Cellular Physiology and Biochemistry

Cell Physiol Biochem 2025;59(S2):2-52
DOI: 10.33594/000000799
Published online: 8 August 2025
Accepted: 3 July 2025

© 2025 The Author(s)
Published by Cell Physiol Biochem Press GmbH&Co. KG, Duesseldorf
www.cellphysiolbiochem.com

This article is licensed under the Creative Commons Attribution 4.0 International License (CC BY). This means that any user shall be free to copy and redistribute the material in any medium or format, also for commercial purposes, provided proper credit is given to the Authors as well as the original publisher.

Review

Role of Gut Microbiota in Modulating Oxidative Stress Induced by Environmental Factors

Natalia Kurhaluk[a] Piotr Kamiński[b,c] Halina Tkaczenko[a]

[a]Institute of Biology, Pomeranian University in Słupsk, Arciszewski St. 22 B, 76-200 Słupsk, Poland, [b]Department of Medical Biology and Biochemistry, Division of Ecology and Environmental Protection, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, M. Skłodowska-Curie St. 9, 85-094 Bydgoszcz, Poland, [c]Department of Biotechnology, Institute of Biological Sciences, Faculty of Biological Sciences, University of Zielona Góra, Prof. Z. Szafran St. 1, 65-516 Zielona Góra, Poland

Key Words
Gut barrier integrity • Immune modulation • Inflammatory pathways • Pollution • Regulation of gut microbiota and pollutants • Microbiota-host interactions • Oxidative stress pathways

Abstract
The widespread presence of environmental pollutants, including toxic metals, microplastics, and antibiotics, has significantly altered gut microbiota composition and functionality, leading to dysbiosis and oxidative stress. These changes contribute to various adverse physiological effects, including systemic inflammation, mitochondrial dysfunction, and intestinal barrier dysfunction. This review provides a comprehensive analysis of the molecular mechanisms by which these environmental factors induce oxidative damage, emphasising the importance of redox imbalance, the overproduction of reactive oxygen species, and inflammatory signalling pathways. Key pathways involved include NF-κB, Nrf2/Keap1, PI3K/AKT, p38-MAPK, JAK/STAT and TLR4/MyD88. These pathways collectively contribute to the progression of chronic inflammatory conditions. Furthermore, this article synthesises findings from 354 studies published between 2016 and 2024, integrating human and animal research evidence. Existing literature suggests that gut dysbiosis exacerbates oxidative stress through impaired short-chain fatty acid production, downregulation of peroxisome proliferator-activated receptor gamma, and disruption of antioxidant enzyme activity. This review explores these mechanisms in more detail. Additionally, the review evaluates studies investigating microbiota-targeted therapeutic interventions to mitigate oxidative stress. These interventions include probiotics, prebiotics, polyphenols, and postbiotics, focusing on their reported modulation of Nrf2 and AMPK signalling pathways. The potential of faecal microbiota transplantation as an innovative approach to restoring a healthy gut ecosystem and counteracting pollutant-induced oxidative damage is also discussed. In light of the growing global exposure to environmental

Natalia Kurhaluk
Department of Animal Physiology, Institute of Biology,
Pomeranian University in Słupsk, Arciszewski St., 22b, 76-200 Słupsk, Poland
E-Mail: natalia.kurhaluk@upsl.edu.pl

pollutants and their associated long-term health implications, it is imperative to gain a deeper understanding of their impact on gut microbiota and oxidative stress. This topic remains at the forefront of biomedical research due to its implications for public health, disease prevention, and developing novel therapeutic strategies.

© 2025 The Author(s). Published by Cell Physiol Biochem Press GmbH&Co. KG

Introduction

Environmental pollutants include many substances that adversely affect ecosystems and human health. Among the most important are toxic metals, including lead (Pb), mercury (Hg), cadmium (Cd), and arsenic (As), which accumulate in soil and water mainly as a result of industrial activities, mining, and improper waste disposal. These metals are characterised by long-term environmental persistence, contributing to widespread contamination [1, 2]. In addition to toxic metals, persistent organic pollutants (POPs), such as polychlorinated biphenyls (PCBs) and dioxins, pose a significant environmental threat [3, 4]. These compounds, mainly by-products of industrial processes, have high potential for bioaccumulation in the food chain [3]. Another emerging environmental concern is the presence of microplastics, i.e., tiny plastic particles resulting from the degradation of larger plastic materials, which have invaded both marine and terrestrial ecosystems, affecting wildlife [5, 6].

Understanding how toxic metals alter gut microbial diversity and function is crucial, as these disruptions contribute to inflammation and oxidative stress, which are key factors in the development of various chronic diseases. Exposure to toxic metals has been shown to disrupt gut microbial diversity and metabolic functions, leading to the proliferation of pathogenic species and the resulting inflammation and oxidative stress [7–9]. Distinct microbial shifts are associated with such exposure, including an increased prevalence of *Firmicutes* and *Proteobacteria* and a reduction in beneficial *Bacteroidetes* populations, exacerbating gut dysbiosis [8]. Identifying these shifts can inform targeted interventions to restore gut homeostasis and mitigate adverse health outcomes.

In addition to traditional pollutants, such as metals and plastics, the widespread use of chemical compounds, including antibiotics, pesticides, and herbicides, poses a significant threat to today's ecosystems [10, 11]. The excessive and often indiscriminate use of these substances in agriculture and medicine has led to their widespread presence in water sources and contributed to the emergence of antibiotic-resistant bacteria [12]. Various environmental pollutants have been shown to significantly affect the composition of the gut microbiota, often leading to dysbiosis and oxidative stress [13, 14]. The gut microbiota, a crucial regulator of human health, plays a fundamental role in metabolism, immune function, and oxidative homeostasis [15].

Redox imbalance resulting from reduced cellular antioxidant capacity leads to the excessive accumulation of ROS, which in turn causes oxidative damage to cell membranes, DNA, and proteins [16]. Furthermore, prolonged exposure to elevated reactive oxygen species (ROS) levels has been shown to activate inflammation-associated signalling pathways such as NF-κB, amplifying oxidative stress and perpetuating inflammatory states [17]. These processes contribute to the progressive deterioration of the gut microbiota composition and the onset of chronic inflammation, creating a self-perpetuating cycle detrimental to overall health [18].

Changes in the gut microbiota associated with exposure to environmental pollutants have been implicated in the pathogenesis of metabolic disorders, including obesity [19, 20], insulin resistance [21], and type 2 diabetes [22, 23]. The gut microbiota is critical in regulating glucose metabolism, lipid storage, and cellular energy homeostasis. Disruption of this microbial ecosystem can lead to hormonal imbalances and impaired nutrient processing [24]. Furthermore, dysbiosis has been linked to an increased risk of cardiovascular disease, as microbial dysbiosis contributes to chronic inflammation and dysregulation of lipid metabolism, which are key risk factors for atherosclerosis and hypertension [25, 26]. Consequently, prolonged exposure to environmental pollutants can significantly increase susceptibility to severe health conditions [27].

It is essential to elucidate their underlying mechanisms to develop effective strategies to mitigate the adverse health effects of environmental pollutants. Research on the gut microbiota should prioritise identifying pollutant sources and their molecular effects on human physiology [13]. In particular, studying the interactions between microbial communities and oxidative processes may offer new therapeutic avenues, including dietary interventions, probiotic supplementation, and antioxidant-based strategies. Furthermore, reducing environmental exposures to toxic metals, microplastics, and excessive antibiotics may be essential to preserve gut microbial homeostasis and prevent related diseases [14].

This study investigates the impact of environmental pollutants, including toxic metals, microplastics, and antibiotics, on the human gut microbiota, and the mechanisms leading to dysbiosis and oxidative stress. The focus is on how exposure to these pollutants may contribute to chronic diseases such as metabolic disorders, inflammatory bowel disease, autoimmune conditions, and cardiovascular pathologies. The main objective is to elucidate the molecular mechanisms involved, particularly redox imbalance, excessive ROS production, and activation of inflammatory pathways, which drive physiological changes in affected individuals. The study also evaluates the long-term health effects of pollutant exposure and assesses the associated public health risks. To achieve this, a thorough review of the scientific literature will be conducted to identify the key pollutants that impact the gut microbiota and to determine their prevalence and distribution across different ecosystems.

Environmental pollutants disrupt the balance and composition of the gut microbiota, triggering an increase in oxidative stress by enhancing the production of reactive oxygen species. This oxidative stress damages gut tissues and microbial communities, thereby exacerbating dysbiosis. Consequently, a self-perpetuating cycle is established where oxidative stress and dysbiosis continuously influence and amplify each other [15]. The study aims to elucidate the molecular mechanisms underlying these phenomena, including redox imbalance, excessive ROS production, and activation of inflammatory pathways. These mechanisms are thought to be responsible for the observed changes in human organisms. In addition, the study was designed to evaluate the long-term effects of exposure to environmental pollutants and to assess the potential risks they pose to public health. The study has been designed to analyse the scientific literature and available research to identify the most critical pollutants affecting the gut microbiota and to assess their prevalence and presence in different ecosystems. An essential component of the study will also be to explore potential health protection methods, such as dietary modification, probiotics, or the use of antioxidants, which could mitigate the adverse effects of dysbiosis and oxidative stress caused by pollutants.

Another key component of the study is to explore potential health-protective strategies, e.g., dietary modification, probiotics, and the use of antioxidants, that may mitigate the adverse effects of dysbiosis and oxidative stress induced by environmental pollutants. This research is inherently interdisciplinary, integrating concepts from microbiology, toxicology, physiology, and molecular biology to provide a holistic perspective on the multifaceted effects of pollutants on the gut microbiota and human health. The novelty of the study lies in the in-depth analysis of key molecular pathways, such as NF-κB, Nrf2/Keap1, PI3K/AKT, p38-MAPK, JAK/STAT, and TLR4/MyD88, which establish mechanistic links between dysbiosis, inflammatory processes, and oxidative stress. In addition, the focus on antibiotic resistance genes as a critical aspect of contemporary health challenges opens new avenues for research into targeted therapeutic interventions.

Materials and Methods

The bibliographic databases used for this study included PubMed, Scopus, and Google Scholar. An initial literature search yielded 501 studies. Following rigorous screening of titles, abstracts, and full texts, 147 studies were excluded due to duplication, irrelevance to the research focus, poor methodological quality, or failure to meet the established inclusion criteria. Thus, a total of 354 studies were retained for

the final analysis. The literature search covered the period from 2016 to 2024 to ensure the most recent and relevant studies were included. Search criteria included articles, reviews, and clinical trials investigating the effects of environmental contaminants, e.g., toxic metals, microplastics, and antibiotics, on gut microbiota, oxidative stress, and dysbiosis. A comprehensive search strategy was implemented using a combination of the following keywords: 'pollutants', 'environmental contaminants', 'gut microbiota', 'dysbiosis', 'oxidative stress', 'heavy metals', 'microplastics', and 'antibiotics' to maximise the retrieval of relevant publications.

The inclusion criteria were carefully defined to find studies published in peer-reviewed journals, research conducted in human or animal models, and articles addressing molecular mechanisms by which contaminants affect the gut microbiota. The exclusion criteria included studies unrelated to the environmental pollutants of interest, articles lacking sufficient data on microbiota changes, and research focusing on non-ecological or non-biological aspects of contaminants. In addition, non-English language articles were excluded unless an English abstract was available. The review prioritised high-quality peer-reviewed sources to ensure the reliability and validity of the findings.

Gut microbiota and its role in metabolic, immune, and neurological homeostasis

Understanding the microbiota-gut-brain axis and neuronal homeostasis is crucial for grasping the systemic effects of oxidative stress induced by environmental factors. The role of specific bacterial taxa in modulating oxidative stress is clearer when considered alongside their broader influence on the interconnected metabolic, immune, and neurological systems. The human gut microbiota mediates this relationship. This complex ecosystem comprises approximately 1,000 bacterial species and is pivotal in maintaining these physiological systems. Representatives of the *Firmicutes phylum*, including the genera *Clostridium*, *Lactobacillus*, and *Ruminococcus*, are particularly important in this context as they ferment dietary fibre into short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate [30, 31]. These metabolites support intestinal barrier integrity, modulate immune responses, and provide an energy source for colonocytes [32]. Dysbiosis, or disturbances in the microbial composition, has been associated with various health conditions, including metabolic disorders, inflammatory diseases, and mental disorders [30-34] (Fig. 1).

The literature on the gut-brain-microbiota axis highlights the complex interplay between gut health, the gut microbiome, and the central nervous system. Bonaz et al. highlight the pivotal role of the vagus nerve as a primary communication pathway within this axis, demonstrating its essential function in mediating interactions between the gut microbiota and the brain. Their review suggests that vagus nerve stimulation may influence the gut microbiota composition while exerting anti-inflammatory effects, offering potential therapeutic applications for gastrointestinal disorders and systemic inflammation [33]. In a previous study, Bonaz et al. further explored the involvement of the vagus nerve in the neuro-immune axis, highlighting its role in modulating immune responses and intestinal permeability. Their findings suggest that vagal signalling has essential implications for the pathophysiology of gastrointestinal disorders, particularly inflammatory bowel disease, thereby linking gut dysfunction to systemic inflammation [34].

Milani et al. and Turroni et al. explore the importance of the gut microbiota in early life and its long-term impact on health [35, 36]. Milani et al. describe the infant gut microbiota as a critical "microbial organ" that plays a fundamental role in developing the immune system and metabolic processes. The composition of this microbiota is influenced by various factors, such as the mode of birth and early nutrition, and its disruption through antibiotic use or dietary factors has been linked to increased susceptibility to infection, allergy, and autoimmune disease later in life [35]. Turroni et al. further expand on the composition of microbial communities in infants and highlight their role in establishing immune homeostasis [36], illustrating the complex interplay between gut microbiota and host health from an early age [35, 37]. In addition, studies have highlighted the impact of early life microbial exposures, including breastfeeding and exposure to diverse environments, on the resilience of the immune system in adulthood [38, 39].

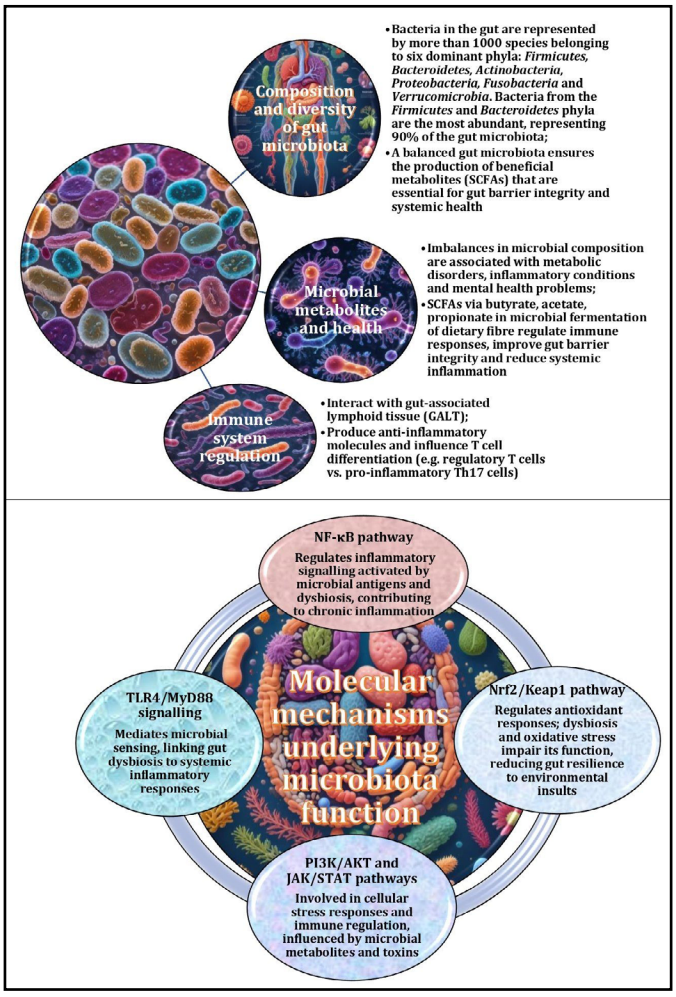

Fig. 1. Changes in the composition and diversity of the gut microbiota have been identified as potential non-invasive biomarkers for the early detection of disease. Specific microbial profiles have been associated with conditions such as inflammatory bowel disease, diabetes and mental disorders, facilitating early diagnosis and personalised therapeutic approaches. Therapeutic interventions include the administration of probiotics and prebiotics to restore microbial balance and enhance SCFA production, the use of faecal microbiota transplantation to treat severe dysbiosis, including recurrent Clostridioides difficile infections, and advanced therapeutic approaches targeting the microbiota through innovative pharmacological agents and dietary interventions to improve health outcomes.

Recent scientific investigations have increasingly focused on elucidating the mechanisms by which the gut microbiota regulate intestinal permeability, to explain their role in the pathogenesis of various gastrointestinal disorders [40]. The human gut microbiome contains several beneficial bacterial taxa essential in maintaining physiological homeostasis. For example, *Lactobacillus* spp. facilitate digestion, enhance immune function, and produce lactic acid [41], while *Bifidobacterium* spp. contribute to the integrity of the intestinal barrier, inhibit the proliferation of pathogenic bacteria, and produce SCFAs [4]. In addition, *Akkermansia muciniphila* has been implicated in strengthening the mucosal barrier and promoting metabolic health [43], while *Faecalibacterium prausnitzii* synthesises anti-inflammatory butyrate, which supports colonic homeostasis [44].

Eubacterium spp. also play an important role in fibre fermentation and SCFA production [45]. However, adverse conditions, such as dysbiosis induced by poor diet, psychological stress, or excessive use of antibiotics, can disrupt the microbial balance and favour the proliferation of opportunistic and potentially pathogenic bacteria [46, 47]. These include *Clostridium difficile*, which is associated with colitis and diarrhoea [48], pathogenic strains of *Escherichia coli*, which contribute to intestinal inflammation and infection [49], *Klebsiella* spp., which are associated with inflammatory bowel disease [50], *Salmonella* spp., a common cause of foodborne illness [51], and members of the *Proteobacteria phylum*, e.g., *Enterobacter* spp., which have been implicated in chronic intestinal inflammation and dysbiosis-related disorders [52, 53]. In addition to traditional risk factors, there is growing evidence that environmental factors, such as pollution, climate change, and overuse of antibiotics, can exacerbate the imbalance of the gut microbiota, leading to the onset of chronic disease and a decline in immune system function [13, 54].

Collectively, these studies provide valuable insights into the multifaceted role of the gut microbiota in maintaining overall health, particularly about gut-brain interactions and immune regulation [33, 35]. The importance of gut barrier integrity and the vagus nerve in maintaining physiological balance has been consistently emphasised in multiple studies [33-35, 37], highlighting their relevance in the pathophysiology of microbiota-related diseases.

Environmental pollutants and gut microbiota dysbiosis

Toxic metals. Existing research on the effects of toxic metals on the gut microbiota highlights the complex interactions between environmental contaminants, microbial communities, and host physiology [7-9]. Several studies have explored these relationships and elucidated the key molecular mechanisms underlying the dysregulation of the gut microbiota by metal exposure. Assefa and Köhler highlight that toxic metal exposure alters microbial diversity and promotes the proliferation of pathogenic species while inducing inflammation and oxidative stress [9]. Richardson et al. further demonstrate that such exposure leads to specific microbial shifts characterised by an increased abundance of *Firmicutes* and *Proteobacteria* and a concomitant decrease in beneficial *Bacteroidetes* populations [8]. Zhang et al. highlight that prolonged exposure to toxic metals reduces gut microbial diversity and disrupts microbial metabolic functions, exacerbating oxidative stress [7].

The existing literature on the effects of toxic metal exposure on the gut microbiota consistently shows that contaminants, such as lead, mercury, and cadmium, significantly alter the microbial composition, resulting in dysbiosis [55, 56]. In addition, the potential role of probiotics in mitigating the adverse effects of toxic metal exposure on the gut microbiota has received attention in the literature [57]. Duan et al. highlight that probiotic supplementation, particularly with *Lactobacillus* and *Bifidobacterium* strains, may help to restore the microbial balance disrupted by contaminants [58]. Probiotics have shown promise in animal models by reducing the intestinal absorption of toxic metals and promoting the proliferation of beneficial bacteria [59, 60]. This has led to the proposal that probiotics could serve as a preventive or therapeutic intervention to reduce the harmful effects of environmental pollutants on gut health.

Arun et al. further discuss the therapeutic potential of probiotics, suggesting that these microorganisms could alleviate oxidative stress, inflammation, and microbial imbalances induced by toxic metal exposure [61]. This protective effect is attributed to the ability of probiotics to modulate the intestinal immune response, reduce ROS production, and support the restoration of intestinal barrier integrity [58]. The ability of probiotics to protect the gut microbiota highlights their potential as an innovative therapeutic strategy to counteract the harmful effects of environmental pollutants [61]. In addition, the metabolite profiles produced by the gut microbiota are crucial for fully understanding the toxicological effects of metal exposure [58]. Santiago et al. propose that metabolites produced by microbial fermentation, particularly SCFAs, are essential for maintaining gut integrity and modulating immune responses [62]. However, dysbiosis resulting from toxic metal exposure may disrupt the production of these metabolites, thereby exacerbating inflammation and compromising gut barrier function [63].

In addition, Bist and Choudhary found that toxic metals, particularly cadmium and lead, promote the overgrowth of pathogenic bacteria, such as *Enterococcus*, *Clostridium*, and *Escherichia coli* [64]. While these bacteria are generally present in low concentrations in a healthy gut, their proliferation in the presence of toxic metals contributes to an inflammatory environment. It disrupts the delicate microbial balance [41, 65]. Overgrowth of these pathogenic bacteria is associated with producing harmful metabolites, including endotoxins, which exacerbate gut inflammation and compromise the immune system [66]. In addition, a shift towards a more pathogenic microbiota can facilitate the translocation of harmful microbes across the gut barrier, leading to infection and systemic inflammation [47].

In a related study, Richardson et al. examined the gut microbiota of rats following

exposure to cadmium and arsenic. They found that the metal exposure induced distinct microbial responses, resulting in shifts in the gut microbiota composition [8]. The study highlighted an increase in *Firmicutes* and *Proteobacteria* and a decrease in *Bacteroidetes*. These changes in the microbial composition were associated with impaired gut function and increased systemic inflammation. Notably, the study also identified changes in microbial metabolites, including SCFAs, essential for maintaining gut integrity and immune responses, contributing to developing chronic diseases, such as liver and kidney damage [8].

A study by Liu et al. investigated the toxic effects of lead (Pb) exposure on *Carassius auratus*, focusing on intestinal damage, oxidative stress, immune response, and microbiota dysbiosis [67]. The study results showed that the Pb exposure led to significant morphological changes in the intestine, including increased wall thickness, goblet cell number, and reduced crypt depth. Their gene expression analysis showed increased oxidative stress and inflammatory markers, while 16S rRNA sequencing revealed decreased microbial diversity and increased pathogenic bacteria. Further analysis of gene expression changes showed a decrease in the expression of claudin-7 and villin-1 and a significant increase in oxidative stress and immune-related markers, such as glutathione transferase (GST), glutathione (GSH), catalase (CAT), interleukins IL-8, IL-10, and IL-1, and tumour necrosis factor α (TNF-α). In addition, 16S rRNA sequencing revealed a decrease in microbial diversity with increased pathogenic bacteria, including *Erysipelotrichaceae*, *Weeksellaceae*, and *Vibrionaceae*, in response to the Pb exposure. This dysbiosis was associated with functional changes in the gut microbiota, including activation of the PPAR signalling pathway and immune dysfunction, suggesting that the gut microbiota may serve as a biomarker for assessing heavy metal toxicity and contamination [67]. In a related study, Liu et al. observed similar results, showing that Pb exposure in silver carp (*Hypophthalmichthys molitrix*) caused significant intestinal structural damage, digestive stress, altered immune response, and microbiota dysbiosis [68]. These findings further highlight the critical role of the gut microbiota in mediating lead toxicity and its overall impact on gut health.

As shown in Fig. 2, the effects of heavy metals on the gut microbiota are complex and can be explored through several key mechanisms. Toxic metals, such as lead, cadmium, and mercury, have been shown to disrupt the gut microbiota by inducing oxidative stress, altering microbial diversity, damaging the gut barrier, impairing metabolite production, causing inflammation, promoting antibiotic resistance, and affecting gut-brain axis communication [56]. These effects may have long-lasting and transgenerational health consequences, highlighting the need for further research (Fig. 2).

Zhang et al. investigated the long-term effects of toxic metal pollution on the gastrointestinal microbiota of *Bufo raddei*. They found that prolonged mercury exposure led to significant changes in the diversity and abundance of gut bacteria [7]. Over time, a decrease in microbial diversity was observed, contributing to increased oxidative stress and inflammatory responses. Similarly, Liu et al. investigated the role of the gut microbiota in mediating cadmium-induced liver injury. They demonstrated that the cadmium exposure disrupted the gut microbiota and interfered with bile acid metabolism – a pathway critical for liver function. Specifically, the cadmium-induced changes in the microbial composition led to an imbalance in bile acid homeostasis, impairing the farnesoid X receptor (FXR) signalling axis, a key regulator of liver function and metabolism. This dysregulation exacerbated liver injury, highlighting the gut microbiota's central role in mediating environmental pollutants' toxic effects [69].

Furthermore, Liu et al. extended these findings by investigating the protective potential of melatonin in attenuating cadmium-induced liver fibrosis. Their results suggest that melatonin administration improves liver function by modulating gut microbiota and bile acid metabolism, thereby counteracting the deleterious effects of toxic metals on the gut-liver axis. These findings suggest that modulation of the gut microbiota may be a promising therapeutic strategy to prevent or treat metal-induced liver injury [70].

In summary, the body of research collectively highlights the critical role of the gut

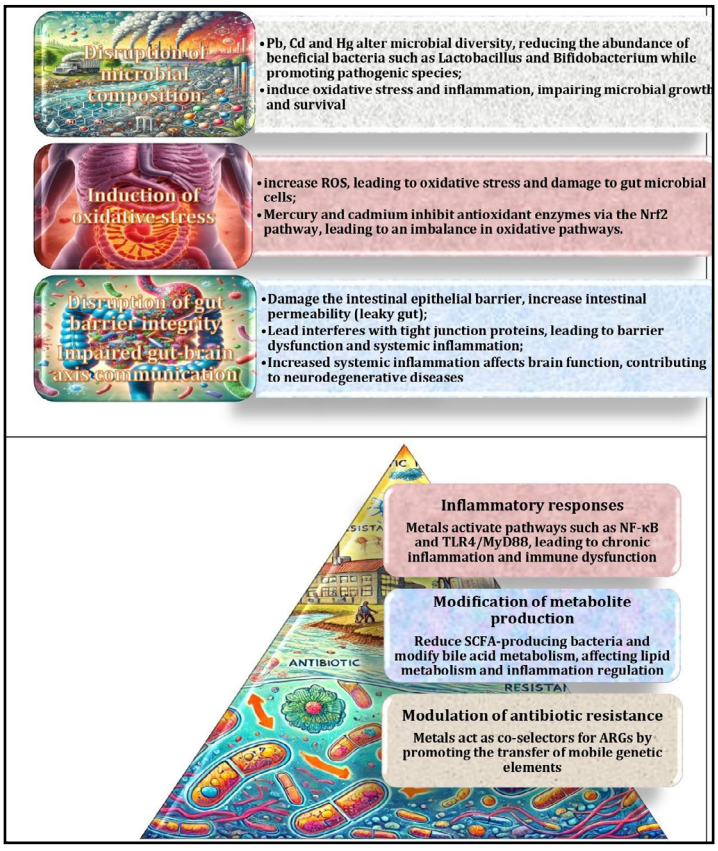

Fig. 2. Key mechanisms of toxic metal effects on gut microbiota and their implications. The impact of toxic metals such as lead, cadmium and mercury on the gut microbiota is complex and can be broadly categorised into several key mechanisms. These include induction of oxidative stress, alteration of microbial diversity, damage to the gut barrier, impairment of metabolite production, induction of inflammation, promotion of antibiotic resistance, and effects on gut-brain axis communication. These mechanisms have the potential to result in long-term and transgenerational health effects.

microbiota in mediating the effects of toxic metal exposure. Studies reported by Porru et al. [55], Bist and Choudhary [64] and Duan et al. [58] demonstrate that restoring microbial balance through probiotic supplementation and other microbiome-based strategies has significant potential to mitigate the adverse health effects of environmental contaminants. Furthermore, understanding the changes in microbial metabolites resulting from pollutant exposure opens up new opportunities for targeted therapeutic interventions. The molecular mechanisms identified in these studies, such as oxidative stress, inflammatory pathways, and altered microbial metabolism, provide valuable insights into the effects of pollutants on gut health and highlight the importance of developing effective strategies to protect the gut microbiota and prevent pollutant-induced diseases.

