress in cells by two methods: Direct stimulation of intracellular ROS production and inhibition of antioxidant enzymes and GSH synthesis, resulting in ROS metabolism (50). The inflammatory response in the gastrointestinal tract is primarily induced by direct stimulation of phagocytosis to secrete proinflammatory cytokines and disruption of intestinal bacterial flora, which leads to an increase in the number of conditionally pathogenic bacteria (41). Inflammation, oxidative stress and DNA damage caused by NPs entering cells activate the apoptotic signaling pathway, leading to cell death. At the biochemical level, NPs mainly affect the production and metabolism of glucose, triglycerides and fatty acids, while at the transcriptional level, NPs primarily affect production of rate-limiting enzymes of glycolipid metabolism, leading to disorders of glycolipid metabolism. The gastrointestinal toxicity effects of MPs and NPs and effects on hepatic glucose metabolism increase the risk of gastroenteritis, hyperglycemia, diabetes mellitus, hepatic hypertrophy, hyperlipidemia and lipodystrophy, posing a threat to human health (79).

Studies on toxic effects and mechanisms of MPs and NPs on the gastrointestinal tract and liver are based on human cells, rodents and aquatic species (43,59). Although the aforementioned studies have provided evidence of the possible toxic effects of MPs and NPs on the gastrointestinal tract and liver in humans, there is lack of knowledge regarding

the absorption, metabolism and excretion of MPs and NPs in the human body. Additionally, the ability of MPs and NPs to cross the human tissue barrier is unclear; further studies are needed to investigate the mechanisms by which MPs and NPs cross the gastrointestinal barrier and the mechanisms underlying the toxic effects caused by MPs and NPs. Studies have found that MPs and NPs impair intestinal barrier function by decreasing intestinal mucus secretion, inhibiting synthesis of tight junction proteins, increasing intestinal permeability and causing disruption of intestinal flora (38,41,47). To the best of our knowledge, however, there is still a lack of research on the specific mechanisms by which MPs and NPs impair the gastrointestinal barrier.

In vitro studies investigating the toxic effects of MPs and NPs on the gastrointestinal tract and liver use concentrations of MPs and NPs that are higher than the actual concentrations humans are exposed to in real life (15,20,30). Therefore, there is a need to understand the toxic metabolism kinetics of MPs and NPs within the context of the actual concentrations to which humans are exposed. Furthermore, there are differences in the immunological capacity and immune status between individuals that should be considered when assessing toxicological effects in humans.

An increasing number of studies have found that MPs and NPs affect the immune system, as evidenced by the induction of intestinal flora dysbiosis by MPs and NPs, leading to immune imbalance and uptake of NPs by lymphocytes (40,57,85). However, studies of toxic effects of MPs and NPs on immune cells are limited, and there is lack of studies investigating the toxic effects of MPs and NPs on the immune system as a whole (59). The gut microbiota, which is not only an important component of immune and metabolic health but also affects the central nervous system, has been shown to communicate through several pathways of the 'brain-gut axis,' as identified using animal models (44,63,86). Therefore, the toxic effects and mechanisms of MPs and NPs on the brain-gut axis following gut flora disruption should be further investigated.

The gastrointestinal tract and liver are key organs for absorption, metabolism and detoxification. The harmful effects of MPs and NPs involve the intestinal-hepatic axis, causing oxidative stress, inflammation, apoptosis and disorders of hepatic glucose and lipid metabolism in the gastrointestinal tract, resulting in gastroenteritis, hyperglycemia and hyperlipidemia (43). MPs and NPs also indirectly affect the brain-gut axis through the intestinal flora. Therefore, the toxic effects of MPs and NPs on the gastrointestinal tract and liver and their mechanisms should be investigated further.