Microplastics. Plastic pollution is a major environmental challenge that originates from terrestrial and aquatic sources and contributes to widespread ecological and human health concerns [71]. The major contributors include plastic packaging, consumer goods, textiles, and industrial products. Single-use plastics, such as bottles, bags, and food packaging, are of particular concern due to their widespread use and significant environmental impacts. In addition, synthetic textiles, including polyester and nylon, have been identified as sources of microplastic contamination, as these materials release plastic particles during washing [72]. Recent studies estimate that washing synthetic textiles can release up to 700,000 microplastic fibres per load, which enter wastewater systems and accumulate in aquatic environments [73]. The increasing reliance on plastic materials in various industries, including agriculture and medicine, further exacerbates the problem [74, 75].

Another important source of plastic pollution is the degradation of larger plastic debris into microplastics and nanoplastics through environmental processes, such as exposure to ultraviolet (UV) radiation, mechanical abrasion, and weathering [76, 77]. These plastic particles enter biological organisms through a variety of pathways. In aquatic ecosystems,

fish and other marine species ingest microplastics and nanoplastics directly or indirectly through contaminated food sources. After ingestion, these particles can accumulate in the digestive tract, enter the circulatory system, or even penetrate internal organs [5, 78].

The health effects of microplastics are an emerging area of concern, particularly about the gut-liver axis [79]. Recently, Zhang et al. have investigated the impact of polystyrene (PS) microplastics on liver injury and demonstrated that PS-induced changes in the gut microbiota significantly contribute to liver damage [80]. Their findings highlight that perturbations in the gut-liver axis occur via inflammatory and oxidative stress pathways. Specifically, increased intestinal permeability facilitates the translocation of harmful microbial metabolites into the bloodstream, promoting hepatic inflammation and oxidative stress. This process involves the activation of pro-inflammatory cytokines, including tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which subsequently trigger NF-κB signalling, further exacerbating liver injury. These findings highlight the critical role of gut microbiota dysbiosis in mediating the systemic effects of microplastic exposure, particularly on liver health [80]. As shown in Fig. 3, microplastics profoundly influence the composition of the gut microbiota, with far-reaching physiological consequences.

The impact of microplastics on the gut microbiota is complex and involves multiple biological mechanisms. These include promotion of biofilm formation, activation of inflammatory pathways through Toll-like receptor 4 (TLR4) and nuclear factor kappa B (NF-κB) signalling, and induction of oxidative stress via ROS generation and c-Jun N-terminal kinase (JNK)/p38 mitogen-activated protein kinase (MAPK) activation [81]. In addition, microplastics alter microbial diversity, compromise gut barrier integrity by impairing tight junctions, and facilitate the release of toxic additives, such as bisphenol A (BPA) and phthalates, which disrupt endocrine signalling [82]. Studies have shown that exposure to microplastics

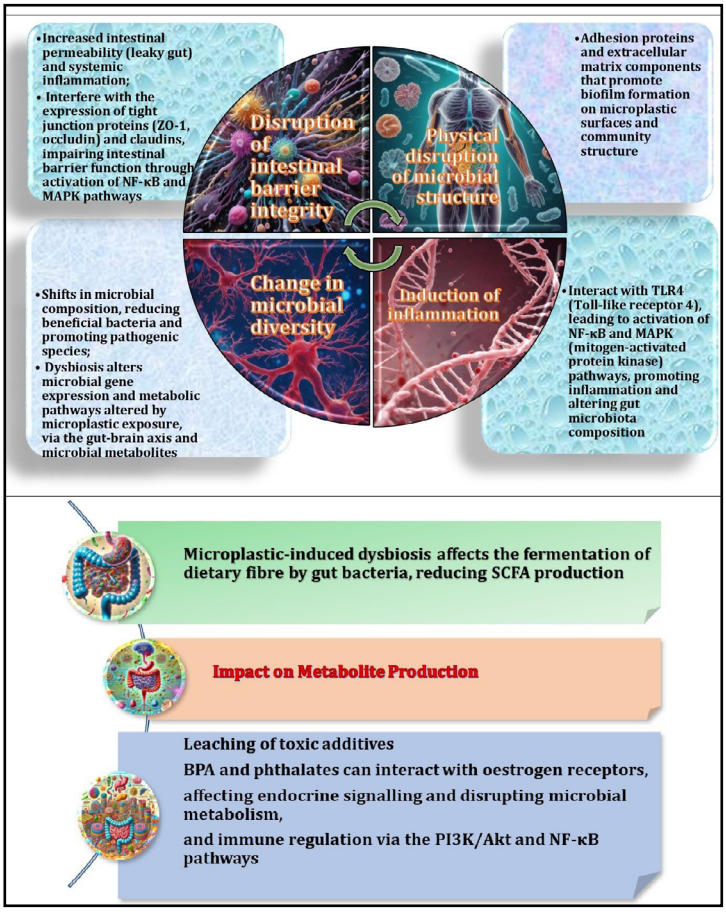

Fig. 3. Key mechanisms of microplastic effects on gut microbiota and their implications. Microplastics affect the gut microbiota by promoting biofilm formation, inducing inflammation through TLR4 and NF-κB pathways, causing oxidative stress through ROS and JNK/p38 MAPK activation, altering microbial diversity, disrupting gut barrier integrity through tight junction impairment, leaching toxic additives such as BPA and phthalates that affect endocrine signalling, and reducing short-chain fatty acid production by interfering with microbial fermentation, all of which contribute to systemic health effects.

can significantly reduce beneficial bacteria, such as *Lactobacillus* and *Bifidobacterium*, while promoting the growth of opportunistic pathogens [79]. They also reduce the production of short-chain fatty acids by interfering with microbial fermentation processes [31]. Together, these mechanisms contribute to systemic health effects.

Ke et al. conducted a pilot study to investigate the presence of microplastics in preschool children and their effects on the gut microbiota composition [83]. Their results indicate that children exposed to microplastics had altered gut microbiota profiles, potentially increasing their susceptibility to diseases associated with microbial dysbiosis. The study also suggests that microplastic exposure contributes to gut epithelial damage, leading to systemic inflammation. An increased abundance of pathogenic bacteria producing lipopolysaccharide (LPS), which exacerbates gut inflammation and triggers immune activation, was also found. These findings suggest that exposure to microplastics early in life, when the immune system is still developing, may have long-term health consequences [83]. Microplastic exposure has also been associated with developmental and neurobehavioural effects in young children, raising concerns about long-term cognitive and immune system effects [84, 85].

Jing et al. investigated the haematopoietic effects of polystyrene (PS) microplastics, focusing on the interplay between gut microbiota, microbial metabolites, and cytokine-mediated immune responses [86]. Their study showed that exposure to PS microplastics resulted in haematopoietic dysfunction, primarily through changes in the gut microbiota composition. The underlying molecular mechanisms included perturbations in microbiota-derived metabolites, e.g. SCFAs, which play a critical role in immune regulation. In addition, PS microplastics stimulated the release of pro-inflammatory cytokines, including IL-6 and TNF-alpha, which contributed to haematopoietic suppression and immune dysregulation through activation of the Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway. These findings highlight the complex interactions between gut microbiota, the immune system, and microplastic-induced inflammatory responses [86].

Similarly, Jin et al. demonstrated that exposure to PS microplastics significantly compromised gut barrier integrity in a mouse model, leading to increased gut permeability, inflammation, and microbial dysbiosis [87]. Their study showed that the exposure to PS microplastics resulted in a shift in the composition of the gut microbiota, characterised by a decrease in beneficial bacterial populations and an overrepresentation of potentially pathogenic species. These microbial changes had downstream effects on metabolic functions, particularly the production of SCFAs, which are essential for maintaining gut homeostasis. Consistent with these findings, Jing et al. further confirmed that PS microplastics induced haematopoietic damage by modulating the gut microbiota composition and increasing the levels of inflammatory cytokines, such as IL-6 and TNF-α. These immune and microbiota perturbations were implicated in impaired blood cell production and systemic inflammation, highlighting the broad physiological consequences of microplastic exposure [87].

These findings highlight the systemic effects of microplastics on health, particularly through the gut-brain axis, as demonstrated in animal models. The effects of environmental contaminants on the gut microbiota composition and the mechanisms underlying these changes are summarised in Table 1.

Collectively, these studies illustrate the interactions of microplastics with the gut microbiota, initiating a cascade of molecular mechanisms that contribute to various adverse health outcomes. Extensive research has elucidated the key pathways involved in these processes, particularly inflammation, oxidative stress, and alterations in intestinal permeability [80, 86, 98]. These molecular perturbations play a central role in mediating the systemic consequences of microplastic exposure, particularly regarding liver function, immune regulation, and haematopoiesis [83, 99]. Future research should identify potential therapeutic interventions, such as probiotics or dietary changes, to mitigate the adverse effects of microplastic-induced gut dysbiosis.

Table 1. Summary of research studies on the effects of environmental pollutants on gut microbiota and health mechanisms

N	Models	Analysed factors	Key results	Mechanisms	Sources
1	Mice exposed to chemical cocktails (pollutants) and supplemented with selenium	Exposure to pollutants (chemical cocktails), selenium supplementation, metallomics, metabolomics, metataxonomics	Exposure to chemical cocktails led to significant changes in the gut microbiota, while selenium supplementation helped modulate these changes, restoring some microbial diversity and improving metabolic functions	Role of selenium in antioxidant defence, modulation of inflammatory pathways, and improvement of the gut microbiota composition through metataxonomics and metabolomics	88
2	Mice exposed to chemical cocktails with selenium supplementation	Chemical cocktail exposure, selenium supplementation, brain metabolomics, gut-brain axis	Chemical cocktail exposure altered brain metabolites, while selenium supplementation had neuroprotective effects by modulating gut-brain signalling	Selenium modulated oxidative stress and the microbial composition via the gut-brain axis, reducing inflammation and improving brain function	89
3	Review article summarising the evidence for the influence of gut microbiota on neurogenesis	Gut microbiota composition, neurogenesis, signalling pathways, and neuroinflammatory responses	Gut microbiota influenced neurogenesis by modulating neuroinflammatory responses and promoting brain plasticity. Dysbiosis impaired neurogenesis and contributed to neurological disease	Microbial metabolites, such as SCFAs, affected the brain via the gut-brain axis; microbial modulation of immune signalling, particularly cytokines and neurotrophic factors	90
4	Animal study investigating the effect of gallic acid on the gut microbiome and immune system	Gallic acid administration, gut microbiome composition, immune response, oxidative stress	Gallic acid improveed gut microbiome diversity, enhanced immune response, and reduced markers of oxidative stress	Gallic acid modulated the gut microbiota composition, boosted antioxidant defences, reduced ROS production, and promoted SCFA production	91
5	Panel study of asthmatic children exposed to air pollution	Air pollution exposure, gut microbiome composition, asthma severity	Air pollution exposure altered gut microbiota in asthmatic children, exacerbating asthma symptoms by promoting inflammation and dysbiosis	Air pollution induced oxidative stress, dysbiosis, and immune system dysregulation, which negatively affected asthma management and gut health	92
6	*In vivo* studies on the effects of bisphenol A (BPA) exposure in relation to obesity and cardiovascular disease	BPA exposure, gut microbiota, obesity, cardiovascular health	BPA exposure altered the gut microbiota composition, promoting obesity and cardiovascular complications in animal models	BPA induced dysbiosis, inflammation, and hormone disruption, affecting metabolic pathways and gut-brain communication	93
7	Medaka fish exposed to low levels of nanoplastics	Exposure to nanoplastics, gut microbiota, physiological and biochemical effects	Nanoplastic exposure disrupted gut microbiota, affecting gut health, metabolism, and immune response in medaka fish	Nanoplastics induced oxidative stress and immune activation, leading to altered gut microbiome and impaired gut function	94
8	Mice exposed to benzo [a]pyrene, treated with isoorientin	Benzo [a]pyrene exposure, isoorientin administration, colon injury, gut microbiota composition	Isoorientin attenuated benzo [a]pyrene-induced colon injury and normalised gut microbiota in mice	Antioxidant properties of isoorientin alleviated oxidative stress, reduced inflammation, and restored gut microbiome balance	95
9	Literature review on the role of gut microbiota in liver oxidative stress and metabolically associated steatotic liver disease (MASLD)	Gut microbiota, hepatic oxidative stress, MASLD, antioxidant role	Dysbiosis exacerbated hepatic oxidative stress and contributed to MASLD. Antioxidants modulated gut microbiota to reduce liver inflammation and improve metabolic outcomes.	Antioxidants regulated the gut microbiota composition, promoted SCFA production, and reduced oxidative damage to the liver, thereby protecting against MASLD	96
10	Filter-feeding amphioxus exposed to microplastics and plastisphere	Microplastic exposure, plasticsphere, gut microbiota, physiological and biochemical responses	Microplastics disrupted gut microbiota, physiological functions, and gene expression in amphioxus, leading to oxidative stress and impaired health	Microplastics induced oxidative damage and gut microbiome dysbiosis and altered gene expression, affecting the overall health of the organism	97

Pesticide-induced toxicity. Extensive research has shown that pesticides profoundly affect the gut microbiota, leading to disruptions in microbial diversity and changes in the balance between commensal and pathogenic species [100]. The effects of various classes of pesticides, including organophosphates and pyrethroids, on the composition and function of the gut microbiota have been well documented, with results indicating a decrease in microbial diversity accompanied by an overgrowth of pathogenic strains [101-103]. Such perturbations have been shown to affect the production of SCFAs, which play a critical role in maintaining the integrity of the gut barrier and modulating immune responses [102]. Furthermore, Meng et al. highlight that these microbial alterations can have systemic effects, including inflammation and metabolic dysregulation, underscoring the sensitivity of the gut microbiota to pesticide exposure and its role as an unintended target of toxic effects [104].

The gut microbiota is increasingly recognised as a central component of the gut-brain axis, influencing a range of systemic physiological processes, including neurological health [105]. Pesticide exposure has been implicated in exacerbating gut dysbiosis, a phenomenon involved in the pathogenesis of neurodegenerative diseases, e.g., Parkinson's disease [106]. The disruption of microbial metabolite profiles induced by pesticide exposure has been shown to promote inflammation and oxidative stress, both of which contribute to neurodegenerative pathways [106]. Recent studies have also identified changes in neurotransmitter synthesis, i.e., decreased levels of gamma-aminobutyric acid (GABA) and serotonin, further linking pesticide-induced gut dysbiosis to neurological dysfunction [107]. In addition, non-target effects of pesticides on the gut microbiota have been found to increase health risks, highlighting the need to understand these interactions to mitigate their long-term consequences [105].

The public health implications of pesticide-induced disruption of the gut microbiota have been widely discussed [103, 106], with studies highlighting the need for a comprehensive assessment of pesticide safety, particularly about unintended effects on microbial ecosystems [101]. These authors further argue that the gut microbiota is a critical mediator in translating environmental exposures into systemic health effects, including immune dysregulation and chronic disease progression. For example, long-term pesticide exposure has been associated with increased susceptibility to inflammatory bowel disease and metabolic disorders, such as obesity and type 2 diabetes, due to microbiota-induced immune dysfunction [101, 103]. In addition, Abou Diwan et al. provide evidence that maternal exposure to pesticides induces microbiota perturbations in both the mother and the offspring, with potential transgenerational effects [108]. Given the broad implications of gut microbiota perturbations for metabolic, immune, and neurological health, addressing these effects is imperative for public health.

Environmental pollutants, gut microbiota dysbiosis, and antibiotic resistance

Perturbations in microbial homeostasis, caused by environmental pollutants such as toxic metals and microplastics, have been shown to significantly alter the composition and diversity of the gut microbiota, leading to dysbiosis. This condition is characterised by reduced beneficial microbial populations, such as *Lactobacillus* and *Bifidobacterium*, and a concurrent increase in opportunistic pathogens like *Escherichia* and *Enterococcus* [56, 109, 110]. For instance, exposure to heavy metals, including cadmium, lead, and mercury, has been demonstrated to disrupt microbial communities [79, 111, 112]. Furthermore, microplastics have been shown to exacerbate dysbiosis by adsorbing environmental toxins and acting as vectors for pathogenic bacteria [112]. These imbalances have been shown to activate molecular pathways, including immune dysregulation and increased intestinal permeability, facilitating oxidative stress.

It has been established that chronic exposure to pollutants, such as bisphenol A (BPA), is associated with elevated ROS production. This, in turn, has been shown to result in oxidative damage to intestinal epithelial cells and compromise barrier integrity [13, 14, 113]. This cascade has been demonstrated to promote chronic inflammation, immune dysfunction, and systemic diseases [79]. Furthermore, microbial dysbiosis has been demonstrated to impact pivotal metabolic processes, including nutrient absorption and bile acid metabolism, thereby exacerbating gastrointestinal disorders and predisposing individuals to metabolic and liver diseases, such as metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), and insulin resistance [21, 114–118].

The long-term ramifications of dysbiosis are further compounded by the emergence of antibiotic resistance (ABR), a phenomenon that is exacerbated by the persistent utilisation of antibiotics and environmental contamination. The presence of pollutants such as antibiotics and heavy metals in the environment has been demonstrated to facilitate the horizontal transfer of antibiotic resistance genes (ARGs), thereby creating reservoirs of resistant bacterial strains [119–122]. Heavy metals, including arsenic and copper, have been demonstrated to co-select for antibiotic resistance. This phenomenon occurs through the induction of stress responses that promote genetic adaptations, thereby enhancing bacterial survival under conditions detrimental to their growth [123, 124]. Consequently, multidrug-resistant bacteria proliferate in the gastrointestinal tract, limiting therapeutic options and preventing pathogenic microorganisms' persistence [125, 126].

It is also important to note that microbial alterations in the gut microbiota can promote the carriage of extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, further complicating antimicrobial treatments [127]. This dynamic interplay between dysbiosis and the dissemination of ABR genes signifies a pivotal public health concern, bearing substantial ramifications for individual and global health security.

Environmental spread of antibiotic resistance genes

Recent research highlights the escalating and multifaceted challenge of antibiotic resistance (AR) in the environment, with profound implications for public health and ecosystem stability. The ubiquitous presence of antibiotic resistance genes (ARGs) in aquatic environments, as demonstrated by Liu et al. [128] and Shao et al. [129], highlights the contamination of natural water bodies and their potential role as reservoirs for the transmission of resistance to humans and animals. This contamination is further exacerbated by the accumulation of heavy metals, microplastics, and other contaminants, which have been shown to co-select for ARGs, enhancing their persistence and mobility within microbial communities. These contaminants are mainly derived from agricultural runoff, wastewater, and improper disposal of pharmaceuticals, facilitating the widespread distribution of ARGs in different ecological systems [130, 131]. In addition, anthropogenic activities, including industrial waste discharges and aquaculture practices, have been identified as significant contributors to the spread of ARGs, further exacerbating the environmental burden of antibiotic resistance [130, 132].

The scientific literature on ARGs has extensively documented the complex mechanisms that govern their persistence and spread in environmental ecosystems, raising significant global public health concerns. Jian et al. provide a comprehensive review of the occurrence, transmission, and mitigation strategies associated with ARGs, highlighting their widespread presence in various environmental matrices, including wastewater, agricultural soils, and natural ecosystems [133]. The authors highlight the critical role of mobile genetic elements (MGEs) in promoting horizontal gene transfer between bacterial populations, thereby accelerating the spread of resistance. In particular, integrons, transposons, and plasmids play a pivotal role in this genetic exchange, enabling bacteria to acquire and disseminate resistance determinants even without direct antibiotic selection pressure [134]. They also identify key factors driving the persistence of ARGs, such as the overuse and misuse of antibiotics in clinical and agricultural settings and environmental contamination through wastewater discharge [133]. Recent metagenomic studies have further demonstrated that ARGs can persist in environmental reservoirs for extended periods, with some resistant bacteria exhibiting enhanced survival strategies, including biofilm formation and efflux pump activation, which confer additional resilience to environmental stressors [135]. Given the potential risks posed by the unchecked spread of ARGs, the authors advocate stringent monitoring and control measures to mitigate the impact of antibiotic resistance on public and environmental health. Emerging bioremediation strategies, such as bacteriophage therapy, advanced oxidation processes, and constructed wetlands, have been proposed as innovative approaches to reduce the prevalence of ARGs in contaminated environments and offer potential ways to mitigate the global threat of antibiotic resistance [130].

Environmental drivers of antibiotic resistance

As highlighted in the relevant literature, significant environmental factors contributing to antibiotic resistance include the presence of microorganisms carrying ARGs in different environmental compartments and the impact of human activities on their spread [10]. For example, Jian et al. highlight that bacteria carrying ARGs are found in various environments, including soil, water, and industrial waste. In particular, improper disposal of antibiotic-contaminated waste, especially through wastewater contamination, has been identified as a significant factor in the spread of antibiotic resistance [133]. In addition, traces of antibiotics and ARGs have been detected in water used for agricultural and livestock purposes, contributing to the spread of these genes and facilitating their further spread among microorganisms in the natural environment [136]. Increased agricultural intensification, with overuse of antibiotics, has further exacerbated the problem by providing a continuous source of resistance genes in the environment [12].

In addition, industrial waste pollution and the use of antibiotics in aquaculture have been identified as significant sources of ARGs in natural ecosystems [137]. Yuan et al. showed that the routine use of antibiotics in fish farming contributes to an increase in antibiotic-resistant bacteria, thereby facilitating the spread of resistance [138]. Aquaculture practices, especially in large-scale operations, have been shown to contribute significantly to environmental contamination with ARGs due to the widespread and often indiscriminate use of antibiotics. Nguyen et al. conducted a comprehensive analysis of current strategies for monitoring ARGs in wastewater treatment and highlighted the challenges associated with detecting and removing these genes from wastewater effluents [136]. Their findings suggest that wastewater treatment plants often fail to effectively eliminate ARGs, spreading resistant bacteria to the surrounding environment. Technological advances in detecting and removing ARGs are needed to mitigate their environmental impact and prevent the further evolution of resistance in bacterial populations.

Yuan et al. review the role of aquaculture in the spread of ARGs, emphasising the contamination of aquatic environments due to the extensive use of antibiotics in fish farming [138]. Their review highlights that the overuse of antibiotics in aquaculture has led to a significant increase in the prevalence of antibiotic-resistant bacteria, capable of transferring ARGs to other microbial populations in the water. This process, known as the 'resistance cycle', not only exacerbates environmental contamination but also poses a potential risk to human health through consuming contaminated seafood [138].

Research focused on the prevalence, distribution, and transfer of ARGs in different environmental settings, highlighting the complex interactions within the One Health framework. Liu et al. investigated the presence of ARGs in the surface water of a subtropical drinking water river-reservoir system, revealing significant contamination in aquatic environments with profound implications for both environmental and human health [128]. Kim et al. investigated the dynamics of ARG gain and loss in multidrug-resistant bacteria, particularly emphasizing the impact of these processes for human and environmental health. Their findings suggest that the environment acts as both a reservoir and a mediator for the persistence and spread of resistance genes [139].

Ajayi et al. provide a comprehensive review of ARGs across different ecosystems, reinforcing the interconnectedness of animal, human, and environmental health and highlighting the need for a holistic approach to managing antimicrobial resistance [140]. Shao et al. reviewed the movement, transformation, and distribution of antibiotics and ARGs in aquatic systems and identified key environmental factors that facilitate the spread of resistance. Their work highlights the importance of the aquatic environment as a conduit for the spread of ARGs, which can exacerbate resistance in both the environment and human populations [129].

Thus, these studies underscore the ubiquitous presence of ARGs in various environments and the need for integrated strategies to combat antimicrobial resistance. The growing body of research highlights the urgent need for comprehensive monitoring, reduction, and remediation of ARGs in the environment. Interdisciplinary approaches involving environmental management, technological innovation in waste treatment, and regulation of antibiotic use in all sectors are essential to effectively protect public health and mitigate the environmental drivers of antibiotic resistance.

Environmental pollutants, oxidative stress, and gut microbiome dysbiosis

Excessive production of ROS is a critical mechanism by which environmental pollution affects the human gut microbiome and overall health. Pollutants, such as heavy metals, pesticides, and particulate matter, generate ROS in biological systems, leading to oxidative stress [16]. In the gut, oxidative stress disrupts the balance of microbial communities, leading to dysbiosis, i.e., an imbalance between beneficial and harmful microbes [141]. Environmental pollutants interfere with antioxidant enzyme activity through various mechanisms, as shown in Fig. 4. They inhibit the expression of antioxidant enzymes, deplete

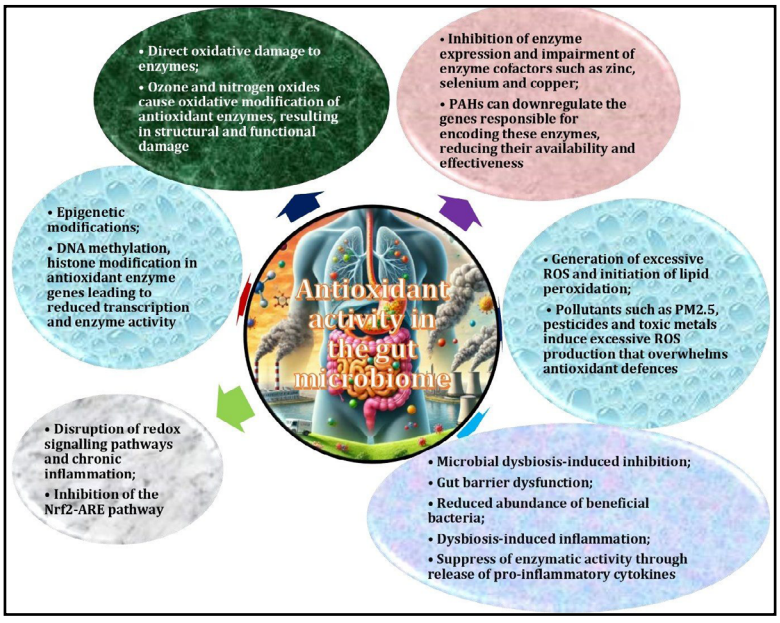

Fig. 4. Mechanisms of pollutant-induced disruption of antioxidant function in the gut microbiome and in the organism. Environmental pollutants interfere with antioxidant enzyme activity by a variety of mechanisms. They inhibit enzyme expression by binding directly to active sites or by downregulating encoding genes, generate excessive reactive oxygen species (ROS) that overwhelm defences, and impair essential cofactors such as zinc and selenium. In addition, toxins induce gut microbiome dysbiosis, oxidative damage to enzymes and epigenetic modifications, while also disrupting redox signalling pathways and gut barrier integrity. Chronic inflammation and lipid peroxidation products further exacerbate oxidative stress and exacerbate the suppression of antioxidant enzyme activity.

essential cofactors, and generate excessive ROS, overwhelming the body's antioxidant defences [142, 143]. In addition, pollutants can alter the activity of key enzymes involved in antioxidant defence, aggravating oxidative stress and exacerbating the negative impact on microbial health [144].

In addition, these pollutants induce gut microbiome dysbiosis, cause oxidative damage to enzymes, and induce chronic inflammation, all of which further suppress enzyme activity [14]. These combined effects contribute to systemic oxidative stress and impaired redox balance, as shown in Fig. 4. This systemic oxidative stress is associated with several metabolic disorders that compromise immune function and increase susceptibility to various diseases [145]. In turn, oxidative stress promotes the production of ROS through microbial metabolism, creating a vicious cycle of oxidative damage. This imbalance can compromise the integrity of the intestinal barrier, exacerbate inflammation, and affect overall systemic health [141].

A wide range of diseases have been linked to prolonged exposure to environmental pollutants and the mechanisms outlined above, including irritable bowel syndrome [146], Crohn's disease [147], ulcerative colitis [148], type 2 diabetes [149], obesity [150], insulin resistance [151], rheumatoid arthritis [152], systemic lupus erythematosus [153], non-alcoholic fatty liver disease [154], liver cirrhosis [155], atherosclerosis [156], hypertension [157], myocardial infarction [158], Alzheimer's disease [159], Parkinson's disease [160], amyotrophic lateral sclerosis [161], colorectal cancer [162], liver cancer [163], chronic obstructive pulmonary disease [164], and asthma [150]. These diseases share standard pathogenic mechanisms driven by environmental pollutants, gut dysbiosis, and oxidative stress, highlighting the need for integrated strategies to address these interrelated factors [146-164].

Paun and Danska [165] emphasised the pivotal role of the gut microbiome in influencing the risk of type 1 and type 2 diabetes, highlighting its bidirectional relationship with systemic metabolic health. Similarly, Zhao et al. established a link between exposure to $PM_{2.5}$ particulate matter and insulin resistance via microbiome-mediated mechanisms [166]. Together, these findings emphasise the complex interplay between environmental pollutants, microbial dysbiosis, and host physiology, and highlight the importance of addressing environmental exposures to mitigate their adverse health effects.

Environmental pollution significantly disrupts antioxidant enzyme activity in the gut microbiome and the organism through various mechanisms. Pollutants, such as heavy metals, particulate matter, and pesticides, have been shown to inhibit the expression or activity of critical enzymes, including superoxide dismutase (SOD) and glutathione peroxidase (GPx). These pollutants act either by binding to the active sites of these enzymes or by down-regulating genes responsible for their synthesis [167]. In addition, pollutants, such as pesticides and heavy metals, can act as direct enzyme inhibitors, interfering with their function at the molecular level [168, 169].

Pollutants also induce dysbiosis, which has been shown to reduce populations of beneficial bacteria that contribute to antioxidant activity [14]. This microbial imbalance further compromises the host's ability to mitigate oxidative damage. Inflammation, often triggered by environmental pollutants, has been shown to suppress antioxidant enzyme synthesis through the action of pro-inflammatory cytokines [79]. This inflammatory response can lead to a cascade of adverse events, ultimately compromising the body's ability to manage oxidative stress effectively. Pollutants can also cause direct oxidative modifications to enzymes, damaging their structure and function [145]. In addition, epigenetic changes, e.g., DNA methylation, have been shown to inhibit the transcription of antioxidant genes, compounding the effects of pollution on enzyme expression [170, 171].

The results of the present study are consistent with those reported by Omar et al., who demonstrated that rifaximin treatment in rats conferred protection against malathion-induced testicular toxicity [172]. This protective effect was attributed to gut microbiome modulation and oxidative stress mitigation through mitophagy. These observations highlight a recurring theme across multiple studies: pollution-induced oxidative stress significantly influences the composition of the gut microbiome, which in turn contributes to a range of systemic health dysfunctions [172]. In support of these conclusions, research focusing on prenatal environmental risk factors, for instance, a study conducted by Love et al., further reinforces the growing recognition of the impact of environmental exposures on microbiome health [173]. This highlights the importance of understanding the mechanism of environmental contaminants in disrupting microbial homeostasis from an early stage of development.

As demonstrated by Klimkaite et al., exposure to pollutants such as air pollution has been shown to induce changes in the airway microbiome, leading to molecular perturbations [174]. This finding is consistent with the research conducted by Gao et al., who demonstrated a direct correlation between oxidative stress and intestinal health. Their study revealed that *Bacillus coagulans*, a probiotic bacterium, can alleviate copper-induced oxidative stress by regulating oxidative pathways and modulating the composition of the gut microbiome [175]. These studies emphasise the complex interconnection between environmental pollutants, microbiome health, and microbial communities' adaptive or protective functions against external stressors. Further evidence indicates that environmental pollution plays a pivotal role in initiating oxidative stress, disrupting the gut microbiome, and influencing systemic health. Pollutants such as microplastics, toxic metals, particulate matter, polycyclic aromatic hydrocarbons, ozone, nitrogen oxides, secondhand smoke, pesticides, ultrafine soot, and general air pollution have been demonstrated to cause immediate oxidative damage [176–179]. These pollutants have also been shown to induce long-term shifts in microbial populations in the gut and other organs. These persistent microbial disturbances contribute to a wide range of diseases, including cognitive disorders, metabolic dysfunctions, and reproductive toxicity [180], emphasising environmental pollution's chronic and multifaceted impacts on health and the challenges it poses for disease prevention and management.

Consequently, the growing body of evidence underscores the urgent need for strategies to reduce environmental exposure to pollutants and protect the gut microbiome to prevent or mitigate the development of chronic diseases. Therefore, a more comprehensive understanding of the interactions between environmental stressors, oxidative stress, and

microbiome health is essential for formulating more effective public health interventions and treatments [13]. This integrated approach to the study of environmental health could lead to improved strategies to mitigate the effects of pollution on human health and well-being.

Molecular pathways linking environmental pollutants to gut microbiota dysregulation

The molecular pathways regulating the gut microbiota in response to environmental pollutants encompass several critical mechanisms, including inflammatory signalling, immune modulation, and gut barrier integrity pathways [181]. In particular, the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, essential for cellular stress responses and inflammatory regulation, have been identified as particularly vulnerable to pollutant exposure. Their dysregulation leads to intestinal inflammation and microbial dysbiosis [182, 183]. Toll-like receptors (TLRs), particularly TLR4 and TLR2, have been observed to be the key mediators of pollutant-induced immune activation, initiating inflammatory cascades that profoundly affect the gut microbiota composition [184, 185]. In addition, pollutants have been shown to impair the function of regulatory T cells (Tregs), essential for maintaining immune tolerance and suppressing excessive inflammation [186].

Perturbations in cytokine homeostasis further exacerbate gut microbiome dysbiosis [187]. Increased levels of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β), and decreased levels of anti-inflammatory cytokines, particularly interleukin-10 (IL-10), contribute to immune dysregulation [188]. Toxins also compromise the integrity of the intestinal barrier by damaging tight junction proteins, including zonula occludens-1 (ZO-1), occludin, and claudin-1, thereby increasing intestinal permeability and facilitating the translocation of harmful microbial products into the systemic circulation [189, 190]. In addition, epithelial growth factors (EGFs) and trefoil factors (TFFs), which are critical for intestinal repair and epithelial cell homeostasis, are impaired by contaminants, preventing proper mucosal regeneration and exacerbating barrier dysfunction [191].

In addition to immune modulation and gut barrier integrity, contaminants have been shown to disrupt microbiota-host interactions by altering the production of SCFAs, including butyrate, acetate, and propionate, which are essential for immune regulation, gut epithelial maintenance, and barrier function [63]. Furthermore, changes in microbial metabolites, such as secondary bile acids and tryptophan-derived indole compounds, have been observed to disrupt both gut microbiota diversity and host metabolic homeostasis [192].

Oxidative stress pathways, particularly through the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, are also affected by pollutants, including heavy metals and air pollution, leading to oxidative damage in the gut and dysbiosis. ROS generated by pollutants further increase inflammation and epithelial injury [193]. In addition, cytochrome P450 (CYP) enzymes, which play a central role in xenobiotic metabolism and detoxification, can modulate microbial exposure to environmental toxins, thereby significantly influencing the composition of the gut microbiota [194]. Also, through cannabinoid receptors CB1 and CB2, the endocannabinoid system (ECS) is susceptible to contaminant-induced alterations, affecting gastrointestinal motility, intestinal permeability, and microbial diversity, which collectively contribute to gut dysfunction and systemic metabolic disorders [195, 196].

The molecular pathways highlight the intricate interplay between environmental pollutants and gut health, underscoring their widespread impact on microbial balance, immune homeostasis, and overall gut functionality, as illustrated in Fig. 5. Importantly, these pathways are not isolated but rather form an interconnected regulatory network in which pollutants can disrupt multiple mechanisms simultaneously. It is hypothesised that such

Fig. 5. Key molecular pathways involved in the regulation of gut microbiota and contaminants. Key molecular pathways regulating gut microbiota and pollutants include inflammation via NF-κB and MAPK pathways, immune modulation via TLRs and Tregs, gut barrier integrity via tight junction proteins and epithelial growth factors, microbial interaction via SCFAs and metabolites, and oxidative stress. The influence of contaminants on these processes and their potential consequences, such as microbiota dysbiosis, gut inflammation and compromised gut health, are the subject of ongoing research.

perturbations contribute to gut dysbiosis, increased inflammation, compromised barrier function, and impaired immune responses, ultimately increasing susceptibility to metabolic, autoimmune, and inflammatory disorders. Understanding these mechanisms is essential for developing targeted interventions to mitigate the adverse effects of environmental pollution on gut and systemic health.

NF-κB as a mediator of environmental pollutant-induced gut microbiota dysbiosis and inflammation. The transcription factor NF-κB is a central regulator of inflammation within the gut microbiome, particularly in response to environmental pollutants [197]. A growing body of research has elucidated how pollutants disrupt gut microbiota homeostasis, contributing to systemic inflammation and disease pathogenesis. For example, polyethylene microplastics (PE-MPs) have been shown to induce gut microbiota dysbiosis in mice, leading to liver injury through activation of the Toll-like receptor 2 (TLR2)/NF-κB/NOD-like receptor family pyrin domain containing 3 (NLRP3) pathway [198]. This finding highlights the inflammatory potential of microplastics, with gut microbial imbalances triggering liver injury via inflammation-related mechanisms. In a related study, Lin et al. demonstrated that nano-sized polystyrene particles exhibit greater toxicity than micro-sized polystyrene particles, primarily due to their more pronounced effects on the gut microbiota composition. This highlights the size-dependent toxicity of microplastics and reinforces their role in exacerbating systemic inflammation and toxicity [199].

Further supporting this line of research, Liu et al. investigated the effects of exposure to oil mist particulate matter and found that it promotes hyperlipidaemia-related inflammation via the microbiota/SCFAs/G-protein-coupled receptor 43 (GPR43) axis and TLR4/NF-κB activation. These findings reveal a complex interplay between environmental pollution, gut microbiome alterations, and inflammation in the regulation of lipid metabolism [200]. Collectively, these studies suggest that various pollutants, e.g., microplastics, airborne particulate matter, and industrial chemicals such as benzimidazole fungicides, disrupt the gut microbiota balance and activate inflammatory pathways, positioning the TLR/NF-κB axis as a central mediator in these processes.

Consistent with these findings, Lu et al. reported that carbendazim, a widely used benzimidazole fungicide in agriculture, induced intestinal inflammation in grass carp (*Ctenopharyngodon idella*) via the TLR5/NF-κB pathway [201]. This observation highlights agricultural pollutants' potential environmental and ecological consequences on gut health. In a parallel study, Duan et al. highlighted the therapeutic potential of ginsenoside Rg3 in alleviating acute radiation proctitis through modulation of the TLR4/MyD88/NF-κB pathway,

highlighting the critical role of TLR/NF-κB signalling in both gut inflammation and microbial homeostasis [202]. Furthermore, Liu et al. demonstrated that exposure to antimicrobials, such as benzalkonium chloride and triclosan, leads to sex-specific changes in the gut microbiota composition and overall health in zebrafish [203]. This suggests that chemical pollutants may have sex-specific effects on the microbiome structure and host health outcomes and warrants further investigation into sex-specific responses to environmental pollutants.

NF-κB is a key transcription factor activated by several inflammatory stimuli, including environmental pollutants, such as particulate matter ($PM_{2.5}$), heavy metals, and microplastics. These pollutants have been shown to disrupt the microbial balance in the gut, leading to inflammatory responses and systemic health complications [204-207]. In addition, extensive research has highlighted a significant impact of environmental pollutants, particularly microplastics, airborne particulate matter, and agricultural pesticides, on the gut microbiota composition and the initiation of systemic inflammation via inflammatory pathways such as the Toll-like receptor (TLR)/NF-κB axis [206, 208, 209]. These pollutants have been shown to induce gut dysbiosis, which subsequently leads to serious health problems, including liver damage, hyperlipidaemia, and gastrointestinal inflammation [76, 101, 102]. Emerging evidence suggests that pollutants also affect tight junction proteins, such as ZO-1, occludin, and claudin-1, thereby increasing intestinal permeability and the risk of inflammatory diseases [210].

These studies highlight the central role of the TLR/NF-κB pathway in mediating pollutant-induced gut microbiota dysbiosis and inflammation [198]. These findings have important implications for understanding the interplay between environmental pollution, gut health, and systemic disease development. They also highlight the need for targeted strategies to mitigate pollutant exposure and its adverse health consequences.

Nrf2/Keap1 pathway regulates oxidative stress and gut microbiome homeostasis. The Nrf2/Keap1 signalling pathway regulates antioxidant responses, protects cells from oxidative stress, and maintains cellular homeostasis [211]. In normal physiological conditions, nuclear factor erythroid 2-related factor 2 (Nrf2) remains bound to Kelch-like ECH-associated protein 1 (Keap1), facilitating its ubiquitination and subsequent degradation, thereby maintaining low basal levels of Nrf2 activity [212]. However, upon exposure to oxidative stress or environmental pollutants, e.g., airborne particulate matter ($PM_{2.5}$), heavy metals, and microplastics, Nrf2 is released from Keap1. It translocates to the nucleus, where it binds to the antioxidant response element (ARE) and upregulates the expression of antioxidant genes and detoxifying enzymes, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1) [213, 214]. This activation is protective by neutralising ROS and preserving cellular structures, particularly within the intestinal epithelium. In gut health, Nrf2 activation is essential for maintaining microbial homeostasis, regulating inflammatory responses, and preventing gut dysbiosis caused by oxidative stress. In particular, prolonged exposure to environmental pollutants can impair Nrf2 activation, leading to an imbalance in antioxidant defences, increased intestinal permeability, and systemic inflammation [215].

From a molecular biological and physiological perspective, Nrf2 activation represents a fundamental cellular defence mechanism against oxidative damage, particularly in the intestinal tract and liver [215]. Saeedi et al. demonstrated that gut-dwelling lactobacilli stimulate hepatic Nrf2 activation, enhancing the liver's resilience to oxidative stress. The study highlighted that lactobacilli modulate the expression of hepatic antioxidant enzymes through Nrf2 signalling, thereby mitigating ROS accumulation resulting from environmental pollutants and dietary imbalances. This highlights the intricate gut-liver axis in which microbiota-derived metabolites influence systemic oxidative responses [216]. Similarly, Wang et al. provided evidence that exposure to fundamental ambient $PM_{2.5}$ particles induces oxidative stress in both lung and gut, leading to Nrf2 activation as a compensatory mechanism to counteract pollutant-induced damage. These findings suggest that the gut microbiota – particularly beneficial bacteria such as lactobacilli – play a critical role in modulating oxidative stress in distant organs via the Nrf2 pathway, thereby enhancing the gut's contribution to systemic protection against environmental pollutants [217].

These studies highlight the Nrf2/Keap1 axis as a key molecular pathway mediating cellular defence against oxidative stress and pollution-induced damage. Given its central role in modulating antioxidant defences, reducing inflammation, and maintaining microbiome homeostasis, targeting Nrf2 offers significant therapeutic potential for preventing and treating pollution-induced diseases. Future research should further explore pharmacological and dietary strategies to enhance Nrf2 activation to counteract oxidative damage and inflammation associated with environmental exposures.

PI3K/AKT and MAPK pathways as key regulators of cellular stress response to environmental pollutants. The PI3K/AKT and p38-MAPK pathways are essential cellular stress response mechanisms for maintaining homeostasis in environmental stressors, including exposure to various pollutants [218]. These signalling cascades enable cells to detect and respond to external stressors, such as oxidative stress, inflammation, and DNA damage, which are often induced by environmental pollutants, including air pollution, heavy metals, and particulate matter. The PI3K/AKT/mTOR signalling pathway is pivotal in regulating fundamental cellular processes, such as cell survival, autophagy, and apoptosis, in response to pollutants and toxins [219, 220]. Studies reported by Guo et al. [221] and Yin et al. [222] provide compelling evidence that metals, such as arsenic and nickel, can activate the PI3K/AKT/mTOR pathway in a variety of organisms, including common carp and mouse models. Specifically, PI3K/AKT/mTOR activation enhances cellular survival under oxidative stress and toxin exposure, thereby reducing apoptosis and mitigating pollutant-induced damage [221, 222].

In particular, Guo et al. (2021) demonstrated that zinc can counteract arsenic-induced toxicity in fish by modulating the PI3K/AKT/mTOR signalling cascade, thereby protecting the intestine from arsenic-induced damage. This finding highlights the adaptive function of this signalling pathway in mitigating the toxic effects of environmental pollutants, particularly heavy metals [221]. Furthermore, the role of PI3K/AKT/mTOR in promoting autophagy was emphasised by Yin et al. (2021), who demonstrated that nickel exposure disrupts cellular homeostasis by impairing autophagic mechanisms [222]. In parallel, this pathway closely interacts with MAPK signalling and autophagic processes to regulate inflammation, metabolism, and immune responses. Studies conducted by Zhang et al. [223] and Lu et al. [224] highlight the importance of the PI3K/AKT/mTOR axis in controlling apoptosis and autophagy in cells exposed to air pollutants, including $PM_{2.5}$ and microplastics. Zhang et al. identified the role of the PI3K/AKT/mTOR pathway in modulating autophagy in alveolar epithelial cells, where chronic exposure to $PM_{2.5}$ promotes apoptosis and disrupts cellular homeostasis. Dysregulation of these pathways due to prolonged pollution exposure has been linked to chronic inflammation, gut dysbiosis, and impaired barrier function, highlighting their relevance in environmental health research [223, 224].

Furthermore, Sun et al. [225] and Dong et al. [226] have shown that environmental pollutants such as bisphenol A activate the PI3K/AKT/mTOR pathway, leading to abnormal autophagy and immune dysfunction. This dysregulation has been implicated in the pathogenesis of autoimmune diseases, highlighting the broader health implications of environmental toxin exposure [225, 226]. Bisphenol A, a widely recognised environmental contaminant commonly found in plastics, profoundly affects cellular stress response mechanisms by disrupting PI3K/AKT/mTOR signalling, altering immune homeostasis and increasing disease susceptibility [226].

In addition, exposure to bisphenol A has been shown to cause a wide range of adverse health effects, particularly when individuals are concurrently exposed to other environmental contaminants. BPA acts as an endocrine-disrupting chemical, interfering with hormonal signalling and leading to developmental disruption, neurotoxicity, and reproductive health disturbances [227]. Early life exposure to BPA has been linked to childhood obesity, neurodevelopmental disorders, and increased susceptibility to metabolic diseases later in life [228]. BPA exposure has also been associated with liver toxicity. It may result in transgenerational effects, as seen in a study reporting liver defects in medaka fish after multiple generations of BPA exposure [229]. Furthermore, combining BPA with other

environmental chemicals, such as phenols, pesticides, and phthalates, has been shown to exacerbate obesity and increase health risks [230]. The complexity of BPA mechanisms highlights the importance of understanding its interaction with other contaminants to assess its long-term effects on human health [231].

The results of studies further highlight the significant effects of environmental toxicants, including microplastics, cadmium, arsenic, and nanoparticles, on various biological systems, particularly through inflammatory responses and cellular damage *via* MAPK signalling [232]. Trophic transfer of nanoplastics leads to intestinal inflammation, dysbiosis, and activation of inflammatory pathways in zebrafish, highlighting the environmental risks of microplastic pollution. Xie et al. [233] and Li et al. [234] showed that polystyrene microplastics induce reproductive toxicity and oxidative stress via MAPK pathways, exerting deleterious effects on multiple organs, including the heart.

Furthermore, Cao et al. observed that cadmium exposure induced apoptosis and mitochondrial damage in BEAS-2B cells through MAPK signalling [235]. Moreover, Liu et al. [236] and Ijomone et al. (2021) [237] observed that heavy metals such as arsenic induce depression and anxiety-like behaviours in mice through ROS/p38 MAPK/NLRP3 inflammasome activation, linking environmental stressors to neurobehavioural health. In addition, Han et al. investigated the effects of nanoparticle exposure on the lungs, demonstrating how viral reactivation can exacerbate lung damage and contribute to emphysema [238]. These studies highlight the widespread activation of MAPK signalling pathways, which are central to the toxicological mechanisms behind the deleterious effects of various environmental pollutants on cellular integrity, inflammation, and general health.

Thus, the PI3K/AKT/mTOR pathway is critical in cellular stress responses to environmental pollutants. This pathway influences cell survival, inflammation, and immune responses and is essential for protecting cells from oxidative stress and regulating apoptosis and autophagy in response to pollutants. The interaction of this pathway with MAPK signalling and its ability to modulate immune responses emphasises its importance in environmental health and disease prevention. Thus, further research into the modulation of these signalling mechanisms offers significant potential for therapeutic intervention in preventing pollution-related diseases.

Role of JAK/STAT signalling in the effects of environmental pollutants, gut microbiome dysbiosis, and immune dysregulation. The gut microbiome plays a critical role in modulating immune responses, and its composition can be significantly altered by various environmental factors, including pollution [13, 14]. Emerging evidence suggests that exposure to pollutants, such as heavy metals, polycyclic aromatic hydrocarbons (PAHs), and persistent organic pollutants (POPs), is associated with changes in microbial diversity that impair host immunity and metabolic functions [63, 109]. In particular, pollutants, excellent particulate matter ($PM_{2.5}$), and chemical compounds have been shown to affect the structure of the microbiome, leading to dysbiosis (an imbalance in microbial communities), which subsequently affects immune function and homeostasis [14].

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) signalling pathway is a fundamental mechanism by which environmental pollution modulates immune responses. This pathway is essential for mediating inflammatory and immune reactions and is critical in cellular proliferation, differentiation, and apoptosis [239, 240]. Dysregulation of this pathway, induced by microbial shifts resulting from contaminant exposure, can lead to chronic inflammation, immune suppression, and the onset of autoimmune and inflammatory diseases [241]. In addition, oxidative stress and changes in gut permeability driven by pollutant-induced microbiome perturbations may further contribute to immune dysfunction, exacerbating inflammatory bowel disease and metabolic syndrome [14, 18].

Several biomarkers can be used to monitor the impact of pollution on both the gut microbiome and the immune system, highlighting the need to maintain microbiome balance in response to environmental stressors. In particular, various biomarkers, such as pro-inflammatory cytokines (e.g. interleukin-6, tumour necrosis factor-α), acute-phase proteins

Fig. 6. Biomarkers associated with the gut microbiome and immune dysregulation, particularly through the JAK/STAT pathway in response to environmental pollution.

(C-reactive protein), faecal calprotectin, and SCFAs, serve as key indicators of microbial and immune dysregulation [242, 243]. Biomarkers associated with the gut microbiome and immune dysregulation, particularly those related to the JAK/STAT pathway in response to contaminant exposure, are shown in Fig. 6.

Furthermore, Jin et al. showed that beryllium sulphate induces epithelial-mesenchymal transition (EMT) via JAK/STAT modulation, illustrating the involvement of this pathway in cellular transformation and fibrosis. Another crucial aspect of the role of the JAK/STAT pathway in immune dysregulation is its relevance in assessing the health effects of pollution [244]. Liu et al. investigated how hydrogen sulphide attenuated myocardial fibrosis via JAK/STAT signalling, demonstrating the potential of the pathway for therapeutic targeting [245]. Similarly, Ji et al. found that nitrogen dioxide exposure exacerbated airway inflammation via JAK/STAT activation, highlighting its role in systemic inflammation and respiratory pathophysiology [246]. In addition, Mobasher et al. reported that *Annona squamosa* extract exhibited protective effects against testicular injury by modulating JAK-1/STAT-3/SOCS-1 signalling, suggesting a potential pharmacological intervention against contaminant-induced toxicity [247]. Furthermore, Kim et al. provided evidence that prenatal exposure to bisphenol compounds induces epigenetic modifications, specifically DNA methylation, which may alter immune function via JAK/STAT signalling [248]. These findings highlight the need for further research into epigenetic regulation as a mediating factor in contaminant-induced immune dysregulation.

In conclusion, these studies highlight the importance of understanding the effect of pollutants on JAK/STAT signalling to assess their impact on gut microbiome health and immune dysregulation. Given the increasing prevalence of pollution-related diseases, targeted therapeutic strategies to restore microbial homeostasis and modulate JAK/STAT activity may offer novel approaches to mitigate pollutant-induced inflammatory and metabolic disorders.

Role of the TLR4/MyD88 pathway in environmental pollutant-induced immune dysregulation and inflammatory disorders. The Toll-like receptor 4 (TLR4)/myeloid differentiation primary response gene 88 (MyD88) signalling pathway has been extensively documented as a critical mediator in microbial sensing and regulation of inflammatory responses through innate immune activation [249]. These functions are closely linked to the gut microbiome and its interactions with environmental contaminants, which can alter the microbial composition and immune homeostasis. TLR4, a well-characterised pattern recognition receptor (PRR), is responsible for recognising microbial components such as lipopolysaccharides (LPS) from Gram-negative bacteria, triggering downstream immune

signalling via the MyD88 adaptor protein, ultimately leading to nuclear factor kappa B (NF-κB) activation and pro-inflammatory cytokine release [250]. Within the gastrointestinal tract, this pathway is fundamental in maintaining immune balance, regulating microbial diversity, and modulating inflammatory responses to external stressors [185].