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Authors' contributions

LZ and YXH conceived the study. LZ and LDR performed the literature review and data analysis. LZ, YFH and YXH contributed to the critical revision of the manuscript. LZ, LDR, YFH and YXH wrote the manuscript and coordinated the revisions. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

References

1. Ragusa A, Svelato A, Santacroce C, Catalano P, Notarstefano V, Carnevali O, Papa F, Rongioletti MCA, Baiocco F, Draghi S, *et al*: Plasticenta: First evidence of microplastics in human placenta. Environ Int 146: 106274, 2021.
2. Rochman CM, Hoh E, Hentschel BT and Kaye S: Long-term field measurement of sorption of organic contaminants to five types of plastic pellets: Implications for plastic marine debris. Environ Sci Technol 47: 1646-1654, 2013.
3. Wang W, Ge J, Yu X and Li H: Environmental fate and impacts of microplastics in soil ecosystems: Progress and perspective. Sci Total Environ 708: 134841, 2020.
4. Prata JC, da Costa JP, Lopes I, Duarte AC and Rocha-Santos T: Environmental exposure to microplastics: An overview on possible human health effects. Sci Total Environ 702: 134455, 2020.
5. Pironti C, Ricciardi M, Motta O, Miele Y, Proto A and Montano L: Microplastics in the environment: intake through the food web, human exposure and toxicological effects. Toxics 9: 224, 2021.
6. Thomas PJ, Perono G, Tommasi F, Pagano G, Oral R, Burić P, Kovačić I, Toscanesi M, Trifuoggi M and Lyons DM: Resolving the effects of environmental micro- and nanoplastics exposure in biota: A knowledge gap analysis. Sci Total Environ 780: 146534, 2021.
7. Amereh F, Amjadi N, Mohseni-Bandpei A, Isazadeh S, Mehrabi Y, Eslami A, Naeiji Z and Rafiee M: Placental plastics in young women from general population correlate with reduced foetal growth in IUGR pregnancies. Environ Pollut 314: 120174, 2022.
8. Leslie HA, van Velzen MJM, Brandsma SH, Vethaak AD, Garcia-Vallejo JJ and Lamoree MH: Discovery and quantification of plastic particle pollution in human blood. Environ Int 163: 107199, 2022.
9. Schwabl P, Köppel S, Königshofer P, Bucsics T, Trauner M, Reiberger T and Liebmann B: Detection of various microplastics in human stool: A prospective case series. Ann Intern Med 171: 453-457, 2019.
10. Tong X, Li B, Li J, Li L, Zhang R, Du Y and Zhang Y: Polyethylene microplastics cooperate with Helicobacter pylori to promote gastric injury and inflammation in mice. Chemosphere 288 (Pt 2): 132579, 2022.
11. Luo T, Wang C, Pan Z, Jin C, Fu Z and Jin Y: Maternal polystyrene microplastic exposure during gestation and lactation altered metabolic homeostasis in the dams and their F1 and F2 offspring. Environ Sci Technol 53: 10978-10992, 2019.
12. Wang L, Wang Y, Xu M, Ma J, Zhang S, Liu S, Wang K, Tian H and Cui J: Enhanced hepatic cytotoxicity of chemically transformed polystyrene microplastics by simulated gastric fluid. J Hazard Mater 410: 124536, 2021.