Exposure to environmental pollutants, including fine $PM_{2.5}$, heavy metals, POPs, and EDCs, has been shown to disrupt the gut microbiome, leading to dysbiosis and aberrant immune activation [13, 109]. Dysbiotic changes, characterised by an increased abundance of pro-inflammatory bacterial taxa and a reduction in beneficial microbial populations, have been shown to lead to overactivation of the TLR4/MyD88 signalling cascade, triggering chronic low-grade inflammation and oxidative stress [251]. This inflammatory state has been implicated in the pathogenesis of numerous diseases, including gastrointestinal disorders (e.g., inflammatory bowel disease and colorectal cancer) [252, 253], metabolic syndromes (e.g., type 2 diabetes and obesity) [254], and systemic inflammatory conditions (e.g. cardiovascular disease and neurodegenerative disorders) [255, 256]. In addition, pollutants have been shown to increase intestinal permeability by compromising tight junction integrity, facilitating endotoxin translocation and systemic immune activation, further exacerbating disease progression [190].

Recent research highlights the central role of the TLR4/MyD88 pathway in mediating the inflammatory effects of environmental pollutants, particularly $PM_{2.5}$, heavy metal contaminants, and wastewater-derived pollutants, which have been shown to have profound effects on both gastrointestinal and respiratory health [257-259]. Specifically, Wu et al. reported that $PM_{2.5}$ exposure-induced lung epithelial injury was exacerbated by TLR4/MyD88-mediated autophagy dysregulation, linking air pollutants to lung inflammation [258]. Similarly, Liu et al. found that exposure to reclaimed water induced acute lung inflammation via the TLR4/MyD88 pathway, further highlighting the role of microbial sensing in pollution-induced respiratory disease [259]. In addition, Wu et al. demonstrated that astragaloside IV, a bioactive compound, alleviated $PM_{2.5}$-induced lung injury by modulating the TLR4/MyD88/NF-κB pathway, offering potential therapeutic interventions for pollution-induced inflammatory diseases [258]. Further investigations have extended these findings, highlighting the role of the TLR4/MyD88 axis in pollutant-induced immune dysregulation across multiple organ systems. He et al. found that urban $PM_{2.5}$ exacerbates allergic lung inflammation via the TLR2/TLR4/MyD88 pathway, leading to airway hyperresponsiveness, a hallmark of asthma [257]. In addition, Wang et al. demonstrated that $PM_{2.5}$ exposure exacerbated airway inflammation in asthmatic mice by activating NF-κB through MyD88 signalling, further supporting the involvement of TLR4/MyD88 in pollution-induced lung pathology [260].

Emerging evidence suggests that targeting the TLR4/MyD88 pathway may be a potential therapeutic approach to mitigate pollutant-induced immune dysregulation. For example, phytochemicals, such as curcumin, resveratrol, and epigallocatechin gallate (EGCG), have been shown to downregulate TLR4/MyD88-mediated inflammation, offering promising avenues for clinical intervention [261-263]. In addition, probiotic supplementation to restore gut microbial homeostasis has been explored to reduce pollutant-induced activation of TLR4/MyD88 signalling, thereby modulating immune responses and alleviating inflammation-related diseases [264].

Collectively, these studies underscore the critical role of the TLR4/MyD88 pathway in environmental pollutant-induced inflammation and highlight its involvement in a range of health disorders, from gastrointestinal and respiratory diseases to metabolic and hepatic dysfunction. Future research should focus on identifying novel biomarkers of pollutant-induced immune activation and developing targeted interventions to modulate TLR4/MyD88 signalling, ultimately improving public health outcomes in polluted environments.

Role of PPAR-γ in gut homeostasis and immune regulation under environmental pollutant-induced suppression. Peroxisome proliferator-activated receptor gamma (PPAR-γ) is a nuclear receptor that is a critical regulator of numerous physiological processes, including immune modulation, regulation of inflammatory responses, lipid and glucose metabolism, and maintenance of gut homeostasis [265]. In particular, its role in promoting anti-inflammatory pathways and modulating the gut microbial composition is essential for maintaining gut health and immune balance. PPAR-γ exerts its effects by controlling the differentiation of regulatory T cells (Tregs), suppressing the production of pro-inflammatory cytokines, and promoting the growth of beneficial gut bacteria, such as those involved in the production of SCFAs, including butyrate [266].

The downregulation of PPAR-γ by contaminant exposure has profound implications for gut health, particularly its effects on intestinal immune homeostasis and epithelial barrier integrity [267]. PPAR-γ plays a central role in modulating the immune system by regulating the balance between pro- and anti-inflammatory responses within gut-associated lymphoid tissue (GALT), preserving epithelial integrity, and inhibiting excessive immune activation in response to microbial antigens [268]. When PPAR-γ activity is suppressed, the resulting immune dysregulation predisposes individuals to chronic low-grade inflammation, which can drive changes in the gut microbiome and promote dysbiosis [269]. This dysbiotic state is often characterised by an overgrowth of pathobionts (*Escherichia coli*, *Clostridium difficile*) and a reduction in beneficial microbes, such as *Bifidobacterium* and *Faecalibacterium*, which produce SCFAs that are essential for maintaining gut barrier function and immune homeostasis [270]. SCFAs, particularly butyrate, serve as energy substrates for intestinal epithelial cells, strengthen tight junction proteins (occludin, claudin-1), and suppress inflammation via epigenetic modifications affecting NF-κB signalling [271, 272].

In addition to altering the composition of the gut microbiota, PPAR-γ downregulation impairs immune tolerance mechanisms, rendering the gut more susceptible to chronic inflammation, increased intestinal permeability (also known as "leaky gut"), and gastrointestinal disorders, such as inflammatory bowel disease and irritable bowel syndrome [273, 274]. Furthermore, disruption of PPAR-γ signalling has been shown to increase intestinal permeability by compromising tight junction integrity, leading to endotoxaemia, a condition in which bacterial endotoxins such as lipopolysaccharides translocate from the intestinal lumen into the systemic circulation, exacerbating immune activation and systemic inflammation [275, 276]. This process has been implicated in the pathogenesis of metabolic disorders, such as obesity, type 2 diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD), as well as neuroinflammatory diseases, such as Parkinson's and Alzheimer's [277].

In summary, accumulating evidence underscores the central role of PPAR-γ in regulating immune responses, maintaining gut microbiota homeostasis, and preserving gut barrier integrity. The pollutant-induced downregulation of PPAR-γ represents a critical molecular mechanism underlying dysbiosis, chronic inflammation, and increased disease susceptibility in multiple organ systems. Further research is warranted to identify novel biomarkers of PPAR-γ suppression and develop targeted interventions to mitigate environmental pollutant-induced gut and systemic inflammation, ultimately improving public health outcomes.

Interplay between gut dysbiosis, oxidative stress, and immune dysregulation

Dysbiosis, defined as an imbalance in the composition and function of the gut microbiome, has been shown to trigger several interrelated mechanisms that contribute to oxidative stress, chronic inflammation, and metabolic dysfunction [18]. Changes in microbial populations have been observed to result in the overproduction of potentially harmful metabolites, including trimethylamine N-oxide (TMAO), hydrogen sulphide (H_2S), and secondary bile acids, which can stimulate ROS production in epithelial cells [278, 279]. Table 2 considers the impact of environmental pollutants on the gut microbiota, particularly concerning the mechanisms of dysbiosis and the resulting health effects observed in animal and human studies.

Table 2. Effects of environmental pollutants on the gut microbiota: mechanisms of dysbiosis and health effects in animal models and human studies

N	Study models/ experimental strategy	Relationships studied	Results, key findings	Molecular mechanisms involved	Sources
1	*In vivo* model in pregnant ewes	Relationship between bisphenol A (BPA) exposure, gut microbiota changes, oxidative stress, intestinal and placental apoptosis, and foetal growth restriction	BPA exposure disrupted gut microbiota and led to significant increases in oxidative stress, apoptosis in both intestinal and placental tissues, and foetal growth restriction	BPA-induced dysbiosis activated oxidative stress pathways, including increased ROS production, and disrupted the gut-placental axis, contributing to apoptosis via mitochondrial dysfunction	280
2	*In vivo* CD-1 mouse model	Effects of bisphenol A (BPA) on gut microbiota and bile acid metabolism, focusing on the activation of FXR/TGR5 pathways	BPA exposure led to hepatic steatosis in mice by altering bile acid metabolism and remodelling gut microbiota, which activated the FXR and TGR5 pathways	BPA-induced intestinal dysbiosis disrupted the normal bile acid pool, triggering FXR/TGR5 pathways and contributing to hepatic steatosis	281
3	*In vivo* rat model of perfluorooctanoic acid (PFOA) exposure	Relationship between PFOA exposure, gut microbiota dysbiosis, and liver injury	PFOA exposure caused significant changes in the gut microbiota composition and was associated with liver damage, including hepatocellular damage	PFOA-mediated dysbiosis activated inflammatory pathways, such as NF-κB, and increased oxidative stress, which contributed to liver damage	282
4	*In vivo* C57BL/6 mouse model of bisphenol P (BPP) exposure	Effects of BPP on gut microbiota, gut barrier integrity, and activation of the LPS/TLR4/NF-κB pathway	BPP exposure caused significant gut microbiota dysbiosis and impaired gut barrier function, leading to systemic inflammation and activation of the TLR4/NF-κB pathway	BPP promoted gut dysbiosis and intestinal permeability, which triggered systemic inflammation via the TLR4/NF-κB axis, exacerbating oxidative stress	283
5	*In vivo* CD-1 mouse model	Role of gut microbiota in mediating the effects of bisphenol A (BPA) exposure on hepatic steatosis via the gut-liver axis	BPA exposure led to significant gut microbiota dysbiosis and activation of the gut-liver axis, contributing to hepatic steatosis	BPA-associated dysbiosis altered gut microbial metabolites, triggering activation of the gut-liver axis and promoting liver fat accumulation	284
6	*In vivo* rat model exposed to bisphenol A (BPA)	Effects of BPA on reproductive toxicity, gut microbiota dysbiosis, and reproductive organ function	BPA exposure disrupted the gut microbiota composition and led to reproductive toxicity, including reduced sperm quality and altered reproductive hormone levels	BPA-induced dysbiosis affected gut microbiota-derived metabolites, which in turn affected the hypothalamic-pituitary-gonadal axis, leading to hormonal imbalances	285
7	*In vivo* CD-1 mouse model of bisphenol A (BPA) exposure and curcumin supplementation	Protective effect of curcumin on BPA-induced hepatic steatosis through modulation of gut microbiota and activation of the gut-liver axis	Curcumin supplementation attenuated BPA-induced hepatic steatosis by restoring the gut microbiota composition and regulating the gut-liver axis	Curcumin reduced BPA-induced inflammation and oxidative stress by modulating gut microbiota, restoring FXR signalling, and reducing liver lipid accumulation	286
8	*In vivo* juvenile crucian carp model exposed to tartrazine	Effects of tartrazine exposure on oxidative stress, immune dysfunction, and gut microbiota dysbiosis	Tartrazine exposure caused oxidative stress, immune dysfunction, and gut microbiota dysbiosis in juvenile crucian carp	Tartrazine exposure induced ROS production, leading to oxidative damage, while dysbiosis promoted immune dysfunction and altered gut integrity	287
9	*In vivo* crucian carp model exposed to diazinon	Effect of diazinon on gut microbiota, oxidative stress, immune dysfunction, and histopathological damage	Diazinon exposure resulted in gut microbiota dysbiosis, histological damage, immune system disruption, and oxidative stress	Diazinon activated oxidative stress pathways and immune dysfunction through dysbiosis, while histopathological damage was associated with increased ROS production	288
10	*In vivo* zebrafish model exposed to polystyrene nano-/microplastics	Impact of microplastics on gut microbiota, oxidative stress, and immune function in zebrafish	Exposure to polystyrene nano-/microplastics induced gut microbiota dysbiosis and oxidative stress and disrupted innate immune responses in zebrafish	Microplastics triggered ROS production and altered the immune response via dysbiosis, impairing innate immunity and promoting oxidative damage	289
11	*In vivo* mouse model exposed to fluorene-9-bisphenol	Effect of fluorene-9-bisphenol exposure on gut microbiota and male reproductive toxicity	Fluorene-9-bisphenol exposure resulted in gut microbiota dysbiosis and significant reproductive toxicity in male mice	Fluorene-9-bisphenol-induced dysbiosis affected gut microbiota-derived metabolites, leading to changes in reproductive hormones and testicular function	290
12	*In vivo* black-spotted frog model exposed to PFOA, PFOS, and 6:2 Cl-PFESA	Hepatotoxicity of PFOA, PFOS, and 6:2 Cl-PFESA and their potential link to gut microbiota changes	Exposure to these chemicals led to hepatotoxicity and significant changes in the gut microbiota composition	The chemical exposure triggered liver damage and dysbiosis, leading to increased inflammation and oxidative stress in the liver	291
13	*In vitro* model using *Bacillus* sp. AM1 isolated from the gut microbiota	The ability of *Bacillus* sp. AM1 to biodegrade bisphenol A (BPA)	*Bacillus* sp. AM1 effectively biodegraded BPA, suggesting its potential for detoxification in the gut	The biodegradation of BPA was mediated by enzymatic pathways in *Bacillus* sp. AM1, reducing the toxic effects of BPA in the gut environment	292

The development of chronic inflammation is often associated with persistent oxidative stress and dysbiosis, with pro-inflammatory cytokines (e.g. IL-6, IL-1β, TNF-α) playing a central role in immune dysregulation [293]. Exposure to environmental pollutants, such as $PM_{2.5}$, toxic metals (e.g., cadmium, lead, mercury), and EDCs (e.g., bisphenol A, dioxins, phthalates), activates intracellular signalling pathways, including NF-κB, JAK/STAT, and MAPK, leading to upregulation of cytokines and inflammatory mediators [294]. This sustained inflammatory response promotes immune dysregulation, establishing a cycle of tissue damage, oxidative stress, and chronic immune activation [294]. Dysbiosis exacerbates this effect by altering antigen presentation, reducing regulatory T-cell (Treg) activity, and impairing immune tolerance, thereby increasing susceptibility to autoimmune disease [295].

Mitochondrial dysfunction is a significant consequence of oxidative stress. It contributes

to systemic metabolic disorders, such as obesity, type 2 diabetes, and non-alcoholic fatty liver disease, through impaired electron transport chain function, impaired ATP production, and increased ROS accumulation. This inefficiency affects cellular energy requirements and contributes to insulin resistance, lipid dysregulation, and altered energy homeostasis [296-298].

The intestinal barrier is critical for maintaining intestinal homeostasis by preventing the translocation of harmful substances and pathogens into the systemic circulation. This barrier is primarily maintained by tight junction proteins, including occludin, claudins, and zonula occludens-1 (ZO-1), which form a selective seal between epithelial cells [190, 299]. However, disruption of these tight junctions, often triggered by oxidative stress, pro-inflammatory cytokines, microbial dysbiosis, and exposure to contaminants, leads to increased intestinal permeability, commonly called 'leaky gut' [190, 275]. When the epithelial barrier is compromised, endotoxins such as LPS access the bloodstream, triggering immune activation, endotoxaemia, and systemic inflammation. This persistent state of inflammation exacerbates epithelial damage, reinforcing a damaging cycle of gut barrier dysfunction and chronic disease development [300, 301].

The systemic effects of gut barrier dysfunction have been extensively studied. Increased intestinal permeability and gut-derived inflammation have been directly linked to metabolic disorders, neurodegenerative diseases, and immune dysregulation [183]. Chronic low-grade inflammation resulting from impaired gut integrity disrupts insulin signalling pathways and lipid metabolism, thereby contributing to the pathogenesis of obesity, insulin resistance, and metabolic syndrome [302]. In addition, translocated bacterial endotoxins and circulating pro-inflammatory mediators have been implicated in the development of neuroinflammatory conditions, including Alzheimer's disease and Parkinson's disease, through mechanisms involving the gut-brain axis, microglial activation, and oxidative damage in neuronal cells [183, 303]. In addition, dysregulation of immune responses by gut-derived antigens promotes immune over-activation and loss of self-tolerance, increasing the risk of autoimmune diseases, e.g., inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis [304, 305]. Gut-derived inflammation also compromises the effectiveness of the host's immune defences, increasing susceptibility to systemic infections and chronic inflammatory conditions [306].

Thus, gut barrier dysfunction is a critical link between environmental exposures, gut dysbiosis, and the onset of systemic disease. Understanding the interplay between microbial imbalances, oxidative stress, and immune dysregulation is essential for developing targeted therapeutic strategies, including microbiome-modulating interventions, antioxidant therapies, and dietary approaches, to restore gut homeostasis and mitigate pollutant-induced health risks.

Therapeutic strategies to restore gut homeostasis

Therapeutic strategies to restore gut homeostasis involve a multifaceted approach, including microbiota modulation through probiotics, prebiotics, synbiotics, faecal microbiota transplantation (FMT), dietary interventions, immune modulation, and targeted antimicrobial therapies [180]. These interventions target the microbial composition, immune function, oxidative stress, and gut barrier integrity to counteract dysbiosis and its associated pathological consequences [307].

Probiotics, prebiotics, and synbiotics are key therapeutic agents synergistically modulating gut microbiota composition, enhancing SCFA production, regulating inflammatory pathways, and strengthening epithelial barrier function [308]. Probiotics, which are live beneficial microorganisms (e.g., *Bifidobacterium*, *Lactobacillus*), facilitate microbial competition by colonising the gut and outcompeting pathogenic species [36, 309].

Prebiotics, including inulin and fructooligosaccharides, are non-digestible dietary fibres that selectively stimulate the growth of beneficial microbes and promote SCFA synthesis [310, 311]. SCFAs, particularly butyrate, acetate, and propionate, play a critical role in maintaining gut health by serving as an energy source for colonocytes, strengthening tight junctions, and modulating the immune response through inhibition of NF-κB signalling [31, 312].

In addition to their role in microbial modulation, probiotics and prebiotics reduce oxidative stress by enhancing antioxidant defence mechanisms [313]. For example, butyrate has been shown to suppress NF-κB activation and promote the expression of antioxidant enzymes, such as superoxide dismutase and catalase, thereby mitigating oxidative damage [314]. Probiotic strains such as *Lactobacillus rhamnosus* have also been shown to stimulate glutathione production, an important intracellular antioxidant that neutralises ROS and protects against inflammation-induced cell damage [315].

Polyphenols, i.e., naturally occurring antioxidants in fruits, vegetables, and tea, play a critical role in gut health by modulating microbial diversity and reducing oxidative stress [316]. These bioactive compounds are metabolised by the gut microbiota into secondary metabolites, which act as signalling molecules that strengthen the gut barrier's integrity and influence immune responses [317]. Postbiotics, i.e., bioactive microbial-derived compounds (SCFAs, peptides, and extracellular vesicles), have emerged as promising therapeutic agents that regulate inflammatory pathways, improve epithelial barrier function, and modulate mitochondrial activity [318].

Faecal microbiota transplantation (FMT) is an advanced therapeutic strategy designed to restore gut homeostasis by reintroducing a diverse and functional microbiome from a healthy donor to a recipient [319]. This intervention has shown clinical efficacy in certain conditions, such as recurrent *Clostridioides difficile* infection and inflammatory bowel disease, by replenishing microbial diversity, reducing pathogen overgrowth, and enhancing SCFA production [320].

Finally, selective antibiotics and postbiotics play a role in modulating the microbial composition by reducing pathogenic bacterial loads while promoting beneficial microbial interactions. Precision antibiotics such as rifaximin have been used to selectively target harmful bacteria without significantly disrupting the commensal microbiota, thereby preserving gut homeostasis [321, 322]. Emerging therapeutic avenues, including microbiome-based personalised medicine and engineered bacterial consortia, hold promise for optimising gut health and mitigating microbiota-associated diseases in the future [323].

These therapeutic interdependencies are illustrated in Fig. 7, highlighting the interrelated

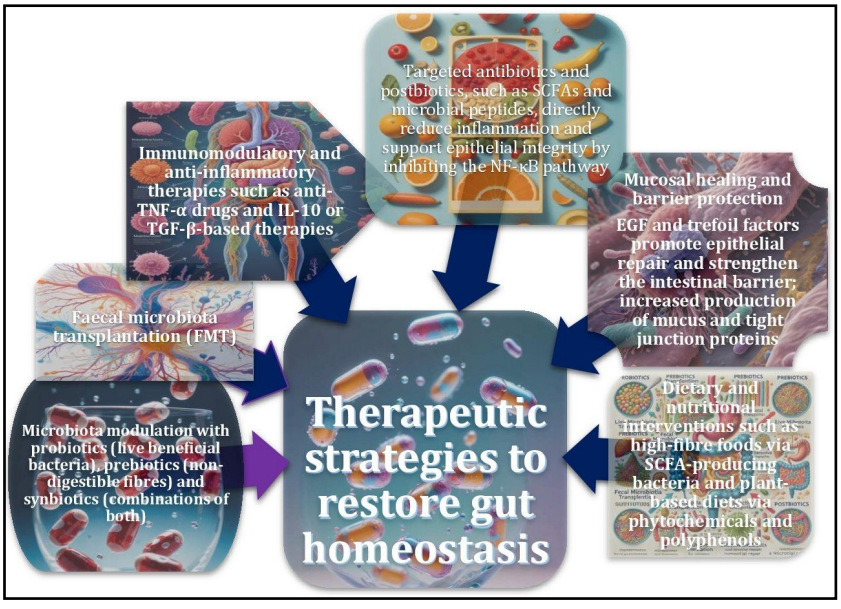

Fig. 7. Therapeutic strategies to restore intestinal homeostasis in the presence of contamination. Therapeutic strategies to restore gut homeostasis include probiotics, prebiotics, synbiotics, FMT, dietary interventions, immune modulation and targeted antibiotics. These strategies work in synergy to balance the microbiota, reduce inflammation and promote gut health.

Table 3. Summary of research on environmental toxins, gut microbiota, protective interventions, key findings, and mechanisms in animal models and human studies. Notes: EGCG – epigallocatechin gallate; TNF-α – tumour necrosis factor-alpha; BPA – bisphenol A; PPAR – peroxisome proliferator-activated receptor; 16S rRNA – 16S ribosomal RNA; MS – multiple sclerosis; NMN – Nicotinamide mononucleotide, a precursor of NAD+ which plays a role in cellular energy metabolism and repair processes; CCA – Canonical Correlation Analysis; PFBS – Perfluorobutane sulphonate, perfluoroalkyl substance

N	Study models/ experimental strategy	Relationships studied	Results, key findings	Molecular mechanisms involved	Sources
1	*In vivo*, mice, BPA and EGCG	Effect of EGCG in preventing BPA-induced metabolic disorders in mice	EGCG alleviates BPA-induced metabolic disorders by improving glucose metabolism and insulin sensitivity	EGCG reduces oxidative stress and affects metabolic pathways, improving insulin resistance	330
2	*In vivo*, rats, BPA and EGCG	Effect of EGCG and green tea extract on BPA-induced metabolic disorders in rats	EGCG and green tea extract alleviate BPA-induced metabolic disorders by reducing oxidative stress and inflammation	EGCG modulates metabolic pathways, reduces inflammatory cytokines, and improves glucose metabolism	331
3	*In vivo*, *Danio rerio* embryos, BPA and EGCG	Protective effect of EGCG against BPA-induced impairment of cardiogenesis in *Danio rerio* embryos	EGCG counteracts BPA-induced heart damage and supports heart development in embryos	EGCG reduces oxidative stress, promotes heart development, and reduces BPA toxicity	332
4	*In vitro*, human pulmonary epithelial cells	Effect of amino acids on epithelial function in lung disease	Amino acids support epithelial function in lung diseases, improving epithelial barrier integrity	Amino acids modulate signalling pathways to help maintain epithelial barrier integrity	333
5	*In vitro*, glial and immune cells	Interaction of melatonin, orexin, and ceramide in mitochondrial dysfunction in glial and immune cells	Melatonin, orexin, and ceramide interact to influence mitochondrial function and immune cell activity	These molecules modulate mitochondrial function in immune and glial cells, thereby influencing inflammation	334
6	*In vivo*, rats, BPA diet and probiotics	Role of probiotics in reducing BPA toxicity through modulation of gut microbiota	Probiotics mitigate BPA toxicity by improving the gut microbiota composition and gut barrier function	Probiotics promote BPA detoxification by modulating gut microbiota and reducing oxidative stress	335
7	*In vivo*, zebrafish larvae, PFBS and probiotics	Effect of probiotics on PFBS toxicity in zebrafish larvae	Probiotics reduce PFBS toxicity in zebrafish larvae and support development	Probiotics improve gut microbiota, reduce inflammation, and support larval development	336
8	*In vivo*, mice, sleep deprivation and NMN	Effect of NMN on sleep deprivation-induced gut microbiota dysbiosis	NMN improves the gut microbiota composition and restores gut resilience after sleep deprivation	NMN modulates gut microbiota and activates immune cells, improving gut barrier integrity	337
9	*In vitro*, human gut microbiota, green tea	Effect of green tea on human gut microbiota	Green tea improves the gut microbiota composition and increases populations of beneficial bacteria	Polyphenols in green tea, particularly EGCG, modulate gut microbiota and support gut health	338
10	Review study, various human and animal models, gut microbiota modulators	Role of various gut microbiota modulators in improving health	Probiotics, prebiotics, and other substances significantly affect the gut microbiota composition and offer therapeutic potential	These agents act by modulating the immune system, reducing oxidative stress, and improving the integrity of the intestinal barrier	339
11	*In vivo*, mice, diet-induced obesity and thyme extract	Effect of thyme extract on gut dysbiosis and inflammation in diet-induced obesity	Thyme extract has antioxidant effects, reduces inflammation, and improves the gut microbiota composition in obese mice	Thyme extract reduces oxidative stress and inflammation and improves gut microbiota balance	340

roles of probiotics, prebiotics, dietary components, and immunomodulatory agents in maintaining gut homeostasis. Future research should focus on refining these interventions to improve their clinical applicability, safety, and long-term efficacy in microbiome-associated disorders.

Role of antioxidants in protecting gut microbiota from oxidative stress induced by environmental pollutants

Antioxidants are critical in protecting the gut microbiota from oxidative stress induced by environmental pollutants [324]. Antioxidants exert their protective effects on gut microbiota health through several molecular pathways. One key pathway is the activation of Nrf2, which induces the expression of antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase. These enzymes are essential in alleviating oxidative stress caused by pollutants [325, 326]. In addition, antioxidants have been shown to suppress the NF-κB pathway, thereby reducing the production of pro-inflammatory cytokines, such as TNF-α and IL-6, which can disrupt the gut microbiome [327, 328]. Antioxidants support the phosphoinositide 3-kinase/Akt (PI3K/Akt) pathway, which promotes cell survival and

resistance to oxidative damage by stabilising tight junction proteins and maintaining the integrity of the intestinal barrier, thereby preventing microbial dysbiosis [329]. By preserving gut barrier function and microbial diversity, antioxidants promote the production of SCFAs, which are essential for gut health [312]. These processes reduce oxidative stress and inflammation and help maintain the balance of beneficial bacteria within the gut microbiota, improving the overall stability of the gut ecosystem. Table 3 provides a detailed summary of experimental models, key findings, and molecular mechanisms from recent studies showing the biological effects of environmental and dietary exposures on gut microbiota health.

Synthetic antioxidants, such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT), are commonly used in food preservation and have been shown to reduce oxidative stress in a similar way to natural antioxidants [341]. In addition, N-acetylcysteine (NAC), a glutathione precursor, enhances the body's intrinsic antioxidant defences and supports gut microbiota health under contaminant exposure [342, 343]. Polyphenols also promote the growth of beneficial microbes, such as *Bifidobacterium* and *Lactobacillus*, which contribute to antioxidant defences by producing beneficial metabolites [344]. By reducing oxidative stress and inflammation, antioxidants positively impact gut barrier integrity, promote microbial diversity, and counteract the adverse effects of environmental pollutants on gut health [141, 324].

Individual variability in microbiota responses to environmental contaminants

A critical area for future research is understanding the individual variability in microbiota responses to environmental contaminants. Genetic factors, including polymorphisms of genes involved in regulating the immune response, play a key role in detoxification enzymes and determining the resistance or susceptibility of the microbiome to harmful environmental factors [345, 346]. These genetic variations can significantly influence the ability of the microbiota to cope with oxidative stress and other forms of damage caused by pollutants [346]. In addition, lifestyle factors (diet, physical activity, and stress levels) have been shown to modulate the microbial composition and functionality, further influencing the microbiota response to pollutant exposure [30]. For example, the diet can enhance or impair the gut's ability to detoxify pollutants [109]. At the same time, physical activity and stress can alter gut permeability and immune system function, affecting microbial diversity and activity [347, 348].

It is essential to unravel the complex interplay between genetic and environmental determinants to fully understand the mechanisms underlying these responses, as this will allow the identification of vulnerable populations who may require targeted interventions. Personalised healthcare approaches that consider genetic predisposition and environmental exposures will be crucial to improve the efficacy of interventions to protect gut microbiota health [349]. Emerging multi-omics techniques, such as metagenomics, transcriptomics, and metabolomics, are promising to advance our understanding of these interactions. These cutting-edge approaches allow comprehensive analysis of the microbiome at multiple levels (DNA, RNA, and metabolites) and have the potential to provide new insights into the influence of environmental factors on microbial ecosystems and associated health outcomes [350, 351]. As these technologies evolve, they are likely to uncover novel biomarkers and therapeutic targets that can inform the development of more effective personalised strategies to mitigate the health effects of pollutant exposure.

Innovations in microbiota-targeted therapies

Innovations in microbiota-targeted therapies represent a promising approach to mitigate pollutant-induced dysbiosis. Precision-based interventions, such as personalised probiotics and prebiotics, aim to restore microbial balance by tailoring treatments to

individual microbiome profiles. These personalised strategies aim to optimise the microbial composition, enhance gut barrier integrity, and improve metabolic functions based on the unique characteristics of the individual's microbiota [352, 353]. In addition, synthetic biology approaches, which involve the development of engineered microbes designed to detoxify pollutants or produce specific metabolites, offer novel therapeutic opportunities. These engineered microbes can potentially be used to degrade environmental toxins or enhance the production of beneficial metabolites, e.g., short-chain fatty acids, which support gut health and reduce inflammatory responses [354].

However, despite these interventions' promise, pollutant exposure's long-term effects on both the microbiota and host health remain poorly understood. The chronic effects of pollutant exposure on microbial dynamics, host immunity, and metabolic processes are not fully understood, and existing studies often focus on short-term outcomes. Longitudinal studies are therefore essential to assess the impact of prolonged exposure to environmental pollutants on microbial diversity, functionality, and resulting health outcomes over time. Such studies would provide critical insights into the cumulative effects of pollutants on the microbiome and its role in disease development, paving the way for developing more effective and sustainable microbiota-targeted therapies.

Conclusion

This review emphasises the significant impact of anthropogenic factors on human health and well-being by exploring the complex relationship between the gut microbiota and environmental pollutants. It highlights how exposure to environmental pollutants, such as toxic metals and microplastics, disrupts microbial homeostasis, with consequences that extend beyond the gastrointestinal tract, affecting systemic inflammation, cardiovascular health, and neurodegenerative diseases. These pollutants can alter the microbial composition and functionality, leading to an imbalance that can lead to chronic health conditions. A particularly worrying factor discussed in the review is the role of antibiotic resistance. The environmental spread of antibiotic resistance genes through mobile genetic elements exacerbates the adverse effects of pollutants on microbial ecosystems, potentially leading to the proliferation of resistant pathogens.

Furthermore, the interplay between pollutant-induced redox imbalances and gut dysbiosis further complicates health risks. This disruption compromises the integrity of the gut barrier, promotes chronic inflammation, and induces oxidative stress, all of which are central to the development of systemic disease. Alterations in microbial populations can disrupt gut immune functions, compromising defence against environmental toxins and pathogens.

The key molecular pathways, including NF-κB, Nrf2/Keap1, PI3K/AKT, p38-MAPK, JAK/STAT, and TLR4/MyD88, have been identified as central regulators. These pathways are crucial in modulating inflammation, immune responses, and antioxidant mechanisms. They provide valuable insights into the molecular mechanisms underlying the effects of pollutant-induced oxidative stress and inflammation. Understanding these pathways is essential for developing effective therapeutic interventions targeting molecular and cellular processes contributing to microbial dysbiosis and associated health problems.

Therapeutic strategies aimed at mitigating the adverse effects of dysbiosis and oxidative stress have been shown to focus on antioxidants, microbial modulation, and advanced therapeutic approaches aimed at restoring gut homeostasis. Such strategies may include prebiotics, probiotics, and bioactive compounds to support beneficial microbiota, alongside targeted antioxidant treatments to reduce oxidative damage. However, significant knowledge gaps remain, particularly regarding the variability of individual microbiota responses

to pollutants and the long-term efficacy of proposed interventions. Individualised treatment plans based on personalised microbiome analysis may prove essential in optimising therapeutic outcomes. By investigating the interactions of pollutants with the microbiome at both the individual and ecological level, researchers can gain critical insights into the broader health effects of environmental pollution. There is also an urgent need to develop targeted therapeutics tailored to individual microbiota profiles. This comprehensive approach is critical to mitigating the health risks of pollution and maintaining systemic well-being in an increasingly polluted world.

Acknowledgments

Natalia Kurhaluk, ORCID: https://orcid.org/0000-0002-4669-1092
Piotr Kamiński, ORCID: https://orcid.org/0000-0003-1978-6018
Halina Tkaczenko, ORCID: https://orcid.org/0000-0003-3951-9005

Disclosure Statement

The authors have no competing interests to declare.

References

1 Tchounwou, P.B.; Yedjou, C.G.; Patlolla, A.K.; Sutton, D.J. Heavy metal toxicity and the environment. *Exp. Suppl.* 2012, *101*, 133-164. https://doi.org/10.1007/978-3-7643-8340-4_6.

2 Balali-Mood, M.; Naseri, K.; Tahergorabi, Z.; Khazdair, M.R.; Sadeghi, M. Toxic Mechanisms of Five Heavy Metals: Mercury, Lead, Chromium, Cadmium, and Arsenic. *Front. Pharmacol*. 2021, *12*, 643972. https://doi.org/10.3389/fphar.2021.643972.

3 Guo, W.; Pan, B.; Sakkiah, S.; Yavas, G.; Ge, W.; Zou, W.; Tong, W.; Hong, H. Persistent Organic Pollutants in Food: Contamination Sources, Health Effects and Detection Methods. *Int. J. Environ. Res. Public Health* 2019, *16*(22), 4361. https://doi.org/10.3390/ijerph16224361.

4 Montano, L.; Pironti, C.; Pinto, G.; Ricciardi, M.; Buono, A.; Brogna, C.; Venier, M.; Piscopo, M.; Amoresano, A.; Motta, O. Polychlorinated Biphenyls (PCBs) in the Environment: Occupational and Exposure Events, Effects on Human Health and Fertility. *Toxics* 2022, *10*(7), 365. https://doi.org/10.3390/toxics10070365.

5 Ziani, K.; Ioniță-Mîndrican, C.B.; Mititelu, M.; Neacșu, S.M.; Negrei, C.; Moroșan, E.; Drăgănescu, D.; Preda, O.T. Microplastics: A Real Global Threat for Environment and Food Safety: A State of the Art Review. *Nutrients* 2023, *15*(3), 617. https://doi.org/10.3390/nu15030617.

6 Ghosh, S.; Sinha, J.K.; Ghosh, S.; Vashisth, K.; Han, S.; Bhaskar, R. Microplastics as an Emerging Threat to the Global Environment and Human Health. *Sustainability* 2023, *15*, 10821.https://doi.org/10.3390/su151410821.

7 Zhang, W.; Guo, R.; Yang, Y.; Ding, J.; Zhang, Y. Long-term effect of heavy-metal pollution on diversity of gastrointestinal microbial community of *Bufo raddei*. *Toxicol. Lett.* 2016, *258*, 192-197. https://doi.org/10.1016/j.toxlet.2016.07.003.

8 Richardson, J.B.; Dancy, B.C.R.; Horton, C.L.; Lee, Y.S.; Madejczyk, M.S.; Xu, Z.Z.; Ackermann, G.; Humphrey, G.; Palacios, G.; Knight, R.; Lewis, J.A. Exposure to toxic metals triggers unique responses from the rat gut microbiota. *Sci. Rep.* 2018, *8*(1), 6578. https://doi.org/10.1038/s41598-018-24931-w.

9 Assefa, S.; Köhler, G. Intestinal Microbiome and Metal Toxicity. *Curr. Opin. Toxicol.* 2020, *19*, 21-27. https://doi.org/10.1016/j.cotox.2019.09.009.

10 Polianciuc, S.I.; Gurzău, A.E.; Kiss, B.; Ștefan, M.G.; Loghin, F. Antibiotics in the environment: causes and consequences. *Med. Pharm. Rep.* 2020, *93*(3), 231-240. https://doi.org/10.15386/mpr-1742.

11 Pathak, V.M.; Verma, V.K.; Rawat, B.S.; Kaur, B.; Babu, N.; Sharma, A.; Dewali, S.; Yadav, M.; Kumari, R.; Singh, S.; Mohapatra, A.; Pandey, V.; Rana, N.; Cunill, J.M. Current status of pesticide effects on environment, human health and it's eco-friendly management as bioremediation: A comprehensive review. *Front. Microbiol.* 2022, *13*, 962619. https://doi.org/10.3389/fmicb.2022.962619.

12 Manyi-Loh, C.; Mamphweli, S.; Meyer, E.; Okoh, A. Antibiotic Use in Agriculture and Its Consequential Resistance in Environmental Sources: Potential Public Health Implications. *Molecules* 2018, *23*(4), 795. https://doi.org/10.3390/molecules23040795.

13 Singh, S.; Sharma, P.; Pal, N.; Kumawat, M.; Shubham, S.; Sarma, D.K.; Tiwari, R.R.; Kumar, M.; Nagpal, R. Impact of Environmental Pollutants on Gut Microbiome and Mental Health via the Gut-Brain Axis. *Microorganisms* 2022, *10*(7), 1457. https://doi.org/10.3390/microorganisms10071457.

14 Rio, P.; Gasbarrini, A.; Gambassi, G.; Cianci, R. Pollutants, microbiota and immune system: frenemies within the gut. *Front. Public Health* 2024, *12*, 1285186. https://doi.org/10.3389/fpubh.2024.1285186.

15 Rowland, I.; Gibson, G.; Heinken, A.; Scott, K.; Swann, J.; Thiele, I.; Tuohy, K. Gut microbiota functions: metabolism of nutrients and other food components. *Eur. J. Nutr.* 2018, *57*(1), 1-24. https://doi.org/10.1007/s00394-017-1445-8.

16 Afzal, S.; Abdul, Manap, A.S.; Attiq, A.; Albokhadaim, I.; Kandeel, M.; Alhojaily, S.M. From imbalance to impairment: the central role of reactive oxygen species in oxidative stress-induced disorders and therapeutic exploration. *Front. Pharmacol.* 2023, *14*, 1269581. https://doi.org/10.3389/fphar.2023.1269581.

17 Mittal, M.; Siddiqui, M.R.; Tran, K.; Reddy, S.P.; Malik, A.B. Reactive oxygen species in inflammation and tissue injury. *Antioxid. Redox Signal.* 2014, *20*(7), 1126-1167. https://doi.org/10.1089/ars.2012.5149.

18 Mostafavi Abdolmaleky, H.; Zhou, J.-R. Gut Microbiota Dysbiosis, Oxidative Stress, Inflammation, and Epigenetic Alterations in Metabolic Diseases. *Antioxidants* 2024, *13*, 985. https://doi.org/10.3390/antiox13080985.

19 Liu, B.N.; Liu, X.T.; Liang, Z.H.; Wang, J.H. Gut microbiota in obesity. *World J. Gastroenterol.* 2021, *27*(25), 3837-3850. https://doi.org/10.3748/wjg.v27.i25.3837.

20 Asadi, A.; Shadab Mehr, N.; Mohamadi, M.H.; Shokri, F.; Heidary, M.; Sadeghifard, N.; Khoshnood, S. Obesity and gut-microbiota-brain axis: A narrative review. *J. Clin. Lab. Anal.* 2022, *36*(5), e24420 https://doi.org/10.1002/jcla.24420.

21 Saad, M.J.; Santos, A.; Prada, P.O. Linking Gut Microbiota and Inflammation to Obesity and Insulin Resistance. *Physiology (Bethesda)* 2016, *31*(4), 283-93. https://doi.org/10.1152/physiol.00041.2015.

22 Gurung, M.; Li, Z.; You, H.; Rodrigues, R.; Jump, D.B.; Morgun, A.; Shulzhenko, N. Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine* 2020, *51*, 102590. https://doi.org/10.1016/j.ebiom.2019.11.051.

23 Zhou, Z.; Sun, B.; Yu, D.; Zhu, C. Gut Microbiota: An Important Player in Type 2 Diabetes Mellitus. *Front. Cell. Infect. Microbiol.* 2022, *12*, 834485. https://doi.org/10.3389/fcimb.2022.834485.

24 Hou, K.; Wu, Z.X.; Chen, X.Y.; Wang, J.Q.; Zhang, D.; Xiao, C.; Zhu, D.; Koya, J.B.; Wei, L.; Li, J.; Chen, Z.S. Microbiota in health and diseases. *Signal Transduct. Target. Ther.* 2022, *7*(1), 135.https://doi.org/10.1038/s41392-022-00974-4.

25 Yoo, J.Y.; Sniffen, S.; McGill Percy, K.C.; Pallaval, V.B.; Chidipi, B. Gut Dysbiosis and Immune System in Atherosclerotic Cardiovascular Disease (ACVD). *Microorganisms* 2022, *10*, 108.https://doi.org/10.3390/microorganisms10010108.

26 Nesci, A.; Carnuccio, C.; Ruggieri, V.; D'Alessandro, A.; Di Giorgio, A.; Santoro, L.; Gasbarrini, A.; Santoliquido, A.; Ponziani, F.R. Gut Microbiota and Cardiovascular Disease: Evidence on the Metabolic and Inflammatory Background of a Complex Relationship. *Int. J. Mol. Sci.* 2023, *24*(10), 9087. https://doi.org/10.3390/ijms24109087.

27 Manisalidis, I.; Stavropoulou, E.; Stavropoulos, A.; Bezirtzoglou, E. Environmental and Health Impacts of Air Pollution: A Review. *Front. Public Health* 2020, *8*, 14. https://doi.org/10.3389/fpubh.2020.00014.

28 Jandhyala, S.M.; Talukdar, R.; Subramanyam, C.; Vuyyuru, H.; Sasikala, M.; Nageshwar Reddy, D. Role of the normal gut microbiota. *World J Gastroenterol*. 2015, *21*(29), 8787-8803. https://doi.org/10.3748/wjg.v21.i29.8787.

29 Gilbert, J.A.; Blaser, M.J.; Caporaso, J.G.; Jansson, J.K.; Lynch, S.V.; Knight, R. Current understanding of the human microbiome. *Nat. Med.* 2018, *24*(4), 392-400. https://doi.org/10.1038/nm.4517.

30 Conlon, M.A.; Bird, A.R. The impact of diet and lifestyle on gut microbiota and human health. *Nutrients* 2014, *7*(1), 17-44. https://doi.org/10.3390/nu7010017.

31 Facchin, S.; Bertin, L.; Bonazzi, E.; Lorenzon, G.; De Barba, C.; Barberio, B.; Zingone, F.; Maniero, D.; Scarpa, M.; Ruffolo, C.; et al. Short-Chain Fatty Acids and Human Health: From Metabolic Pathways to Current Therapeutic Implications. *Life* 2024, *14*, 559. https://doi.org/10.3390/life14050559.

32 Fusco, W.; Lorenzo, M.B.; Cintoni, M.; Porcari, S.; Rinninella, E.; Kaitsas, F.; Lener, E.; Mele, M.C.; Gasbarrini, A.; Collado, M.C.; Cammarota, G.; Ianiro, G. Short-Chain Fatty-Acid-Producing Bacteria: Key Components of the Human Gut Microbiota. *Nutrients* 2023, *15*(9), 2211. https://doi.org/10.3390/nu15092211.

33 Bonaz, B.; Bazin, T.; Pellissier, S. The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis. *Front. Neurosci.* 2018, *12*, 49. https://doi.org/10.3389/fnins.2018.00049.

34 Bonaz, B.; Sinniger, V.; Pellissier, S. The Vagus Nerve in the Neuro-Immune Axis: Implications in the Pathology of the Gastrointestinal Tract. *Front. Immunol.* 2017, *8*, 1452. https://doi.org/10.3389/fimmu.2017.01452.

35 Milani, C.; Duranti, S.; Bottacini, F.; Casey, E.; Turroni, F.; Mahony, J.; Belzer, C.; Delgado Palacio, S.; Arboleya Montes, S.; Mancabelli, L.; Lugli, G.A.; Rodriguez, J.M.; Bode, L.; de Vos, W.; Gueimonde, M.; Margolles, A.; van Sinderen, D.; Ventura, M. The First Microbial Colonizers of the Human Gut: Composition, Activities, and Health Implications of the Infant Gut Microbiota. *Microbiol. Mol. Biol. Rev.* 2017, *81*(4), e00036-17. https://doi.org/10.1128/MMBR.00036-17.

36 Turroni, F.; Milani, C.; Duranti, S.; Lugli, G.A.; Bernasconi, S.; Margolles, A.; Di Pierro, F.; van Sinderen, D.; Ventura, M. The infant gut microbiome as a microbial organ influencing host well-being. *Ital. J. Pediatr.* 2020, *46*(1), 16 https://doi.org/10.1186/s13052-020-0781-0.

37 Mayer, E.A. Gut feelings: the emerging biology of gut-brain communication. *Nat. Rev. Neurosci.* 2011, *12*(8), 453-466. https://doi.org/10.1038/nrn3071.

38 Taylor, S.L.; Simpson, J.L.; Rogers, G.B. The influence of early-life microbial exposures on long-term respiratory health. *Paediatr. Respir. Rev.* 2021, *40*, 15-23. https://doi.org/10.1016/j.prrv.2021.05.003.

39 Dera, N.; Kosińska-Kaczyńska, K.; Żeber-Lubecka, N.; Brawura-Biskupski-Samaha, R.; Massalska, D.; Szymusik, I.; Dera, K.; Ciebiera, M. Impact of Early-Life Microbiota on Immune System Development and Allergic Disorders. *Biomedicines* 2025, *13*, 121. https://doi.org/10.3390/biomedicines13010121.

40 Ulluwishewa, D.; Anderson, R.C.; McNabb, W.C.; Moughan, P.J.; Wells, J.M.; Roy, N.C. Regulation of tight junction permeability by intestinal bacteria and dietary components. *J. Nutr.* 2011, *141*(5), 769-776. https://doi.org/10.3945/jn.110.135657.

41 Dempsey, E.; Corr, S.C. *Lactobacillus* spp. for Gastrointestinal Health: Current and Future Perspectives. *Front. Immunol.* 2022, *13*, 840245. https://doi.org/10.3389/fimmu.2022.840245.

42 Abdulqadir, R.; Engers, J.; Al-Sadi, R. Role of *Bifidobacterium* in Modulating the Intestinal Epithelial Tight Junction Barrier: Current Knowledge and Perspectives. *Curr. Dev. Nutr.* 2023, *7*(12), 102026. https://doi.org/10.1016/j.cdnut.2023.102026.

43 Mo, C.; Lou, X.; Xue, J.; Shi, Z.; Zhao, Y.; Wang, F.; Chen, G. The influence of *Akkermansia muciniphila* on intestinal barrier function. *Gut Pathog.* 2024, *16*(1), 41 https://doi.org/10.1186/s13099-024-00635-7.

44 Ferreira-Halder, C.V.; Faria, A.V.S.; Andrade, S.S. Action and function of *Faecalibacterium prausnitzii* in health and disease. *Best Pract. Res. Clin. Gastroenterol.* 2017, *31*(6), 643-648. https://doi.org/10.1016/j.bpg.2017.09.011.

45 Mukherjee, A,; Lordan, C.; Ross, R.P.; Cotter, P.D. Gut microbes from the phylogenetically diverse genus *Eubacterium* and their various contributions to gut health. *Gut Microbes* 2020, *12*(1), 1802866. https://doi.org/10.1080/19490976.2020.1802866.

46 Patangia, D.V.; Anthony Ryan, C.; Dempsey, E.; Paul Ross, R.; Stanton, C. Impact of antibiotics on the human microbiome and consequences for host health. *Microbiologyopen* 2022, *11*(1), e1260. https://doi.org/10.1002/mbo3.1260.

47 Dahiya, D.; Nigam, P.S. Antibiotic-Therapy-Induced Gut Dysbiosis Affecting Gut Microbiota-Brain Axis and Cognition: Restoration by Intake of Probiotics and Synbiotics. *Int. J. Mol. Sci.* 2023, *24*(4), 3074. https://doi.org/10.3390/ijms24043074.

48 Hookman, P.; Barkin, J.S. *Clostridium difficile* associated infection, diarrhea and colitis. *World J. Gastroenterol.* 2009, *15*(13), 1554-1580. https://doi.org/10.3748/wjg.15.1554.

49 Mirsepasi-Lauridsen, H.C.; Vallance, B.A.; Krogfelt, K.A.; Petersen, A.M. *Escherichia coli* Pathobionts Associated with Inflammatory Bowel Disease. *Clin. Microbiol. Rev.* 2019, *32*(2), e00060-18. https://doi.org/10.1128/CMR.00060-18.

50 Zhang, Q.; Su, X.; Zhang, C.; Chen, W.; Wang, Y.; Yang, X.; Liu, D.; Zhang, Y.; Yang, R. *Klebsiella pneumoniae* Induces Inflammatory Bowel Disease Through Caspase-11-Mediated IL18 in the Gut Epithelial Cells. *Cell. Mol. Gastroenterol. Hepatol.* 2023, *15*(3), 613-632. https://doi.org/10.1016/j.jcmgh.2022.11.005.

51 Popa, G.L.; Papa, M.I. *Salmonella* spp. infection – a continuous threat worldwide. *Germs* 2021, *11*(1), 88-96. https://doi.org/10.18683/germs.2021.1244.

52 Zeng, M.Y.; Inohara, N.; Nuñez, G. Mechanisms of inflammation-driven bacterial dysbiosis in the gut. *Mucosal Immunol.* 2017, *10*(1), 18-26. https://doi.org/10.1038/mi.2016.75.

53 Baldelli, V.; Scaldaferri, F.; Putignani, L.; Del Chierico, F. The Role of *Enterobacteriaceae* in Gut Microbiota Dysbiosis in Inflammatory Bowel Diseases. *Microorganisms* 2021, *9*(4), 697. https://doi.org/10.3390/microorganisms9040697.

54 Konstantinidis, T.; Tsigalou, C.; Karvelas, A.; Stavropoulou, E.; Voidarou, C.; Bezirtzoglou, E. Effects of Antibiotics upon the Gut Microbiome: A Review of the Literature. *Biomedicines* 2020, *8*(11), 502. https://doi.org/10.3390/biomedicines8110502.

55 Porru, S.; Esplugues, A.; Llop, S.; Delgado-Saborit, J.M. The effects of heavy metal exposure on brain and gut microbiota: A systematic review of animal studies. *Environ. Pollut.* 2024, *348*, 123732. https://doi.org/10.1016/j.envpol.2024.123732.

56 Zhu, Q.; Chen, B.; Zhang, F.; Zhang, B.; Guo, Y.; Pang, M.; Huang, L.; Wang, T. Toxic and essential metals: metabolic interactions with the gut microbiota and health implications. *Front. Nutr.* 2024, *11*, 1448388. https://doi.org/10.3389/fnut.2024.1448388.

57 Feng, P.; Ye, Z.; Kakade, A.; Virk, A.K.; Li, X.; Liu, P. A Review on Gut Remediation of Selected Environmental Contaminants: Possible Roles of Probiotics and Gut Microbiota. *Nutrients* 2018, *11*(1), 22. https://doi.org/10.3390/nu11010022.

58 Duan, H.; Yu, L.; Tian, F.; Zhai, Q.; Fan, L.; Chen, W. Gut microbiota: A target for heavy metal toxicity and a probiotic protective strategy. *Sci. Total Environ.* 2020, *742*, 140429. https://doi.org/10.1016/j.scitotenv.2020.140429.

59 Djurasevic, S.; Jama, A.; Jasnic, N.; Vujovic, P.; Jovanovic, M.; Mitic-Culafic, D.; Knezevic-Vukcevic, J.; Cakic-Milosevic, M.; Ilijevic, K.; Djordjevic, J. The Protective Effects of Probiotic Bacteria on Cadmium Toxicity in Rats. *J. Med. Food* 2017, *20*(2), 189-196. https://doi.org/10.1089/jmf.2016.0090.

60 Majlesi, M.; Shekarforoush, S.S.; Ghaisari, H.R.; Nazifi, S.; Sajedianfard, J.; Eskandari, M.H. Effect of Probiotic *Bacillus Coagulans* and *Lactobacillus Plantarum* on Alleviation of Mercury Toxicity in Rat. *Probiotics Antimicrob. Proteins* 2017, *9*(3), 300-309. https://doi.org/10.1007/s12602-016-9250-x.

61 Arun, K.B.; Madhavan, A.; Sindhu, R.; Emmanual, S.; Binod, P.; Pugazhendhi, A.; Sirohi, R.; Reshmy, R.; Awasthi, M.K.; Gnansounou, E.; Pandey, A. Probiotics and gut microbiome – Prospects and challenges in remediating heavy metal toxicity. *J. Hazard. Mater.* 2021, *420*, 126676. https://doi.org/10.1016/j.jhazmat.2021.126676.

62 Santiago, M.S.A.; Avellar, M.C.W.; Perobelli, J.E. Could the gut microbiota be capable of making individuals more or less susceptible to environmental toxicants? *Toxicology* 2024, *503*, 153751. https://doi.org/10.1016/j.tox.2024.153751.

63 Teffera, M.; Veith, A.C.; Ronnekleiv-Kelly, S.; Bradfield, C.A.; Nikodemova, M.; Tussing-Humphreys, L.; Malecki, K. Diverse mechanisms by which chemical pollutant exposure alters gut microbiota metabolism and inflammation. *Environ. Int.* 2024, *190*, 108805. https://doi.org/10.1016/j.envint.2024.108805.

64 Bist, P.; Choudhary, S. Impact of Heavy Metal Toxicity on the Gut Microbiota and Its Relationship with Metabolites and Future Probiotics Strategy: a Review. *Biol. Trace Elem. Res.* 2022, *200*(12), 5328-5350. https://doi.org/10.1007/s12011-021-03092-4.