13. Yee MS, Hii LW, Looi CK, Lim WM, Wong SF, Kok YY, Tan BK, Wong CY and Leong CO: Impact of microplastics and nanoplastics on human health. Nanomaterials (Basel) 11: 496, 2021.
14. Hesler M, Aengenheister L, Ellinger B, Drexel R, Straskraba S, Jost C, Wagner S, Meier F, von Briesen H, Büchel C, *et al*: Multi-endpoint toxicological assessment of polystyrene nano- and microparticles in different biological models in vitro. Toxicol In Vitro 61: 104610, 2019.
15. Cortés C, Domenech J, Salazar M, Pastor S, Marcos R and Hernández A: Nanoplastics as a potential environmental health factor: Effects of polystyrene nanoparticles on human intestinal epithelial Caco-2 cells. Environ Sci Nano 7: 272-285, 2020.
16. Dong X, Liu X, Hou Q and Wang Z: From natural environment to animal tissues: A review of microplastics(nanoplastics) translocation and hazards studies. Sci Total Environ 855: 158686, 2023.
17. Campanale C, Massarelli C, Savino I, Locaputo V and Uricchio VF: A detailed review study on potential effects of microplastics and additives of concern on human health. Int J Environ Res Public Health 17: 1212, 2020.
18. Barboza LGA, Dick Vethaak A, Lavorante BRBO, Lundebye AK and Guilhermino L: Marine microplastic debris: An emerging issue for food security, food safety and human health. Mar Pollut Bull 133: 336-348, 2018.
19. Bouwmeester H, Hollman PC and Peters RJ: Potential health impact of environmentally released micro- and nanoplastics in the human food production chain: Experiences from nanotoxicology. Environ Sci Technol 49: 8932-8947, 2015.
20. Domenech J, Hernández A, Rubio L, Marcos R and Cortés C: Interactions of polystyrene nanoplastics with in vitro models of the human intestinal barrier. Arch Toxicol 94: 2997-3012, 2020.
21. Hussain N, Jaitley V and Florence AT: Recent advances in the understanding of uptake of microparticulates across the gastrointestinal lymphatics. Adv Drug Deliv Rev 50: 107-142, 2001.
22. Eldridge JH, Meulbroek JA, Staas JK, Tice TR and Gilley RM: Vaccine-containing biodegradable microspheres specifically enter the gut-associated lymphoid tissue following oral administration and induce a disseminated mucosal immune response. Adv Exp Med Biol 251: 191-202, 1989.
23. Jani PU, McCarthy DE and Florence AT: Nanosphere and microsphere uptake via Peyer's patches: Observation of the rate of uptake in the rat after a single oral dose. Int J Pharm 86: 239-246, 1992.
24. Volkheimer G: Hematogenous dissemination of ingested polyvinyl chloride particles. Ann N Y Acad Sci 246: 164-171, 1975.
25. Banerjee A and Shelver WL: Micro- and nanoplastic induced cellular toxicity in mammals: A review. Sci Total Environ 755 (Pt 2): 142518, 2021.
26. Varela JA, Bexiga MG, Åberg C, Simpson JC and Dawson KA: Quantifying size-dependent interactions between fluorescently labeled polystyrene nanoparticles and mammalian cells. J Nanobiotechnology 10: 39, 2012.
27. Nowak M, Brown TD, Graham A, Helgeson ME and Mitragotri S: Size, shape, and flexibility influence nanoparticle transport across brain endothelium under flow. Bioeng Transl Med 5: e10153, 2020.
28. Firdessa R, Oelschlaeger TA and Moll H: Identification of multiple cellular uptake pathways of polystyrene nanoparticles and factors affecting the uptake: Relevance for drug delivery systems. Eur J Cell Biol 93: 323-337, 2014.
29. Gratton SE, Ropp PA, Pohlhaus PD, Luft JC, Madden VJ, Napier ME and DeSimone JM: The effect of particle design on cellular internalization pathways. Proc Natl Acad Sci USA 105: 11613-11618, 2008.
30. Carr KE, Smyth SH, McCullough MT, Morris JF and Moyes SM: Morphological aspects of interactions between microparticles and mammalian cells: Intestinal uptake and onward movement. Prog Histochem Cytochem 46: 185-252, 2012.
31. Schmidt C, Lautenschlaeger C, Collnot EM, Schumann M, Bojarski C, Schulzke JD, Lehr CM and Stallmach A: Nano- and microscaled particles for drug targeting to inflamed intestinal mucosa: A first in vivo study in human patients. J Control Release 165: 139-145, 2013.
32. Li S and Malmstadt N: Deformation and poration of lipid bilayer membranes by cationic nanoparticles. Soft Matter 9: 4969-4976, 2013.
33. Xie W, You J, Zhi C and Li L: The toxicity of ambient fine particulate matter (PM2.5) to vascular endothelial cells. J Appl Toxicol 41: 713-723, 2021.