65 Hills, R.D. Jr.; Pontefract, B.A.; Mishcon, H.R.; Black, C.A.; Sutton, S.C.; Theberge, C.R. Gut Microbiome: Profound Implications for Diet and Disease. *Nutrients* 2019, *11*(7), 1613. https://doi.org/10.3390/nu11071613.

66 Pickard, J.M.; Zeng, M.Y.; Caruso, R.; Núñez, G. Gut microbiota: Role in pathogen colonization, immune responses, and inflammatory disease. *Immunol. Rev.* 2017, *279*(1), 70-89 https://doi.org/10.1111/imr.12567.

67 Liu, H.; Zhang, H.; Yu, Q.; Zhang, S.; Tu, X.; Zhuang, F.; Fu, S. Lead induced structural and functional damage and microbiota dysbiosis in the intestine of crucian carp (*Carassius auratus*). *Front. Microbiol.* 2023, *14*, 1239323. https://doi.org/10.3389/fmicb.2023.1239323.

68 Liu, H.; Qian, K.; Zhang, S.; Yu, Q.; Du, Y.; Fu, S. Lead exposure induces structural damage, digestive stress, immune response and microbiota dysbiosis in the intestine of silver carp (*Hypophthalmichthys molitrix*). *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* 2022, *262*, 109464. https://doi.org/10.1016/j.cbpc.2022.109464.

69 Liu, Y.; Kang, W.; Liu, S.; Li, J.; Liu, J.; Chen, X.; Gan, F.; Huang, K. Gut microbiota-bile acid-intestinal Farnesoid X receptor signaling axis orchestrates cadmium-induced liver injury. *Sci. Total Environ.* 2022, *849*, 157861. https://doi.org/10.1016/j.scitotenv.2022.157861.

70 Liu, X.; Kang, W.; Li, J.; Li, X.; Yang, P.; Shi, M.; Wang, Z.; Wang, Y.; Medina, A.D.P.A.; Liu, D.; Zhu, F.; Shen, H.; Huang, K.; Chen, X.; Liu, Y. Melatonin Ameliorates Cadmium-Induced Liver Fibrosis Via Modulating Gut Microbiota and Bile Acid Metabolism. *J. Pineal Res.* 2024, *76*(8), e70005. https://doi.org/10.1111/jpi.70005.

71 Bidashimwa, D.; Hoke, T.; Huynh, T.B.; Narkpitaks, N.; Priyonugroho, K.; Ha, T.T.; Burns, A.; Weissman, A. Plastic pollution: how can the global health community fight the growing problem? *BMJ Glob. Health* 2023, *8*(Suppl. 3), e012140. https://doi.org/10.1136/bmjgh-2023-012140.

72 Fayshal, M.A. Current practices of plastic waste management, environmental impacts, and potential alternatives for reducing pollution and improving management. *Heliyon* 2024, *10*(23), e40838. https://doi.org/10.1016/j.heliyon.2024.e40838.

73 Napper, I.E.; Thompson, R.C. Release of synthetic microplastic plastic fibres from domestic washing machines: Effects of fabric type and washing conditions. *Mar. Pollut. Bull.* 2016, *112*(1-2), 39-45. https://doi.org/10.1016/j.marpolbul.2016.09.025.

74 Kibria, M.G.; Masuk, N.I.; Safayet, R.; Nguyen, H.Q.; Mourshed, M. Plastic Waste: Challenges and Opportunities to Mitigate Pollution and Effective Management. *Int. J. Environ. Res.* 2023, *17*(1), 20. https://doi.org/10.1007/s41742-023-00507-z.

75 Lakhiar, I.A.; Yan, H.; Zhang, J.; Wang, G.; Deng, S.; Bao, R.; Zhang, C.; Syed, T.N.; Wang, B.; Zhou, R.; et al. Plastic Pollution in Agriculture as a Threat to Food Security, the Ecosystem, and the Environment: An Overview. *Agronomy* 2024, *14*, 548. https://doi.org/10.3390/agronomy14030548.

76 Lin, Y.D.; Huang, P.H.; Chen, Y.W.; Hsieh, C.W.; Tain, Y.L.; Lee, B.H.; Hou, C.Y.; Shih, M.K. Sources, Degradation, Ingestion and Effects of Microplastics on Humans: A Review. *Toxics* 2023, *11*(9), 747. https://doi.org/10.3390/toxics11090747.

77 Dube, E.; Okuthe, G.E. Plastics and Micro/Nano-Plastics (MNPs) in the Environment: Occurrence, Impact, and Toxicity. *Int. J. Environ. Res. Public Health* 2023, *20*(17), 6667. https://doi.org/10.3390/ijerph20176667.

78 Tursi, A.; Baratta, M.; Easton, T.; Chatzisymeon, E.; Chidichimo, F.; De Biase, M.; De Filpo, G. Microplastics in aquatic systems, a comprehensive review: origination, accumulation, impact, and removal technologies. *RSC Adv.* 2022, *12*(44), 28318-28340. https://doi.org/10.1039/d2ra04713f.

79 Bora, S.S.; Gogoi, R.; Sharma, M.R.; Anshu, Borah, M.P.; Deka, P.; Bora, J.; Naorem, R.S.; Das, J.; Teli, A.B. Microplastics and human health: unveiling the gut microbiome disruption and chronic disease risks. *Front. Cell. Infect. Microbiol.* 2024, *14*, 1492759. https://doi.org/10.3389/fcimb.2024.1492759.

80 Zhang, K.; Yang, J.; Chen, L.; He, J.; Qu, D.; Zhang, Z.; Liu, Y.; Li, X.; Liu, J.; Li, J.; Xie, X.; Wang, Q. Gut Microbiota Participates in Polystyrene Microplastics-Induced Hepatic Injuries by Modulating the Gut-Liver Axis. *ACS Nano* 2023, *17*(15), 15125-15145. https://doi.org/10.1021/acsnano.3c04449.

81 Kadac-Czapska, K.; Ośko, J.; Knez, E.; Grembecka, M. Microplastics and Oxidative Stress-Current Problems and Prospects. *Antioxidants (Basel)* 2024, 13(5), 579. https://doi.org/10.3390/antiox13050579.

82 Lang, T.; Jelić, F.; Wechselberger, C. From Cradle to Grave: Microplastics – A Dangerous Legacy for Future Generations. *Environments* 2024, *11*, 263 https://doi.org/10.3390/environments11120263.

83 Ke, D.; Zheng, J.; Liu, X.; Xu, X.; Zhao, L.; Gu, Y.; Yang, R.; Liu, S.; Yang, S.; Du, J.; Chen, B.; He, G.; Dong, R. Occurrence of microplastics and disturbance of gut microbiota: a pilot study of preschool children in Xiamen, China. *EBioMedicine* 2023, *97*, 104828. https://doi.org/10.1016/j.ebiom.2023.104828.

84 Amran, N.H.; Zaid, S.S.M.; Mokhtar, M.H.; Manaf, L.A.; Othman, S. Exposure to Microplastics during Early Developmental Stage: Review of Current Evidence. *Toxics* 2022, *10*(10), 597. https://doi.org/10.3390/toxics10100597.

85 Zaheer, J.; Kim, H.; Ko, I.O.; Jo, E.K.; Choi, E.J.; Lee, H.J.; Shim, I.; Woo, H.J.; Choi, J.; Kim, G.H.; Kim, J.S. Pre/post-natal exposure to microplastic as a potential risk factor for autism spectrum disorder. *Environ. Int.* 2022, *161*, 107121. https://doi.org/10.1016/j.envint.2022.107121.

86 Jing, J.; Zhang, L.; Han, L.; Wang, J.; Zhang, W.; Liu, Z.; Gao, A. Polystyrene micro-/nanoplastics induced hematopoietic damages via the crosstalk of gut microbiota, metabolites, and cytokines. *Environ. Int.* 2022, *161*, 107131. https://doi.org/10.1016/j.envint.2022.107131.

87 Jin, Y.; Lu, L.; Tu, W.; Luo, T.; Fu, Z. Impacts of polystyrene microplastic on the gut barrier, microbiota and metabolism of mice. *Sci. Total Environ.* 2019, *649*, 308-317. https://doi.org/10.1016/j.scitotenv.2018.08.353.

88 Arias-Borrego, A.; Selma-Royo, M.; Collado, M.C.; Abril, N.; García-Barrera, T. Impact of "chemical cocktails" exposure in shaping mice gut microbiota and the role of selenium supplementation combining metallomics, metabolomics, and metataxonomics. *J. Hazard. Mater.* 2022, *438*, 129444. https://doi.org/10.1016/j.jhazmat.2022.129444.

89 Parra-Martínez, C.; Selma-Royo, M.; Callejón-Leblic, B.; Collado, M.C.; Abril, N.; García-Barrera, T. Mice brain metabolomics after the exposure to a "chemical cocktail" and selenium supplementation through the gut-brain axis. *J. Hazard. Mater.* 2022, *438*, 129443. https://doi.org/10.1016/j.jhazmat.2022.129443.

90 Sarubbo, F.; Cavallucci, V.; Pani, G. The Influence of Gut Microbiota on Neurogenesis: Evidence and Hopes. *Cells* 2022, *11*(3), 382. https://doi.org/10.3390/cells11030382.

91 Yang, K.; Zhang, L.; Liao, P.; Xiao, Z.; Zhang, F.; Sindaye, D.; Xin, Z.; Tan, C.; Deng, J.; Yin, Y.; Deng, B. Impact of Gallic Acid on Gut Health: Focus on the Gut Microbiome, Immune Response, and Mechanisms of Action. *Front. Immunol.* 2020, *11*, 580208. https://doi.org/10.3389/fimmu.2020.580208.

92 Zheng, P.; Zhang, B.; Zhang, K.; Lv, X.; Wang, Q.; Bai, X. The Impact of Air Pollution on Intestinal Microbiome of Asthmatic Children: A Panel Study. *Biomed. Res. Int.* 2020, *2020*, 5753427. https://doi.org/10.1155/2020/5753427.

93 Naomi, R.; Yazid, M.D.; Bahari, H.; Keong, Y.Y.; Rajandram, R.; Embong, H.; Teoh, S.H.; Halim, S.; Othman, F. Bisphenol A (BPA) Leading to Obesity and Cardiovascular Complications: A Compilation of Current *In vivo* Study. *Int. J. Mol. Sci.* 2022, *23*(6), 2969. https://doi.org/10.3390/ijms23062969.

94 Zhou, Y.; Gui, L.; Wei, W.; Xu, E.G.; Zhou, W.; Sokolova, I.M.; Li, M.; Wang, Y. Low particle concentrations of nanoplastics impair the gut health of medaka. *Aquat. Toxicol.* 2023, *256*, 106422. https://doi.org/10.1016/j.aquatox.2023.106422.

95 He, S.; Li, X.; Li, C.; Deng, H.; Shao, Y.; Yuan, L. Isoorientin attenuates benzo [a]pyrene-induced colonic injury and gut microbiota disorders in mice. *Food Res. Int.* 2019, *126*, 108599. https://doi.org/10.1016/j.foodres.2019.108599.

96 Termite, F.; Archilei, S.; D'Ambrosio, F.; Petrucci, L.; Viceconti, N.; Iaccarino, R.; Liguori, A.; Gasbarrini, A.; Miele, L. Gut Microbiota at the Crossroad of Hepatic Oxidative Stress and MASLD. *Antioxidants (Basel)* 2025, *14*(1), 56. https://doi.org/10.3390/antiox14010056.

97 Cheng, J.; Meistertzheim, A.L.; Leistenschneider, D.; Philip, L.; Jacquin, J.; Escande, M.L.; Barbe, V.; Ter Halle, A.; Chapron, L.; Lartaud, F.; Bertrand, S.; Escriva, H.; Ghiglione, J.F. Impacts of microplastics and the associated plastisphere on physiological, biochemical, genetic expression and gut microbiota of the filter-feeder amphioxus. *Environ. Int.* 2023, *172*, 107750. https://doi.org/10.1016/j.envint.2023.107750.

98 Li, B.; Ding, Y.; Cheng, X.; Sheng, D.; Xu, Z.; Rong, Q.; Wu, Y.; Zhao, H.; Ji, X.; Zhang, Y. Polyethylene microplastics affect the distribution of gut microbiota and inflammation development in mice. *Chemosphere* 2020, *244*, 125492. https://doi.org/10.1016/j.chemosphere.2019.125492.

99 Yong, C.Q.Y.; Valiyaveettil, S.; Tang, B.L. Toxicity of Microplastics and Nanoplastics in Mammalian Systems. *Int. J. Environ. Res. Public Health* 2020, *17*(5), 1509. https://doi.org/10.3390/ijerph17051509.

100 Yuan, X.; Pan, Z.; Jin, C.; Ni, Y.; Fu, Z.; Jin, Y. Gut microbiota: An underestimated and unintended recipient for pesticide-induced toxicity. *Chemosphere* 2019, *227*, 425-434. https://doi.org/10.1016/j.chemosphere.2019.04.088.

101 Giambò, F.; Teodoro, M.; Costa, C.; Fenga, C. Toxicology and Microbiota: How Do Pesticides Influence Gut Microbiota? A Review. *Int. J. Environ. Res. Public Health* 2021, *18*, 5510. https://doi.org/10.3390/ijerph18115510.

102 Ueyama, J.; Hayashi, M.; Hirayama, M.; Nishiwaki, H.; Ito, M.; Saito, I.; Tsuboi, Y.; Isobe, T.; Ohno, K. Effects of Pesticide Intake on Gut Microbiota and Metabolites in Healthy Adults. *Int. J. Environ. Res. Public Health* 2022, *20*(1), 213. https://doi.org/10.3390/ijerph20010213.

103 Ali, A.; AlHussaini, K.I. Pesticides: Unintended Impact on the Hidden World of Gut Microbiota. *Metabolites* 2024, *14*(3), 155. https://doi.org/10.3390/metabo14030155.

104 Meng, Z.; Liu, L.; Yan, S.; Sun, W.; Jia, M.; Tian, S.; Huang, S.; Zhou, Z.; Zhu, W. Gut Microbiota: A Key Factor in the Host Health Effects Induced by Pesticide Exposure? *J. Agric. Food Chem.* 2020, *68*(39), 10517-10531. https://doi.org/10.1021/acs.jafc.0c04678.

105 Kulcsarova, K.; Bang, C.; Berg, D.; Schaeffer, E. Pesticides and the Microbiome-Gut-Brain Axis: Convergent Pathways in the Pathogenesis of Parkinson's Disease. *J. Parkinsons Dis.* 2023, *13*(7), 1079-1106. https://doi.org/10.3233/JPD-230206.

106 Sharma, T.; Sirpu Natesh, N.; Pothuraju, R.; Batra, S.K.; Rachagani, S. Gut microbiota: a non-target victim of pesticide-induced toxicity. *Gut Microbes* 2023, *15*(1), 2187578. https://doi.org/10.1080/19490976.2023.2187578.

107 Bamicha, V.; Pergantis, P.; Drigas, A. The Effect of Gut Microbiome, Neurotransmitters, and Digital Insights in Autism. *Appl. Microbiol.* 2024, *4*, 1677-1701. https://doi.org/10.3390/applmicrobiol4040114.

108 Abou Diwan, M.; Djekkoun, N.; Boucau, M.C.; Corona, A.; Dehouck, L.; Biendo, M.; Gosselet, F.; Bach, V.; Candela, P.; Khorsi-Cauet, H. Maternal exposure to pesticides induces perturbations in the gut microbiota and blood-brain barrier of dams and the progeny, prevented by a prebiotic. *Environ. Sci. Pollut. Res. Int.* 2024, *31*(49), 58957-58972. https://doi.org/10.1007/s11356-024-34969-1.

109 Chiu, K.; Warner, G.; Nowak, R.A.; Flaws, J.A.; Mei, W. The Impact of Environmental Chemicals on the Gut Microbiome. *Toxicol. Sci.* 2020, *176*(2), 253-284. https://doi.org/10.1093/toxsci/kfaa065.

110 Tu, P.; Xue, J.; Niu, H.; Tang, Q.; Mo, Z.; Zheng, X.; Wu, L.; Chen, Z.; Cai, Y.; Wang, X. Deciphering Gut Microbiome Responses upon Microplastic Exposure via Integrating Metagenomics and Activity-Based Metabolomics. *Metabolites* 2023, *13*(4), 530. https://doi.org/10.3390/metabo13040530.

111 Peng, Z.; Liao, Y.; Yang, W.; Liu, L. Metal(loid)-gut microbiota interactions and microbiota-related protective strategies: A review. *Environ. Int.* 2024, *192*, 109017. https://doi.org/10.1016/j.envint.2024.109017.

112 Sofield, C.E.; Anderton, R.S.; Gorecki, A.M. Mind over Microplastics: Exploring Microplastic-Induced Gut Disruption and Gut-Brain-Axis Consequences. *Curr. Issues Mol. Biol.* 2024, *46*(5), 4186-4202. https://doi.org/10.3390/cimb46050256.

113 Meli, R.; Monnolo, A.; Annunziata, C.; Pirozzi, C.; Ferrante, M.C. Oxidative Stress and BPA Toxicity: An Antioxidant Approach for Male and Female Reproductive Dysfunction. *Antioxidants (Basel)* 2020, *9*(5), 405. https://doi.org/10.3390/antiox9050405.

114 Wu, J.; Wang, K.; Wang, X.; Pang, Y.; Jiang, C. The role of the gut microbiome and its metabolites in metabolic diseases. *Protein Cell* 2021, *12*(5), 360-373. https://doi.org/10.1007/s13238-020-00814-7.

115 Larabi, A.B.; Masson, H.L.P.; Bäumler, A.J. Bile acids as modulators of gut microbiota composition and function. *Gut Microbes* 2023, *15*(1), 2172671. https://doi.org/10.1080/19490976.2023.2172671.

116 Safari, Z.; Gérard, P. The links between the gut microbiome and non-alcoholic fatty liver disease (NAFLD). *Cell. Mol. Life Sci.* 2019, *76*(8), 1541-1558. https://doi.org/10.1007/s00018-019-03011-w.

117 Tilg, H.; Adolph, T.E.; Dudek, M.; Knolle, P. Non-alcoholic fatty liver disease: the interplay between metabolism, microbes and immunity. *Nat. Metab.* 2021, *3*(12), 1596-1607. https://doi.org/10.1038/s42255-021-00501-9.

118 Iatcu, C.O.; Steen, A.; Covasa, M. Gut Microbiota and Complications of Type-2 Diabetes. *Nutrients* 2021, *14*(1), 166. https://doi.org/10.3390/nu14010166.

119 Kraemer, S.A.; Ramachandran, A.; Perron, G.G. Antibiotic Pollution in the Environment: From Microbial Ecology to Public Policy. *Microorganisms* 2019, *7*(6), 180. https://doi.org/10.3390/microorganisms7060180.

120 Dickinson, A.W.; Power, A.; Hansen, M.G.; Brandt, K.K.; Piliposian, G.; Appleby, P.; O'Neill, P.A.; Jones, R.T.; Sierocinski, P.; Koskella, B.; Vos, M. Heavy metal pollution and co-selection for antibiotic resistance: A microbial palaeontology approach. *Environ. Int.* 2019, *132*, 105117. https://doi.org/10.1016/j.envint.2019.105117.

121 Tuvo, B.; Scarpaci, M.; Bracaloni, S.; Esposito, E.; Costa, A.L.; Ioppolo, M.; Casini, B. Microplastics and Antibiotic Resistance: The Magnitude of the Problem and the Emerging Role of Hospital Wastewater. *Int. J. Environ. Res. Public Health* 2023, *20*(10), 5868. https://doi.org/10.3390/ijerph20105868.

122 Tang, K.H.D.; Li, R. Aged Microplastics and Antibiotic Resistance Genes: A Review of Aging Effects on Their Interactions. *Antibiotics (Basel)* 2024, *13*(10), 941. https://doi.org/10.3390/antibiotics13100941.

123 Anedda, E.; Farrell, M.L.; Morris, D.; Burgess, C.M. Evaluating the impact of heavy metals on antimicrobial resistance in the primary food production environment: A scoping review. *Environ. Pollut.* 2023, *320*, 121035. https://doi.org/10.1016/j.envpol.2023.121035.

124 Gillieatt, B.F.; Coleman, N.V. Unravelling the mechanisms of antibiotic and heavy metal resistance co-selection in environmental bacteria. *FEMS Microbiol. Rev.* 2024, *48*(4), fuae017. https://doi.org/10.1093/femsre/fuae017.
125 Huemer, M.; Mairpady Shambat, S.; Brugger, S.D.; Zinkernagel, A.S. Antibiotic resistance and persistence-Implications for human health and treatment perspectives. *EMBO Rep.* 2020, *21*(12), e51034. https://doi.org/10.15252/embr.202051034.
126 Chinemerem Nwobodo, D.; Ugwu, M.C.; Oliseloke Anie, C.; Al-Ouqaili, M.T.S.; Chinedu Ikem, J.; Victor Chigozie, U.; Saki, M. Antibiotic resistance: The challenges and some emerging strategies for tackling a global menace. *J. Clin. Lab. Anal.* 2022, *36*(9), e24655. https://doi.org/10.1002/jcla.24655.
127 Woerther, P.L.; Burdet, C.; Chachaty, E.; Andremont, A. Trends in human fecal carriage of extended-spectrum β-lactamases in the community: toward the globalization of CTX-M. *Clin. Microbiol. Rev.* 2013, *26*(4), 744-58. https://doi.org/10.1128/CMR.00023-13.
128 Liu, L.; Guang, S.B.; Xin, Y.; Li, J.; Lin, G.F.; Zeng, L.Q.; He, S.Q.; Zheng, Y.M.; Chen, G.Y.; Zhao, Q.B. Antibiotic resistant genes profile in the surface water of subtropical drinking water river-reservoir system. *Environ. Pollut.* 2023, *337*, 122619. https://doi.org/10.1016/j.envpol.2023.122619.
129 Shao, S.; Hu, Y.; Cheng, J.; Chen, Y. Research progress on distribution, migration, transformation of antibiotics and antibiotic resistance genes (ARGs) in aquatic environment. *Crit. Rev. Biotechnol.* 2018, *38*(8), 1195-1208. https://doi.org/10.1080/07388551.2018.1471038.
130 Larsson, D.G.J.; Flach, C.F. Antibiotic resistance in the environment. *Nat. Rev. Microbiol.* 2022, *20*(5), 257-269. https://doi.org/10.1038/s41579-021-00649-x.
131 Salam, M.A.; Al-Amin, M.Y.; Salam, M.T.; Pawar, J.S.; Akhter, N.; Rabaan, A.A.; Alqumber, M.A.A. Antimicrobial Resistance: A Growing Serious Threat for Global Public Health. *Healthcare (Basel)* 2023, *11*(13), 1946. https://doi.org/10.3390/healthcare11131946.
132 Czatzkowska, M.; Wolak, I.; Harnisz, M.; Korzeniewska, E. Impact of Anthropogenic Activities on the Dissemination of ARGs in the Environment-A Review. *Int. J. Environ. Res. Public Health* 2022, *19*(19), 12853. https://doi.org/10.3390/ijerph191912853.
133 Jian, Z.; Zeng, L.; Xu, T.; Sun, S.; Yan, S.; Yang, L.; Huang, Y.; Jia, J.; Dou, T. Antibiotic resistance genes in bacteria: Occurrence, spread, and control. *J. Basic Microbiol.* 2021, *61*(12), 1049-1070. https://doi.org/10.1002/jobm.202100201.
134 Bhat, B.A.; Mir, R.A.; Qadri, H.; Dhiman, R.; Almilaibary, A.; Alkhanani, M.; Mir, M.A. Integrons in the development of antimicrobial resistance: critical review and perspectives. *Front. Microbiol.* 2023, *14*, 1231938. https://doi.org/10.3389/fmicb.2023.1231938.
135 Flores-Vargas, G.; Bergsveinson, J.; Lawrence, J.R.; Korber, D.R. Environmental Biofilms as Reservoirs for Antimicrobial Resistance. *Front. Microbiol.* 2021, *12*, 766242. https://doi.org/10.3389/fmicb.2021.766242.
136 Nguyen, A.Q.; Vu, H.P.; Nguyen, L.N.; Wang, Q.; Djordjevic, S.P.; Donner, E.; Yin, H.; Nghiem, L.D. Monitoring antibiotic resistance genes in wastewater treatment: Current strategies and future challenges. *Sci. Total Environ.* 2021, *783*, 146964. https://doi.org/10.1016/j.scitotenv.2021.146964.
137 Thiang, E.L.; Lee, C.W.; Takada, H.; Seki, K.; Takei, A.; Suzuki, S.; Wang A.; Bong, C.W. Antibiotic residues from aquaculture farms and their ecological risks in Southeast Asia: a case study from Malaysia. *Ecosystem Health and Sustainability,* 2021, *7*(1). https://doi.org/10.1080/20964129.2021.1926337.
138 Yuan, X.; Lv, Z.; Zhang, Z.; Han, Y.; Liu, Z.; Zhang, H. A Review of Antibiotics, Antibiotic Resistant Bacteria, and Resistance Genes in Aquaculture: Occurrence, Contamination, and Transmission. *Toxics* 2023, *11*(5), 420. https://doi.org/10.3390/toxics11050420.
139 Kim, M.; Park, J.; Kang, M.; Yang, J.; Park, W. Gain and loss of antibiotic resistant genes in multidrug resistant bacteria: One Health perspective. *J. Microbiol.* 2021, *59*(6), 535-545. https://doi.org/10.1007/s12275-021-1085-9.
140 Ajayi, A.O.; Odeyemi, A.T.; Akinjogunla, O.J.; Adeyeye, A.B.; Ayo-Ajayi, I. Review of antibiotic-resistant bacteria and antibiotic resistance genes within the one health framework. *Infect. Ecol. Epidemiol.* 2024, *14*(1), 2312953. https://doi.org/10.1080/20008686.2024.2312953.
141 Kunst, C.; Schmid, S.; Michalski, M.; Tümen, D.; Buttenschön, J.; Müller, M.; Gülow, K. The Influence of Gut Microbiota on Oxidative Stress and the Immune System. *Biomedicines* 2023, *11*, 1388. https://doi.org/10.3390/biomedicines11051388.
142 Anetor, G.O.; Nwobi, N.L.; Igharo, G.O.; Sonuga, O.O.; Anetor, J.I. Environmental Pollutants and Oxidative Stress in Terrestrial and Aquatic Organisms: Examination of the Total Picture and Implications for Human Health. *Front. Physiol.* 2022, *13*, 931386. https://doi.org/10.3389/fphys.2022.931386.

143 Itziou, A.; Balis, V.; Lakioti, E.; Karayannis, V.; Tsanaktsidis, C. Environmental Pollution and Oxidative Stress: Health Effects During Pregnancy: A Review. *Appl. Sci.* 2024, *14*, 9884. https://doi.org/10.3390/app14219884.

144 Poljšak, B.; Fink, R. The protective role of antioxidants in the defence against ROS/RNS-mediated environmental pollution. *Oxid. Med. Cell. Longev.* 2014, *2014*, 671539. https://doi.org/10.1155/2014/671539.

145 Pizzino, G.; Irrera, N.; Cucinotta, M.; Pallio, G.; Mannino, F.; Arcoraci, V.; Squadrito, F.; Altavilla, D.; Bitto, A. Oxidative Stress: Harms and Benefits for Human Health. *Oxid. Med. Cell. Longev.* 2017, *2017*, 8416763. https://doi.org/10.1155/2017/8416763.