34. Gopinath PM, Saranya V, Vijayakumar S, Mythili Meera M, Ruprekha S, Kunal R, Pranay A, Thomas J, Mukherjee A and Chandrasekaran N: Assessment on interactive prospectives of nanoplastics with plasma proteins and the toxicological impacts of virgin, coronated and environmentally released-nanoplastics. Sci Rep 9: 8860, 2019.
35. Hollóczki O and Gehrke S: Nanoplastics can change the secondary structure of proteins. Sci Rep 9: 16013, 2019.
36. Goodman KE, Hare JT, Khamis ZI, Hua T and Sang QA: Exposure of human lung cells to polystyrene microplastics significantly retards cell proliferation and triggers morphological changes. Chem Res Toxicol 34: 1069-1081, 2021.
37. Xu M, Halimu G, Zhang Q, Song Y, Fu X, Li Y, Li Y and Zhang H: Internalization and toxicity: A preliminary study of effects of nanoplastic particles on human lung epithelial cell. Sci Total Environ 694: 133794, 2019.
38. Hirt N and Body-Malapel M: Immunotoxicity and intestinal effects of nano- and microplastics: A review of the literature. Part Fibre Toxicol 17: 57, 2020.
39. Cheng W, Li X, Zhou Y, Yu H, Xie Y, Guo H, Wang H, Li Y, Feng Y and Wang Y: Polystyrene microplastics induce hepatotoxicity and disrupt lipid metabolism in the liver organoids. Sci Total Environ 806 (Pt 1): 150328, 2022.
40. Li B, Ding Y, Cheng X, Sheng D, Xu Z, Rong Q, Wu Y, Zhao H, Ji X and Zhang Y: Polyethylene microplastics affect the distribution of gut microbiota and inflammation development in mice. Chemosphere 244: 125492, 2020.
41. Liu S, Li H, Wang J, Wu B and Guo X: Polystyrene microplastics aggravate inflammatory damage in mice with intestinal immune imbalance. Sci Total Environ 833: 155198, 2022.
42. Deng Y, Yan Z, Shen R, Wang M, Huang Y, Ren H, Zhang Y and Lemos B: Microplastics release phthalate esters and cause aggravated adverse effects in the mouse gut. Environ Int 143: 105916, 2020.
43. Shi C, Han X, Guo W, Wu Q, Yang X, Wang Y, Tang G, Wang S, Wang Z, Liu Y, *et al*: Disturbed Gut-liver axis indicating oral exposure to polystyrene microplastic potentially increases the risk of insulin resistance. Environ Int 164: 107273, 2022.
44. Jin Y, Lu L, Tu W, Luo T and Fu Z: Impacts of polystyrene microplastic on the gut barrier, microbiota and metabolism of mice. Sci Total Environ 649: 308-317, 2019.
45. Hwang J, Choi D, Han S, Choi J and Hong J: An assessment of the toxicity of polypropylene microplastics in human derived cells. Sci Total Environ 684: 657-669, 2019.
46. Ding Y, Zhang R, Li B, Du Y, Li J, Tong X, Wu Y, Ji X and Zhang Y: Tissue distribution of polystyrene nanoplastics in mice and their entry, transport, and cytotoxicity to GES-1 cells. Environ Pollut 280: 116974, 2021.
47. Domenech J, de Britto M, Velázquez A, Pastor S, Hernández A, Marcos R and Cortés C: Long-term effects of polystyrene nanoplastics in human intestinal caco-2 cells. Biomolecules 11: 1442, 2021.
48. Eleutherio ECA, Silva Magalhães RS, de Araújo Brasil A, Monteiro Neto JR and de Holanda Paranhos L: SOD1, more than just an antioxidant. Arch Biochem Biophys 697: 108701, 2021.
49. Johnson P: Antioxidant enzyme expression in health and disease: Effects of exercise and hypertension. Comp Biochem Physiol C Toxicol Pharmacol 133: 493-505, 2002.
50. Jakubczyk K, Dec K, Kałduńska J, Kawczuga D, Kochman J and Janda K: Reactive oxygen species-sources, functions, oxidative damage. Pol Merkur Lekarski 48: 124-127, 2020.
51. Wang X, Zheng H, Zhao J, Luo X, Wang Z and Xing B: Photodegradation elevated the toxicity of polystyrene microplastics to grouper (Epinephelus moara) through disrupting hepatic lipid homeostasis. Environ Sci Technol 54: 6202-6212, 2020.
52. DeLoid GM, Cao X, Bitounis D, Singh D, Llopis PM, Buckley B and Demokritou P: Toxicity, uptake, and nuclear translocation of ingested micro-nanoplastics in an in vitro model of the small intestinal epithelium. Food Chem Toxicol 158: 112609, 2021.
53. He Y, Li Z, Xu T, Luo D, Chi Q, Zhang Y and Li S: Polystyrene nanoplastics deteriorate LPS-modulated duodenal permeability and inflammation in mice via ROS drived-NF-κB/NLRP3 pathway. Chemosphere 307 (Pt 1): 135662, 2022.
54. Deng Y, Zhang Y, Lemos B and Ren H: Tissue accumulation of microplastics in mice and biomarker responses suggest widespread health risks of exposure. Sci Rep 7: 46687, 2017.
55. Rubio L, Marcos R and Hernández A: Potential adverse health effects of ingested micro- and nanoplastics on humans. Lessons learned from in vivo and in vitro mammalian models. J Toxicol Environ Health B Crit Rev 23: 51-68, 2020.