146 Marynowski, M.; Likońska, A.; Zatorski, H.; Fichna, J. Role of environmental pollution in irritable bowel syndrome. *World J. Gastroenterol.* 2015, *21*(40), 11371-8. https://doi.org/10.3748/wjg.v21.i40.11371.

147 Tenailleau, Q.M.; Lanier, C.; Gower-Rousseau, C.; Cuny, D.; Deram, A.; Occelli, F. Crohn's disease and environmental contamination: Current challenges and perspectives in exposure evaluation. *Environ. Pollut.* 2020, *263*(Pt. B), 114599. https://doi.org/10.1016/j.envpol.2020.114599.

148 Fu, C.; Wang, Q.; Chen, Y.; Zhang, Y. Exploring the causal relationship between airborne particulate matter and ulcerative colitis: A two-sample mendelian randomization study. *PLoS One* 2024, *19*(3), e0300066. https://doi.org/10.1371/journal.pone.0300066.

149 Hectors, T.L.; Vanparys, C.; van der Ven, K.; Martens, G.A.; Jorens, P.G.; Van Gaal, L.F.; Covaci, A.; De Coen, W.; Blust, R. Environmental pollutants and type 2 diabetes: a review of mechanisms that can disrupt beta cell function. *Diabetologia* 2011, *54*(6), 1273-1290. https://doi.org/10.1007/s00125-011-2109-5.

150 Limaye, S.; Salvi, S. Obesity and asthma: the role of environmental pollutants. *Immunol. Allergy Clin. North Am.* 2014, *34*(4), 839-855. https://doi.org/10.1016/j.iac.2014.07.005.

151 Hectors, T.L.; Vanparys, C.; Van Gaal, L.F.; Jorens, P.G.; Covaci, A.; Blust, R. Insulin resistance and environmental pollutants: experimental evidence and future perspectives. *Environ. Health Perspect.* 2013, *121*(11-12), 1273-1281. https://doi.org/10.1289/ehp.1307082.

152 Alpízar-Rodríguez, D.; Finckh, A. Environmental factors and hormones in the development of rheumatoid arthritis. *Semin. Immunopathol.* 2017, *39*(4), 461-468. https://doi.org/10.1007/s00281-017-0624-2.

153 Mak, A.; Tay, S.H. Environmental factors, toxicants and systemic lupus erythematosus. *Int. J. Mol. Sci.* 2014, *15*(9), 16043-15056. https://doi.org/10.3390/ijms150916043.

154 Zhang, Y.; Li, K.; Kong, A.; Zhou, Y.; Chen, D.; Gu, J.; Shi, H. Dysregulation of autophagy acts as a pathogenic mechanism of non-alcoholic fatty liver disease (NAFLD) induced by common environmental pollutants. *Ecotoxicol. Environ. Saf.* 2021, *217*, 112256. https://doi.org/10.1016/j.ecoenv.2021.112256.

155 Horvatits, T.; Tamminga, M.; Liu, B.; Sebode, M.; Carambia, A.; Fischer, L.; Püschel, K.; Huber, S.; Fischer, E.K. Microplastics detected in cirrhotic liver tissue. *EBioMedicine* 2022, *82*, 104147 https://doi.org/10.1016/j.ebiom.2022.104147.

156 Pulliero, A.; Godschalk, R.; Andreassi, M.G.; Curfs, D.; Van Schooten, F.J.; Izzotti, A. Environmental carcinogens and mutational pathways in atherosclerosis. *Int. J. Hyg. Environ. Health* 2015, *218*(3), 293-312. https://doi.org/10.1016/j.ijheh.2015.01.007.

157 Salamanca-Fernández, E.;, Vela-Soria, F.; Rodríguez-Barranco, M.; Arrebola-Moreno, A.; Iribarne-Durán, L.M.; Olea, N.; Sánchez, M.J.; Arrebola, J.P. Serum levels of non-persistent environmental pollutants and risk of incident hypertension in a sub-cohort from the EPIC study. *Environ. Res.* 2021, *193*, 110491. https://doi.org/10.1016/j.envres.2020.110491.

158 Claeys, M.J.; Rajagopalan, S.; Nawrot, T.S.; Brook, R.D. Climate and environmental triggers of acute myocardial infarction. *Eur. Heart J.* 2017, *38*(13), 955-960. https://doi.org/10.1093/eurheartj/ehw151.

159 Mir, R.H.; Sawhney, G.; Pottoo, F.H.; Mohi-Ud-Din, R.; Madishetti, S.; Jachak, S.M.; Ahmed, Z.; Masoodi, M.H. Role of environmental pollutants in Alzheimer's disease: a review. *Environ. Sci. Pollut. Res. Int.* 2020, *27*(36), 44724-44742. https://doi.org/10.1007/s11356-020-09964-x.

160 Goldman, S.M. Environmental toxins and Parkinson's disease. *Annu. Rev. Pharmacol. Toxicol.* 2014, *54*, 141-164. https://doi.org/10.1146/annurev-pharmtox-011613-135937.

161 Swash, M.; Eisen, A. Hypothesis: amyotrophic lateral sclerosis and environmental pollutants. *Muscle Nerve* 2020, *62*(2), 187-191. https://doi.org/10.1002/mus.26855.

162 Gulis, G.; Fitz, O.; Wittgruber, J.; Suchanová, G. Colorectal cancer and environmental pollution. *Cent. Eur. J. Public Health* 1998, *6*(3), 188-191.

163 Gan, T.; Bambrick, H.; Tong, S.; Hu, W. Air pollution and liver cancer: A systematic review. *J. Environ. Sci. (China)* 2023, *126*, 817-826. https://doi.org/10.1016/j.jes.2022.05.037.

164 Moore, E.; Chatzidiakou, L.; Kuku, M.O.; Jones, R.L.; Smeeth, L.; Beevers, S.; Kelly, F.J.; Barratt, B.; Quint, J.K. Global Associations between Air Pollutants and Chronic Obstructive Pulmonary Disease Hospitalizations. A Systematic Review. *Ann. Am. Thorac. Soc.* 2016, *13*(10), 1814-1827. https://doi.org/10.1513/AnnalsATS.201601-064OC.

165 Paun, A.; Danska, J.S. Modulation of type 1 and type 2 diabetes risk by the intestinal microbiome. *Pediatr. Diabetes* 2016, *17*(7), 469-477. https://doi.org/10.1111/pedi.12424.

166 Zhao, L.; Fang, J.; Tang, S.; Deng, F.; Liu, X.; Shen, Y.; Liu, Y.; Kong, F.; Du, Y.; Cui, L.; Shi, W.; Wang, Y.; Wang, J.; Zhang, Y.; Dong, X.; Gao, Y.; Dong, L.; Zhou, H.; Sun, Q.; Dong, H.; Peng, X.; Zhang, Y.; Cao, M.; Wang, Y.; Zhi, H.; Du, H.; Zhou, J.; Li, T.; Shi, X. $PM_{2.5}$ and Serum Metabolome and Insulin Resistance, Potential Mediation by the Gut Microbiome: A Population-Based Panel Study of Older Adults in China. *Environ. Health Perspect*. 2022, *130*(2), 27007 https://doi.org/10.1289/EHP9688.

167 Jomova, K.; Alomar, S.Y.; Alwasel, S.H.; Nepovimova, E.; Kuca, K.; Valko, M. Several lines of antioxidant defense against oxidative stress: antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants. *Arch. Toxicol.* 2024, *98*(5), 1323-1367. https://doi.org/10.1007/s00204-024-03696-4.

168 Alengebawy, A.;Abdelkhalek, S.T.;Qureshi, S.R.; Wang, M.Q. Heavy Metals and Pesticides Toxicity in Agricultural Soil and Plants: Ecological Risks and Human Health Implications. *Toxics* 2021, *9*(3), 42. https://doi.org/10.3390/toxics9030042.

169 Jomova, K.; Raptova, R.; Alomar, S.Y.; Alwasel, S.H.; Nepovimova, E.; Kuca, K.; Valko, M. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. *Arch. Toxicol.* 2023, *97*(10), 2499-2574 https://doi.org/10.1007/s00204-023-03562-9.

170 Hou, L.; Zhang, X.; Wang, D.; Baccarelli, A. Environmental chemical exposures and human epigenetics. *Int. J. Epidemiol.* 2012, *41*(1), 79-105. https://doi.org/10.1093/ije/dyr154.

171 Ho, S.M.; Johnson, A.; Tarapore, P.; Janakiram, V.; Zhang, X.; Leung, Y.K. Environmental epigenetics and its implication on disease risk and health outcomes. *ILAR J.* 2012, *53*(3-4), 289-305. https://doi.org/10.1093/ilar.53.3-4.289.

172 Omar, N.N.; Mosbah, R.A.; Sarawi, W.S.; Rashed, M.M.; Badr, A.M. Rifaximin Protects against Malathion-Induced Rat Testicular Toxicity: A Possible Clue on Modulating Gut Microbiome and Inhibition of Oxidative Stress by Mitophagy. *Molecules* 2022, *27*(13), 4069. https://doi.org/10.3390/molecules27134069.

173 Love, C.; Sominsky, L.; O'Hely, M.; Berk, M.; Vuillermin, P.; Dawson, S.L. Prenatal environmental risk factors for autism spectrum disorder and their potential mechanisms. *BMC Med.* 2024, *22*(1), 393. https://doi.org/10.1186/s12916-024-03617-3.

174 Klimkaite, L.; Liveikis, T.; Kaspute, G.; Armalyte, J.; Aldonyte, R. Air pollution-associated shifts in the human airway microbiome and exposure-associated molecular events. *Future Microbiol.* 2023, *18*, 607-623. https://doi.org/10.2217/fmb-2022-0258.

175 Gao, Y.; Yu, T.; Wu, Y.; Huang, X.; Teng, J.; Zhao, N.; Zheng, X.; Yan, F. *Bacillus coagulans* (*Weizmannia coagulans*) XY2 attenuates Cu-induced oxidative stress via DAF-16/FoxO and SKN-1/Nrf2 pathways and gut microbiota regulation. *J. Hazard. Mater.* 2023, *457*, 131741. https://doi.org/10.1016/j.jhazmat.2023.131741.

176 Salim, S.Y.; Kaplan, G.G.; Madsen, K.L. Air pollution effects on the gut microbiota: a link between exposure and inflammatory disease. *Gut Microbes* 2014, *5*(2), 215-9. https://doi.org/10.4161/gmic.27251.

177 Liu, W.; Feng, H.; Zheng, S.; Xu, S.; Massey, I.Y.; Zhang, C.; Wang, X.; Yang, F. Pb Toxicity on Gut Physiology and Microbiota. *Front. Physiol.* 2021, *12*, 574913. https://doi.org/10.3389/fphys.2021.574913.

178 Gupta, N.; Yadav, V.K.; Gacem, A.; Al-Dossari, M.; Yadav, K.K.; Abd El-Gawaad, N.S.; Ben Khedher, N.; Choudhary, N.; Kumar, P.; Cavalu, S. Deleterious Effect of Air Pollution on Human Microbial Community and Bacterial Flora: A Short Review. *Int. J. Environ. Res. Public Health* 2022, *19*(23), 15494. . ://doi.org/10.3390/ijerph192315494.

179 Gao, B.; Chen, L.; Wu, L.; Zhang, S.; Zhao, S,.; Mo, Z.; Chen, Z.; Tu, P. Association between microplastics and the functionalities of human gut microbiome. *Ecotoxicol. Environ. Saf.* 2025, *290*, 117497. https://doi.org/10.1016/j.ecoenv.2024.117497.

180 Ugwu, O.P.; Alum, E.U.; Okon, M.B.; Obeagu, E.I. Mechanisms of microbiota modulation: Implications for health, disease, and therapeutic interventions. *Medicine (Baltimore)* 2024, *103*(19), e38088. https://doi.org/10.1097/MD.0000000000038088.

181 Zhang, R.; Ding, N.; Feng, X.; Liao, W. The gut microbiome, immune modulation, and cognitive decline: insights on the gut-brain axis. *Front. Immunol.* 2025, *16*, 1529958. https://doi.org/10.3389/fimmu.2025.1529958.

182 Wang, B.; Shen, J. NF-κB Inducing Kinase Regulates Intestinal Immunity and Homeostasis. *Front. Immunol.* 2022, *13*, 895636. https://doi.org/10.3389/fimmu.2022.895636.

183 Kearns, R. Gut-Brain Axis and Neuroinflammation: The Role of Gut Permeability and the Kynurenine Pathway in Neurological Disorders. *Cell. Mol. Neurobiol.* 2024, *44*(1), 64. https://doi.org/10.1007/s10571-024-01496-z.

184 Hug, H.; Mohajeri, M.H.; La Fata, G. Toll-Like Receptors: Regulators of the Immune Response in the Human Gut. *Nutrients* 2018, *10*, 203. https://doi.org/10.3390/nu10020203.

185 Chen, L.; Zhang, L.; Hua, H.; Liu, L.; Mao, Y.; Wang, R. Interactions between toll-like receptors signaling pathway and gut microbiota in host homeostasis. *Immun. Inflamm. Dis.* 2024, *12*(7), e1356. https://doi.org/10.1002/iid3.1356.

186 Rivas-Arancibia, S.; Hernández-Orozco, E.; Rodríguez-Martínez, E.; Valdés-Fuentes, M.; Cornejo-Trejo, V.; Pérez-Pacheco, N.; Dorado-Martínez, C.; Zequeida-Carmona, D.; Espinosa-Caleti, I. Ozone Pollution, Oxidative Stress, Regulatory T Cells and Antioxidants. *Antioxidants* 2022, *11*, 1553. https://doi.org/10.3390/antiox11081553.

187 Toor, D.; Wsson, M.K,.; Kumar, P.; Karthikeyan, G.; Kaushik, N.K.; Goel, C.; Singh, S.; Kumar, A.; Prakash, H. Dysbiosis Disrupts Gut Immune Homeostasis and Promotes Gastric Diseases. *Int. J. Mol. Sci.* 2019, *20*(10), 2432. https://doi.org/10.3390/ijms20102432.

188 Popko, K.; Gorska, E.; Stelmaszczyk-Emmel, A.; Plywaczewski, R.; Stoklosa, A.; Gorecka, D.; Pyrzak, B.; Demkow, U. Proinflammatory cytokines Il-6 and TNF-α and the development of inflammation in obese subjects. *Eur. J. Med. Res.* 2010, *15* Suppl. 2(Suppl. 2), 120-122. https://doi.org/10.1186/2047-783x-15-s2-120.

189 Ghosh, S.; Whitley, C.S.; Haribabu, B.; Jala, V.R. Regulation of Intestinal Barrier Function by Microbial Metabolites. *Cell. Mol. Gastroenterol. Hepatol.* 2021, *11*(5), 1463-1482. https://doi.org/10.1016/j.jcmgh.2021.02.007.

190 Stolfi, C.; Maresca, C.; Monteleone, G.; Laudisi, F. Implication of Intestinal Barrier Dysfunction in Gut Dysbiosis and Diseases. *Biomedicines* 2022, *10*, 289. https://doi.org/10.3390/biomedicines10020289.

191 Olivo-Martínez, Y.; Bosch, M.; Badia, J.; Baldomà, L. Modulation of the Intestinal Barrier Integrity and Repair by Microbiota Extracellular Vesicles through the Differential Regulation of Trefoil Factor 3 in LS174T Goblet Cells. *Nutrients* 2023, *15*, 2437. https://doi.org/10.3390/nu15112437.

192 Wang, J.; Zhu, N.; Su, X.; Gao, Y.; Yang, R. Gut-Microbiota-Derived Metabolites Maintain Gut and Systemic Immune Homeostasis. *Cells* 2023, *12*(5), 793. https://doi.org/10.3390/cells12050793.

193 Zheng, F.; Gonçalves, F.M.; Abiko, Y.; Li, H.; Kumagai, Y.; Aschner, M. Redox toxicology of environmental chemicals causing oxidative stress. *Redox Biol.* 2020, *34*, 101475. https://doi.org/10.1016/j.redox.2020.101475.

194 Esteves, F.; Rueff, J.; Kranendonk, M. The Central Role of Cytochrome P450 in Xenobiotic Metabolism – A Brief Review on a Fascinating Enzyme Family. *J. Xenobiot.* 2021, *11*(3), 94-114. https://doi.org/10.3390/jox11030007.

195 Srivastava, R.K.; Lutz, B.; Ruiz de Azua, I. The Microbiome and Gut Endocannabinoid System in the Regulation of Stress Responses and Metabolism. *Front. Cell. Neurosci.* 2022, *16*, 867267. https://doi.org/10.3389/fncel.2022.867267.

196 Crowley, K.; Kiraga, Ł.; Miszczuk, E.; Skiba, S.; Banach, J.; Latek, U.; Mendel, M.; Chłopecka, M. Effects of Cannabinoids on Intestinal Motility, Barrier Permeability, and Therapeutic Potential in Gastrointestinal Diseases. *Int. J. Mol. Sci.* 2024, *25*(12), 6682. https://doi.org/10.3390/ijms25126682.

197 Peng, C.; Ouyang, Y.; Lu, N.; Li, N. The NF-κB Signaling Pathway, the Microbiota, and Gastrointestinal Tumorigenesis: Recent Advances. *Front. Immunol.* 2020, *11*, 1387. https://doi.org/10.3389/fimmu.2020.01387.

198 Xu, R.; Cao, J.W.; Lv, H.L.; Geng, Y.; Guo, M.Y. Polyethylene microplastics induced gut microbiota dysbiosis leading to liver injury via the TLR2/NF-κB/NLRP3 pathway in mice. *Sci. Total Environ.* 2024, *917*, 170518. https://doi.org/10.1016/j.scitotenv.2024.170518.

199 Lin, H.; Li, X.; Gao, H.; Hu, W.; Yu, S.; Li, X.; Lei, L.; Yang, F. The role of gut microbiota in mediating increased toxicity of nano-sized polystyrene compared to micro-sized polystyrene in mice. *Chemosphere* 2024, *358*, 142275. https://doi.org/10.1016/j.chemosphere.2024.142275.

200 Liu, H.; Nie, H.; Shi, Y.; Lai, W.; Bian, L.; Tian, L.; Li, K.; Xi, Z.; Lin, B. Oil mistparticulate matter exposure induces hyperlipidemia-related inflammation via microbiota/ SCFAs/GPR43 axis inhibition and TLR4/NF-κB activation. *Environ. Pollut.* 2024, *344*, 123331. https://doi.org/10.1016/j.envpol.2024.123331.

201 Lu, Z.J.; Shi, W.J.; Qiao, L.K.; Ma, D.D.; Zhang, J.G.; Yao, C.R.; Li, S.Y.; Long, X.B.; Ying, G.G. Benzimidazole Fungicide Carbendazim Induces Gut Inflammation through the TLR5/NF-κB Pathway in Grass Carp. *Environ. Sci. Technol.* 2025, *59*(5), 2473-2483. https://doi.org/10.1021/acs.est.4c12695.

202 Duan, X.; Cai, H.; Hu, T.; Lin, L.; Zeng, L.; Wang, H.; Cao, L.; Li, X. Ginsenoside Rg3 treats acute radiation proctitis through the TLR4/MyD88/NF-κB pathway and regulation of intestinal flora. *Front. Cell. Infect. Microbiol.* 2023, *12*, 1028576. https://doi.org/10.3389/fcimb.2022.1028576.

203 Liu, Y.; Lin, S.; Wang, C.; Li, T.; Zheng, G.; Sun, W.; An, L.; Bai, Y.; Wu, F. Sex-Specific Effects of Environmental Exposure to the Antimicrobial Agents Benzalkonium Chloride and Triclosan on the Gut Microbiota and Health of Zebrafish (*Danio rerio*). *Environ. Sci. Technol.* 2024, *58*(35), 15450-15462. https://doi.org/10.1021/acs.est.4c03205.

204 Chen, F.; Shi, X. Signaling from toxic metals to NF-kappaB and beyond: not just a matter of reactive oxygen species. *Environ. Health Perspect.* 2002, *110* Suppl. 5(Suppl. 5), 807-811. https://doi.org/10.1289/ehp.02110s5807.

205 Øvrevik, J.; Refsnes, M.; Låg, M.; Holme, J.A.; Schwarze, P.E. Activation of Proinflammatory Responses in Cells of the Airway Mucosa by Particulate Matter: Oxidant- and Non-Oxidant-Mediated Triggering Mechanisms. *Biomolecules* 2015, *5*, 1399-1440. https://doi.org/10.3390/biom5031399.

206 Cao, J.; Xu, R.; Geng, Y.; Xu, S.; Guo, M. Exposure to polystyrene microplastics triggers lung injury via targeting toll-like receptor 2 and activation of the NF-κB signal in mice. *Environ. Pollut.* 2023, *320*, 121068. https://doi.org/10.1016/j.envpol.2023.121068.

207 Wang, J.; Yan, Y.; Si, H.; Li, J.; Zhao, Y.; Gao, T.; Pi, J.; Zhang, R.; Chen, R.; Chen, W.; Zheng, Y.; Jiang, M. The effect of real-ambient $PM_{2.5}$ exposure on the lung and gut microbiomes and the regulation of Nrf2. *Ecotoxicol. Environ. Saf.* 2023, *254*, 114702. https://doi.org/10.1016/j.ecoenv.2023.114702.

208 Han, B.; Li, X.; Ai, R.S.; Deng, S.Y.; Ye, Z.Q.; Deng, X.; Ma, W.; Xiao, S.; Wang, J.Z.; Wang, L.M.; Xie, C.; Zhang, Y.; Xu, Y.; Zhang, Y. Atmospheric particulate matter aggravates cns demyelination through involvement of TLR-4/NF-kB signaling and microglial activation. *Elife* 2022, *11*, e72247 https://doi.org/10.7554/eLife.72247.

209 Lopes-Ferreira, M.; Farinha, L.R.L.; Costa, Y.S.O.; Pinto, F.J.; Disner, G.R.; da Rosa, J.G.D.S.; Lima, C. Pesticide-Induced Inflammation at a Glance. *Toxics* 2023, *11*(11), 896. https://doi.org/10.3390/toxics11110896.

210 Poritz, L.S.; Harris, L.R. 3rd; Kelly, A.A.; Koltun, W.A. Increase in the tight junction protein claudin-1 in intestinal inflammation. *Dig. Dis. Sci.* 2011, *56*(10), 2802-2809. https://doi.org/10.1007/s10620-011-1688-9.

211 Bellezza, I,.; Giambanco, I.; Minelli, A.; Donato, R. Nrf2-Keap1 signaling in oxidative and reductive stress. *Biochim. Biophys. Acta Mol. Cell. Res.* 2018, *1865*(5), 721-733. https://doi.org/10.1016/j.bbamcr.2018.02.010.

212 He, F.; Ru, X.; Wen, T. NRF2, a Transcription Factor for Stress Response and Beyond. *Int. J. Mol. Sci.* 2020, *21*(13), 4777. https://doi.org/10.3390/ijms21134777.

213 Pardo, M.; Qiu, X.; Zimmermann, R.; Rudich, Y. Particulate Matter Toxicity Is Nrf2 and Mitochondria Dependent: The Roles of Metals and Polycyclic Aromatic Hydrocarbons. *Chem. Res. Toxicol.* 2020, *33*(5), 1110-1120. https://doi.org/10.1021/acs.chemrestox.0c00007.

214 Park, B.; London, N.R. Jr.; Tharakan, A.; Rengasamy, P.; Rajagopalan, S.; Biswal, S.; Pinto, J.M.; Ramanathan, M.Jr. Particulate matter air pollution exposure disrupts the Nrf2 pathway in sinonasal epithelium via epigenetic alterations in a murine model. *Int. Forum Allergy Rhinol.* 2022, *12*(11), 1424-1427. https://doi.org/10.1002/alr.23010.

215 Ngo, V.; Duennwald, M.L. Nrf2 and Oxidative Stress: A General Overview of Mechanisms and Implications in Human Disease. *Antioxidants (Basel)* 2022, *11*(12), 2345. https://doi.org/10.3390/antiox11122345.

216 Saeedi, B.J.; Liu, K.H.; Owens, J.A.; Hunter-Chang, S.; Camacho, M.C.; Eboka, R.U.; Chandrasekharan, B.; Baker, N.F.; Darby, T.M.; Robinson, B.S.; Jones, R.M.; Jones, D.P.; Neish, A.S. Gut-Resident *Lactobacilli* Activate Hepatic Nrf2 and Protect Against Oxidative Liver Injury. *Cell Metab.* 2020, *31*(5), 956-968.e5 https://doi.org/10.1016/j.cmet.2020.03.006.

217 Wang, L.; Zhao, Z.; Zhao, L.; Zhao, Y.; Yang, G.; Wang, C.; Gao, L.; Niu, C.; Li, S. *Lactobacillus plantarum* DP189 Reduces α-SYN Aggravation in MPTP-Induced Parkinson's Disease Mice via Regulating Oxidative Damage, Inflammation, and Gut Microbiota Disorder. *J. Agric. Food Chem.* 2022, *70*(4), 1163-1173. https://doi.org/10.1021/acs.jafc.1c07711.

218 Xu, Y.; Li, N.; Xiang, R.; Sun, P. Emerging roles of the p38 MAPK and PI3K/AKT/mTOR pathways in oncogene-induced senescence. *Trends Biochem. Sci.* 2014, *39*(6), 268-276. https://doi.org/10.1016/j.tibs.2014.04.004.

219 Su, R.; Jin, X.; Zhang, W.; Li, Z.; Liu, X.; Ren, J. Particulate matter exposure induces the autophagy of macrophages via oxidative stress-mediated PI3K/AKT/mTOR pathway. *Chemosphere* 2017, *167*, 444-453. https://doi.org/10.1016/j.chemosphere.2016.10.024.

220 Han, X.; Zhuang, Y. $PM_{2.5}$ induces autophagy-mediated cell apoptosis via PI3K/AKT/mTOR signaling pathway in mice bronchial epithelium cells. *Exp. Ther. Med.* 2021, *21*(1), 1. https://doi.org/10.3892/etm.2020.9433.

221 Guo, M.; Wang, Y.; Zhao, H.; Wang, D.; Yin, K.; Liu, Y.; Li, B.; Xing, M. Zinc antagonizes common carp (*Cyprinus carpio*) intestinal arsenic poisoning through PI3K/AKT/mTOR signaling cascade and MAPK pathway. *Aquat. Toxicol.* 2021, 240, 105986. https://doi.org/10.1016/j.aquatox.2021.105986.

222 Yin, H.; Zuo, Z.; Yang, Z.; Guo, H.; Fang, J.; Cui, H.; Ouyang, P.; Chen, X.; Chen, J.; Geng, Y.; Chen, Z.; Huang, C.; Zhu, Y. Nickel induces autophagy via PI3K/AKT/mTOR and AMPK pathways in mouse kidney. *Ecotoxicol. Environ. Saf.* 2021, 223, 112583. https://doi.org/10.1016/j.ecoenv.2021.112583.

223 Zhang, F.; Ma, H.; Wang, Z.L.; Li, W.H.; Liu, H.; Zhao, Y.X. The PI3K/AKT/mTOR pathway regulates autophagy to induce apoptosis of alveolar epithelial cells in chronic obstructive pulmonary disease caused by $PM_{2.5}$ particulate matter. *J. Int. Med. Res.* 2020, *48*(7), 300060520927919. https://doi.org/10.1177/0300060520927919.