56. Powell JJ, Thoree V and Pele LC: Dietary microparticles and their impact on tolerance and immune responsiveness of the gastrointestinal tract. Br J Nutr 98 (Suppl 1): S59-S63, 2007.
57. Huang D, Zhang Y, Long J, Yang X, Bao L, Yang Z, Wu B, Si R, Zhao W, Peng C, *et al*: Polystyrene microplastic exposure induces insulin resistance in mice via dysbacteriosis and pro-inflammation. Sci Total Environ 838 (Pt 1): 155937, 2022.
58. Forte M, Iachetta G, Tussellino M, Carotenuto R, Prisco M, De Falco M, Laforgia V and Valiante S: Polystyrene nanoparticles internalization in human gastric adenocarcinoma cells. Toxicol In Vitro 31: 126-136, 2016.
59. Reuter S, Gupta SC, Chaturvedi MM and Aggarwal BB: Oxidative stress, inflammation, and cancer: How are they linked? Free Radic Biol Med 49: 1603-1616, 2010.
60. Yan X, Zhang Y, Lu Y, He L, Qu J, Zhou C, Hong P, Sun S, Zhao H, Liang Y, *et al*: The complex toxicity of tetracycline with polystyrene spheres on gastric cancer cells. Int J Environ Res Public Health 17: 2808, 2020.
61. Chen Z, Wang C, Yu N, Si L, Zhu L, Zeng A, Liu Z and Wang X: INF2 regulates oxidative stress-induced apoptosis in epidermal HaCaT cells by modulating the HIF1 signaling pathway. Biomed Pharmacother 111: 151-161, 2019.
62. Vethaak AD and Legler J: Microplastics and human health. Science 371: 672-674, 2021.
63. Lu L, Wan Z, Luo T, Fu Z and Jin Y: Polystyrene microplastics induce gut microbiota dysbiosis and hepatic lipid metabolism disorder in mice. Sci Total Environ 631-632: 449-458, 2018.
64. Wan Z, Wang C, Zhou J, Shen M, Wang X, Fu Z and Jin Y: Effects of polystyrene microplastics on the composition of the microbiome and metabolism in larval zebrafish. Chemosphere 217: 646-658, 2019.
65. Zhao Y, Bao Z, Wan Z, Fu Z and Jin Y: Polystyrene microplastic exposure disturbs hepatic glycolipid metabolism at the physiological, biochemical, and transcriptomic levels in adult zebrafish. Sci Total Environ 710: 136279, 2020.
66. Shi L and Tu BP: Acetyl-CoA and the regulation of metabolism: mechanisms and consequences. Curr Opin Cell Biol 33: 125-131, 2015.
67. Zhou P, Santoro A, Peroni OD, Nelson AT, Saghatelian A, Siegel D and Kahn BB: PAHSAs enhance hepatic and systemic insulin sensitivity through direct and indirect mechanisms. J Clin Invest 129: 4138-4150, 2019.
68. Syed I, Lee J, Moraes-Vieira PM, Donaldson CJ, Sontheimer A, Aryal P, Wellenstein K, Kolar MJ, Nelson AT, Siegel D, *et al*: Palmitic acid hydroxystearic acids activate GPR40, which is involved in their beneficial effects on glucose homeostasis. Cell Metab 27: 419-427.e4, 2018.
69. Vijayakumar A, Aryal P, Wen J, Syed I, Vazirani RP, Moraes-Vieira PM, Camporez JP, Gallop MR, Perry RJ, Peroni OD, *et al*: Absence of carbohydrate response element binding protein in adipocytes causes systemic insulin resistance and impairs glucose transport. Cell Rep 21: 1021-1035, 2017.
70. Wen B, Zhang N, Jin SR, Chen ZZ, Gao JZ, Liu Y, Liu HP and Xu Z: Microplastics have a more profound impact than elevated temperatures on the predatory performance, digestion and energy metabolism of an Amazonian cichlid. Aquat Toxicol 195: 67-76, 2018.
71. Schlein C, Talukdar S, Heine M, Fischer AW, Krott LM, Nilsson SK, Brenner MB, Heeren J and Scheja L: FGF21 lowers plasma triglycerides by accelerating lipoprotein catabolism in white and brown adipose tissues. Cell Metab 23: 441-453, 2016.
72. Iizuka K, Takeda J and Horikawa Y: Glucose induces FGF21 mRNA expression through ChREBP activation in rat hepatocytes. FEBS Lett 583: 2882-2886, 2009.
73. Bi Y, Chang Y, Liu Q, Mao Y, Zhai K, Zhou Y, Jiao R and Ji G: ERp44/CG9911 promotes fat storage in Drosophila adipocytes by regulating ER Ca(2+) homeostasis. Aging (Albany NY) 13: 15013-15031, 2021.
74. Simha V and Garg A: Lipodystrophy: Lessons in lipid and energy metabolism. Curr Opin Lipidol 17: 162-169, 2006.
75. Iizuka K, Takao K and Yabe D: ChREBP-mediated regulation of lipid metabolism: Involvement of the gut microbiota, liver, and adipose tissue. Front Endocrinol (Lausanne) 11: 587189, 2020.
76. Nunes-Nesi A, Araújo WL, Obata T and Fernie AR: Regulation of the mitochondrial tricarboxylic acid cycle. Curr Opin Plant Biol 16: 335-343, 2013.
77. Bougarne N, Weyers B, Desmet SJ, Deckers J, Ray DW, Staels B and De Bosscher K: Molecular actions of PPARalpha in lipid metabolism and inflammation. Endocr Rev 39: 760-802, 2018.
78. Wang Q, Wu Y, Zhang W, Shen T, Li H, Wu J, Zhang L, Qin L, Chen R, Gu W, *et al*: Lipidomics and transcriptomics insight into impacts of microplastics exposure on hepatic lipid metabolism in mice. Chemosphere 308 (Pt 3): 136591, 2022.
79. Fan X, Wei X, Hu H, Zhang B, Yang D, Du H, Zhu R, Sun X, Oh Y and Gu N: Effects of oral administration of polystyrene nanoplastics on plasma glucose metabolism in mice. Chemosphere 288 (Pt 3): 132607, 2022.
80. Islinger M, Cardoso MJ and Schrader M: Be different-the diversity of peroxisomes in the animal kingdom. Biochim Biophys Acta 1803: 881-897, 2010.
81. Marion-Letellier R, Savoye G and Ghosh S: Fatty acids, eicosanoids and PPAR gamma. Eur J Pharmacol 785: 44-49, 2016.
82. Bhatt-Wessel B, Jordan TW, Miller JH and Peng L: Role of DGAT enzymes in triacylglycerol metabolism. Arch Biochem Biophys 655: 1-11, 2018.
83. Stone SJ, Myers HM, Watkins SM, Brown BE, Feingold KR, Elias PM and Farese RV Jr: Lipopenia and skin barrier abnormalities in DGAT2-deficient mice. J Biol Chem 279: 11767-11776, 2004.
84. Stock V, Fahrenson C, Thuenemann A, Dönmez MH, Voss L, Böhmert L, Braeuning A, Lampen A and Sieg H: Impact of artificial digestion on the sizes and shapes of microplastic particles. Food Chem Toxicol 135: 111010, 2020.
85. Zhao L, Shi W, Hu F, Song X, Cheng Z and Zhou J: Prolonged oral ingestion of microplastics induced inflammation in the liver tissues of C57BL/6J mice through polarization of macrophages and increased infiltration of natural killer cells. Ecotoxicol Environ Saf 227: 112882, 2021.
86. Qiao J, Chen R, Wang M, Bai R, Cui X, Liu Y, Wu C and Chen C: Perturbation of gut microbiota plays an important role in micro/nanoplastics-induced gut barrier dysfunction. Nanoscale 13: 8806-8816, 2021.