224 Lu, H.; Yin, K.; Su, H.; Wang, D.; Zhang, Y.; Hou, L.; Li, J.B.; Wang, Y.; Xing, M. Polystyrene microplastics induce autophagy and apoptosis in birds lungs via PTEN/PI3K/AKT/mTOR. *Environ. Toxicol.* 2023, *38*(1), 78-89. https://doi.org/10.1002/tox.23663.

225 Sun, W.; Lei, Y.; Jiang, Z.; Wang, K.; Liu, H.; Xu, T. BPA and low-Se exacerbate apoptosis and mitophagy in chicken pancreatic cells by regulating the PTEN/PI3K/AKT/mTOR pathway. *J. Adv. Res.* 2025, *67*, 61-69. https://doi.org/10.1016/j.jare.2024.01.029.

226 Dong, Y.; Gao, L.; Sun, Q.; Jia, L.; Liu, D. Increased levels of IL-17 and autoantibodies following Bisphenol A exposure were associated with activation of PI3K/AKT/mTOR pathway and abnormal autophagy in MRL/lpr mice. *Ecotoxicol. Environ. Saf.* 2023, *255*, 114788. https://doi.org/10.1016/j.ecoenv.2023.114788.

227 Santoro, A.; Chianese, R.; Troisi, J.; Richards, S.; Nori, S.L.; Fasano, S.; Guida, M.; Plunk, E.; Viggiano, A.; Pierantoni, R.; Meccariello, R. Neuro-toxic and Reproductive Effects of BPA. *Curr. Neuropharmacol.* 2019, *17*(12), 1109-1132 https://doi.org/10.2174/1570159X17666190726112101.

228 Braun, J.M. Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. *Nat. Rev. Endocrinol.* 2017, *13*(3), 161-173. https://doi.org/10.1038/nrendo.2016.186.

229 Chakraborty, S.; Dissanayake, M.; Godwin, J.; Wang, X.; Bhandari, R.K. Ancestral BPA exposure caused defects in the liver of medaka for four generations. *Sci. Total Environ.* 2023, *856*(Pt. 1), 159067. https://doi.org/10.1016/j.scitotenv.2022.159067.

230 Zhang, Y.; Dong, T.; Hu, W.; Wang, X.; Xu, B.; Lin, Z.; Hofer, T.; Stefanoff, P.; Chen, Y.; Wang, X.; Xia, Y. Association between exposure to a mixture of phenols, pesticides, and phthalates and obesity: Comparison of three statistical models. *Environ. Int.* 2019, *123*, 325-336. https://doi.org/10.1016/j.envint.2018.11.076.

231 Sonavane, M.; Gassman, NR. Bisphenol A co-exposure effects: a key factor in understanding BPA's complex mechanism and health outcomes. *Crit Rev Toxicol.* 2019, *49*(5), 371-386. https://doi.org/10.1080/10408444.2019.1621263.

232 Sultan, M.; Cai, Z.X.; Bao, L.; Duan, J.J.; Liu, Y.Y.; Yang, G.; Pei, D.S. Trophic transfer induced gut inflammation, dysbiosis, and inflammatory pathways in zebrafish via *Artemia franciscana*: A differential analysis of nanoplastic toxicity. *J. Hazard. Mater.* 2024, *480*, 136030. https://doi.org/10.1016/j.jhazmat.2024.136030.

233 Xie, X.; Deng, T.; Duan, J.; Xie, J.; Yuan, J.; Chen, M. Exposure to polystyrene microplastics causes reproductive toxicity through oxidative stress and activation of the p38 MAPK signaling pathway. *Ecotoxicol. Environ. Saf.* 2020, *190*, 110133. https://doi.org/10.1016/j.ecoenv.2019.110133.

234 Li, J.; Weng, H.; Liu, S.; Li, F.;Xu, K.; Wen, S.; Chen, X.; Li, C.; Nie, Y.; Liao, B.; Wu, J.; Kantawong, F.; Xie, X.; Yu, F.; Li, G. Embryonic exposure of polystyrene nanoplastics affects cardiac development. *Sci. Total Environ.* 2024, *906*, 167406. https://doi.org/10.1016/j.scitotenv.2023.167406.

235 Cao, X.; Fu, M.; Bi, R.; Zheng, X.; Fu, B.; Tian, S.; Liu, C.; Li, Q.; Liu, J. Cadmium induced BEAS-2B cells apoptosis and mitochondria damage via MAPK signaling pathway. *Chemosphere* 2021, *263*, 128346. .://doi.org/10.1016/j.chemosphere.2020.128346.

236 Liu, X,.; Zhang, R.; Fan, J.; Chen, Y.; Wang, H.; Ge, Y.; Liang, H.; Li, W.; Liu, H.; Lv, Z.; Dou, W.; Jiang, H.; Li, X. The role of ROS/p38 MAPK/NLRP3 inflammasome cascade in arsenic-induced depression-/anxiety-like behaviors of mice. *Ecotoxicol. Environ. Saf.* 2023, *261*, 115111. https://doi.org/10.1016/j.ecoenv.2023.115111.

237 Ijomone, O.M.; Iroegbu, J.D.; Aschner, M.; Bornhorst, J. Impact of environmental toxicants on p38- and ERK-MAPK signaling pathways in the central nervous system. *Neurotoxicology* 2021, *86*, 166-171. https://doi.org/10.1016/j.neuro.2021.08.005.

238 Han, L.; Haefner, V.; Yu, Y.; Han, B.; Ren, H.; Irmler, M.; Beckers, J.; Liu, Q.; Feuchtinger, A.; Yildirim, A.O.; Adler, H.; Stoeger, T. Nanoparticle-Exposure-Triggered Virus Reactivation Induces Lung Emphysema in Mice. *ACS Nano* 2023, *17*(21), 21056-21072. https://doi.org/10.1021/acsnano.3c04111.

239 Sarapultsev, A.; Gusev, E.; Komelkova, M.; Utepova, I.; Luo, S.; Hu, D. JAK-STAT signaling in inflammation and stress-related diseases: implications for therapeutic interventions. *Mol. Biomed.* 2023, *4*(1), 40. https://doi.org/10.1186/s43556-023-00151-1.

240 Hu, Q.; Bian, Q.; Rong, D.; Wang, L.; Song, J.; Huang, H.S.; Zeng, J.; Mei, J.; Wang, P.Y. JAK/STAT pathway: Extracellular signals, diseases, immunity, and therapeutic regimens. *Front. Bioeng. Biotechnol.* 2023, *11*, 1110765 https://doi.org/10.3389/fbioe.2023.1110765.

241 Hu, X.; Li, J.; Fu, M.; Zhao, X.; Wang, W. The JAK/STAT signaling pathway: from bench to clinic. *Signal Transduct. Target Ther.* 2021, *6*(1), 402. https://doi.org/10.1038/s41392-021-00791-1.

242 Giovannini, S.; Onder, G.; Liperoti, R.; Russo, A.; Carter, C.; Capoluongo, E.; Pahor, M.; Bernabei, R.; Landi, F. Interleukin-6, C-reactive protein, and tumor necrosis factor-alpha as predictors of mortality in frail, community-living elderly individuals. *J. Am. Geriatr. Soc.* 2011, *59*(9), 1679-1685. https://doi.org/10.1111/j.1532-5415.2011.03570.x.

243 Heinzel, S.; Jureczek, J.; Kainulainen, V.; Nieminen, A.I.; Suenkel, U.; von Thaler, A.K.; Kaleta, C.; Eschweiler, G.W.; Brockmann, K.; Aho, V.T.E.; Auvinen, P.; Maetzler, W.; Berg, D.; Scheperjans, F. Elevated fecal calprotectin is associated with gut microbial dysbiosis, altered serum markers and clinical outcomes in older individuals. *Sci. Rep.* 2024, *14*(1), 13513. https://doi.org/10.1038/s41598-024-63893-0.

244 Jin, H.; Liu, Y.; Lei, Y.; Li, G.; Huang, L.; Zhang, Z. Hsa_circ_0004214 involved in the epithelial-mesenchymal transition induced by beryllium sulfate through modulating JAK-STAT signaling pathway. *Toxicol. Res. (Camb.)* 2024, *13*(3), tfae067. https://doi.org/10.1093/toxres/tfae067.

245 Liu, M.; Li, Y.; Liang, B.; Li, Z.; Jiang, Z.; Chu, C.; Yang, J. Hydrogen sulfide attenuates myocardial fibrosis in diabetic rats through the JAK/STAT signaling pathway. *Int. J. Mol. Med.* 2018, 41(4), 1867-1876. https://doi.org/10.3892/ijmm.2018.3419.

246 Ji, X.; Han, M.; Yun, Y.; Li, G.; Sang, N. Acute nitrogen dioxide (NO_2) exposure enhances airway inflammation via modulating Th1/Th2 differentiation and activating JAK-STAT pathway. *Chemosphere* 2015, *120*, 722-8. https://doi.org/10.1016/j.chemosphere.2014.10.039.

247 Mobasher, M.A.; Alsirhani, A.M.; Alwaili, M.A.; Baakdah, F.; Eid, T.M.; Alshanbari, F.A.; Alzahri, R.Y.; Alkhodair, S.A.; El-Said, K.S. *Annona squamosa* Fruit Extract Ameliorates Lead Acetate-Induced Testicular Injury by Modulating JAK-1/STAT-3/SOCS-1 Signaling in Male Rats. *Int. J. Mol. Sci.* 2024, *25*(10), 5562. https://doi.org/10.3390/ijms25105562.

248 Kim, S.H.; Yu, S.Y.; Choo, J.H.; Kim, J.; Ahn, K.; Hwang, S.Y. Epigenetic Methylation Changes in Pregnant Women: Bisphenol Exposure and Atopic Dermatitis. *Int. J. Mol. Sci.* 2024, *25*(3), 1579. https://doi.org/10.3390/ijms25031579.

249 Wu, Y.F.; Li, Z.Y.; Dong, L.L.; Li, W.J.; Wu, Y.P.; Wang, J.; Chen, H.P.; Liu, H.W.; Li, M.; Jin, C.L.; Huang, H.Q.; Ying, S.M.; Li, W.; Shen, H.H.; Chen, Z.H. Inactivation of MTOR promotes autophagy-mediated epithelial injury in particulate matter-induced airway inflammation. *Autophagy* 2020, *16*(3), 435-450. https://doi.org/10.1080/15548627.2019.1628536.

250 Ciesielska, A.; Matyjek, M.; Kwiatkowska, K. TLR4 and CD14 trafficking and its influence on LPS-induced pro-inflammatory signaling. *Cell. Mol. Life Sci.* 2021, *78*(4), 1233-1261. https://doi.org/10.1007/s00018-020-03656-y.

251 Rong, Z.; Huang, Y.; Cai, H.; Chen, M.; Wang, H.; Liu, G.; Zhang, Z.; Wu, J. Gut Microbiota Disorders Promote Inflammation and Aggravate Spinal Cord Injury Through the TLR4/MyD88 Signaling Pathway. *Front. Nutr.* 2021, *8*, 702659. https://doi.org/10.3389/fnut.2021.702659.

252 Dai, Y.; Lu, Q.; Li, P.; Zhu, J.; Jiang, J.; Zhao, T.; Hu, Y.; Ding, K.; Zhao, M. Xianglian Pill attenuates ulcerative colitis through TLR4/MyD88/NF-κB signaling pathway. *J. Ethnopharmacol*. 2023, *300*, 115690. https://doi.org/10.1016/j.jep.2022.115690.

253 Lai, X.; Liu, B.; Wan, Y.; Zhou, P.; Li, W.; Hu, W.; Gong, W. Metformin alleviates colitis-associated colorectal cancer via inhibition of the TLR4/MyD88/NFκB/MAPK pathway and macrophage M2 polarization. *Int. Immunopharmacol*. 2025, *144*, 113683. https://doi.org/10.1016/j.intimp.2024.113683.

254 Duan, Y.; Dai, H.; An, Y.; Cheng, L.; Shi, L.; Lv, Y.; Li, H.; Wang, C.; He, C.; Zhang, H.; Huang, Y.; Fu, W.; Meng, Y.; Zhao, B. Mulberry Leaf Flavonoids Inhibit Liver Inflammation in Type 2 Diabetes Rats by Regulating TLR4/MyD88/NF-κB Signaling Pathway. *Evid. Based Complement. Alternat. Med*. 2022, *2022*, 3354062. https://doi.org/10.1155/2022/3354062.

255 Wang, L.; Yang, J.W.; Lin, L.T.; Huang, J.; Wang, X.R.; Su, X.T.; Cao, Y.; Fisher, M.; Liu, C.Z. Acupuncture Attenuates Inflammation in Microglia of Vascular Dementia Rats by Inhibiting miR-93-Mediated TLR4/MyD88/NF-κB Signaling Pathway. *Oxid. Med. Cell. Longev*. 2020, *2020*, 8253904. https://doi.org/10.1155/2020/8253904.

256 Zhao, Z.; Ning, J.; Bao, X.Q.; Shang, M.; Ma, J.; Li, G.; Zhang, D. Fecal microbiota transplantation protects rotenone-induced Parkinson's disease mice via suppressing inflammation mediated by the lipopolysaccharide-TLR4 signaling pathway through the microbiota-gut-brain axis. *Microbiome* 2021, *9*(1), 226. https://doi.org/10.1186/s40168-021-01107-9.

257 He, M.; Ichinose, T.; Yoshida, Y.; Arashidani, K.; Yoshida, S.; Takano, H.; Sun, G.; Shibamoto, T. Urban PM2.5 exacerbates allergic inflammation in the murine lung via a TLR2/TLR4/MyD88-signaling pathway. *Sci. Rep.* 2017, *7*(1), 11027. https://doi.org/10.1038/s41598-017-11471-y.

258 Wu, Y.; Xiao, W.; Pei, C.; Wang, M.; Wang, X.; Huang, D.; Wang, F.; Wang, Z. Astragaloside IV alleviates $PM_{2.5}$-induced lung injury in rats by modulating TLR4/MyD88/NF-κB signalling pathway. *Int. Immunopharmacol.* 2021, *91*, 107290. https://doi.org/10.1016/j.intimp.2020.107290.

259 Liu, G.; Lu, Y.; Shi, L.; Ren, Y.; Kong, J.; Zhang, M.; Chen, M.; Liu, W. TLR4-MyD88 signaling pathway is responsible for acute lung inflammation induced by reclaimed water. *J. Hazard. Mater.* 2020, *396*, 122586. https://doi.org/10.1016/j.jhazmat.2020.122586.

260 Wang, L.; Cui, Y.; Liu, H.; Wu, J.; Li, J.; Liu, X. $PM_{2.5}$ aggravates airway inflammation in asthmatic mice: activating NF-κB via MyD88 signaling pathway. *Int. J. Environ. Health Res.* 2023, *33*(6), 563-574. https://doi.org/10.1080/09603123.2022.2041561.

261 Panaro, M.A.; Corrado, A.; Benameur, T.; Paolo, C.F.; Cici, D.; Porro, C. The Emerging Role of Curcumin in the Modulation of TLR-4 Signaling Pathway: Focus on Neuroprotective and Anti-Rheumatic Properties. *Int. J. Mol. Sci.* 2020, *21*, 2299. https://doi.org/10.3390/ijms21072299.

262 Yang, J.Z.; Zhang, K.K.; Liu, Y.; Li, X.W.; Chen, L.J.; Liu, J.L.; Li, J.H.; Chen, L.; Hsu, C.; Zeng, J.H.; Xie, X.L.; Wang, Q. Epigallocatechin-3-gallate ameliorates polystyrene microplastics-induced anxiety-like behavior in mice by modulating gut microbe homeostasis. *Sci. Total Environ.* 2023, *892*, 164619 https://doi.org/10.1016/j.scitotenv.2023.164619.

263 Shi, Z.; Jiao, Y.; Lai, Z.; Liu, J.; Yang, B.; Hu, M.; Meng, J. Evaluation of the protective role of resveratrol on LPS-induced septic intestinal barrier function via TLR4/MyD88/NF-κB signaling pathways. *Sci. Rep.* 2025, *15*(1), 828. https://doi.org/10.1038/s41598-025-85148-2.

264 Pan, I.; Umapathy, S. Probiotics an emerging therapeutic approach towards gut-brain-axis oriented chronic health issues induced by microplastics: A comprehensive review. *Heliyon* 2024, *10*(11), e32004. https://doi.org/10.1016/j.heliyon.2024.e32004.

265 Sobolev, V.V.; Tchepourina, E.; Korsunskaya, I.M.; Geppe, N.A.; Chebysheva, S.N.; Soboleva, A.G.; Mezentsev, A. The Role of Transcription Factor PPAR-γ in the Pathogenesis of Psoriasis, Skin Cells, and Immune Cells. *Int. J. Mol. Sci.* 2022, *23*(17), 9708. https://doi.org/10.3390/ijms23179708.

266 Posta, E.; Fekete, I.; Varkonyi, I.; Zold, E.; Barta, Z. The Versatile Role of Peroxisome Proliferator-Activated Receptors in Immune-Mediated Intestinal Diseases. *Cells* 2024, *13*, 1688. https://doi.org/10.3390/cells13201688.

267 Grabacka, M.; Płonka, P.M.; Pierzchalska, M. The PPARα Regulation of the Gut Physiology in Regard to Interaction with Microbiota, Intestinal Immunity, Metabolism, and Permeability. *Int. J. Mol. Sci.* 2022, *23*(22), 14156. https://doi.org/10.3390/ijms232214156.

268 Christofides, A.; Konstantinidou, E.; Jani, C.; Boussiotis, V.A. The role of peroxisome proliferator-activated receptors (PPAR) in immune responses. *Metabolism* 2021, *114*, 154338. https://doi.org/10.1016/j.metabol.2020.154338.

269 Hasan, A.U.; Rahman, A.; Kobori, H. Interactions between Host PPARs and Gut Microbiota in Health and Disease. *Int. J. Mol. Sci.* 2019, *20*, 387. https://doi.org/10.3390/ijms20020387.

270 Gagliardi, A.; Totino, V.; Cacciotti, F.; Iebba, V.; Neroni, B.; Bonfiglio, G.; Trancassini, M.; Passariello, C.; Pantanella, F.; Schippa, S. Rebuilding the Gut Microbiota Ecosystem. *Int. J. Environ. Res. Public Health* 2018, *15*(8), 1679. https://doi.org/10.3390/ijerph15081679.

271 Pérez-Reytor, D.; Puebla, C.; Karahanian, E.; García, K. Use of Short-Chain Fatty Acids for the Recovery of the Intestinal Epithelial Barrier Affected by Bacterial Toxins. *Front. Physiol.* 2021, *12*, 650313. https://doi.org/10.3389/fphys.2021.650313.

272 O'Riordan, K.J.; Collins, M.K.; Moloney, G.M.; Knox, E.G.; Aburto, M.R.; Fülling, C.; Morley, S.J.; Clarke, G.; Schellekens, H.; Cryan, J.F. Short chain fatty acids: Microbial metabolites for gut-brain axis signalling. *Mol. Cell Endocrinol.* 2022, *546*, 111572. https://doi.org/10.1016/j.mce.2022.111572.

273 Yuan, G.; Chen, X.; Li, D. Modulation of peroxisome proliferator-activated receptor gamma (PPAR γ) by conjugated fatty acid in obesity and inflammatory bowel disease. *J. Agric. Food Chem.* 2015, *63*(7), 1883-1895. https://doi.org/10.1021/jf505050c.

274 Roudsari, N.M.; Lashgari, N.A.; Zandi, N.; Pazoki, B.; Momtaz, S.; Sahebkar, A.; Abdolghaffari, A.H. PPARγ: A turning point for irritable bowel syndrome treatment. *Life Sci.* 2020, *257*, 118103. https://doi.org/10.1016/j.lfs.2020.118103.

275 Massier, L.; Blüher, M.; Kovacs, P.; Chakaroun, R.M. Impaired Intestinal Barrier and Tissue Bacteria: Pathomechanisms for Metabolic Diseases. *Front. Endocrinol. (Lausanne)* 2021, *12*, 616506. https://doi.org/10.3389/fendo.2021.616506.

276 Shemtov, S.J.; Emani, R.; Bielska, O.; Covarrubias, A.J.; Verdin, E.; Andersen, J.K.; Winer, D.A. The intestinal immune system and gut barrier function in obesity and ageing. *FEBS J.* 2023, *290*(17), 4163-4186. https://doi.org/10.1111/febs.16558.

277 Bischoff, S.C.; Barbara, G.; Buurman, W.; Ockhuizen, T.; Schulzke, J.D.; Serino, M.; Tilg, H.; Watson, A.; Wells, J.M. Intestinal permeability – a new target for disease prevention and therapy. *BMC Gastroenterol.* 2014, *14*, 189. https://doi.org/10.1186/s12876-014-0189-7.

278 Janeiro, M.H.; Ramírez, M.J.; Milagro, F.I.; Martínez, J.A.; Solas, M. Implication of Trimethylamine N-Oxide (TMAO) in Disease: Potential Biomarker or New Therapeutic Target. *Nutrients* 2018, *10*, 1398. https://doi.org/10.3390/nu10101398.

279 Stummer, N.; Feichtinger, R.G.; Weghuber, D.; Kofler, B.; Schneider, A.M. Role of Hydrogen Sulfide in Inflammatory Bowel Disease. *Antioxidants* 2023, *12*, 1570. https://doi.org/10.3390/antiox12081570.

280 Zhang, H.; Zha, X.; Zhang, B.; Zheng, Y.; Elsabagh, M.; Wang, H.; Wang, M. Gut microbiota contributes to bisphenol A-induced maternal intestinal and placental apoptosis, oxidative stress, and fetal growth restriction in pregnant ewe model by regulating gut-placental axis. *Microbiome* 2024, *12*(1), 28. https://doi.org/10.1186/s40168-024-01749-5.

281 Hong, T.; Zou, J.; He, Y.; Zhang, H.; Liu, H.; Mai, H.; Yang, J.; Cao, Z.; Chen, X.; Yao, J.; Feng, D. Bisphenol A induced hepatic steatosis by disturbing bile acid metabolism and FXR/TGR5 signaling pathways via remodeling the gut microbiota in CD-1 mice. *Sci. Total Environ.* 2023, *889*, 164307. https://doi.org/10.1016/j.scitotenv.2023.164307.

282 Wang, G.; Pan, R.; Liang, X.; Wu, X.; Wu, Y.; Zhang, H.; Zhao, J.; Chen, W. Perfluorooctanoic acid-induced liver injury is potentially associated with gut microbiota dysbiosis. *Chemosphere* 2021, *266*, 129004. https://doi.org/10.1016/j.chemosphere.2020.129004.

283 Ma, N.; Ma, D.; Liu, X.; Zhao, L.; Ma, L.; Ma, D.; Dong, S. Bisphenol P exposure in C57BL/6 mice caused gut microbiota dysbiosis and induced intestinal barrier disruption via LPS/TLR4/NF-κB signaling pathway. *Environ. Int.* 2023, *175*, 107949. https://doi.org/10.1016/j.envint.2023.107949.

284 Feng, D.; Zhang, H.; Jiang, X.; Zou, J.; Li, Q.; Mai, H.; Su, D.; Ling, W.; Feng, X. Bisphenol A exposure induces gut microbiota dysbiosis and consequent activation of gut-liver axis leading to hepatic steatosis in CD-1 mice. *Environ. Pollut.* 2020, *265*(Pt. A), 114880. https://doi.org/10.1016/j.envpol.2020.114880.

285 Liu, R.; Cai, D.; Li, X.; Liu, B.; Chen, J.; Jiang, X.; Li, H.; Li, Z.; Teerds, K.; Sun, J.; Bai, W.; Jin, Y. Effects of Bisphenol A on reproductive toxicity and gut microbiota dysbiosis in male rats. *Ecotoxicol. Environ. Saf.* 2022, *239*, 113623. https://doi.org/10.1016/j.ecoenv.2022.113623.

286 Hong, T.; Jiang, X.; Zou, J.; Yang, J.; Zhang, H.; Mai, H.; Ling, W.; Feng, D. Hepatoprotective effect of curcumin against bisphenol A-induced hepatic steatosis via modulating gut microbiota dysbiosis and related gut-liver axis activation in CD-1 mice. *J. Nutr. Biochem.* 2022, *109*, 109103. https://doi.org/10.1016/j.jnutbio.2022.109103.

287 Wu, L.; Lv, X.; Zhang, Y.; Xin, Q.; Zou, Y.; Li, X. Tartrazine exposure results in histological damage, oxidative stress, immune disorders and gut microbiota dysbiosis in juvenile crucian carp (*Carassius carassius*). *Aquat. Toxicol.* 2021, *241*, 105998. https://doi.org/10.1016/j.aquatox.2021.105998.

288 Tang, J.; Wang, W.; Jiang, Y.; Chu, W. Diazinon exposure produces histological damage, oxidative stress, immune disorders and gut microbiota dysbiosis in crucian carp (*Carassius auratus gibelio*). *Environ. Pollut.* 2021, *269*, 116129. https://doi.org/10.1016/j.envpol.2020.116129.

289 Pei, X.; Heng, X.; Chu, W. Polystyrene nano/microplastics induce microbiota dysbiosis, oxidative damage, and innate immune disruption in zebrafish. *Microb. Pathog.* 2022, *163*, 105387. https://doi.org/10.1016/j.micpath.2021.105387.

290 Jiang, D.; Yang, Y.; Han, X.; Li, Q.; Jiao, J.; Ma, Y.; Chao, L. Gut microbiota combined with metabolome dissects Fluorene-9-bisphenol exposure-induced male reproductive toxicity. *Environ. Pollut.* 2025, *364*(Pt. 1), 125339. https://doi.org/10.1016/j.envpol.2024.125339.

291 Lin, H.; Wu, H.; Liu, F.; Yang, H.; Shen, L.; Chen, J.; Zhang, X.; Zhong, Y.; Zhang, H.; Liu, Z. Assessing the hepatotoxicity of PFOA, PFOS, and 6:2 Cl-PFESA in black-spotted frogs (*Rana nigromaculata*) and elucidating potential association with gut microbiota. *Environ. Pollut.* 2022, *312*, 120029. https://doi.org/10.1016/j.envpol.2022.120029.

292 López-Moreno, A.; Torres-Sánchez, A.; Acuña, I.; Suárez, A.; Aguilera, M. Representative *Bacillus* sp. AM1 from Gut Microbiota Harbor Versatile Molecular Pathways for Bisphenol A Biodegradation. *Int. J. Mol. Sci.* 2021, *22*(9), 4952. https://doi.org/10.3390/ijms22094952.

293 DeGruttola, A.K.; Low, D.; Mizoguchi, A.; Mizoguchi, E. Current Understanding of Dysbiosis in Disease in Human and Animal Models. *Inflamm. Bowel Dis.* 2016, *22*(5), 1137-1150. https://doi.org/10.1097/MIB.0000000000000750.

294 Zhao, M.; Chu, J.; Feng, S.; Guo, C.; Xue, B.; He, K.; Li, L. Immunological mechanisms of inflammatory diseases caused by gut microbiota dysbiosis: A review. *Biomed. Pharmacother*. 2023, *164*, 114985. https://doi.org/10.1016/j.biopha.2023.114985.

295 Shim, J.A.; Ryu, J.H.; Jo, Y.; Hong, C. The role of gut microbiota in T cell immunity and immune mediated disorders. *Int. J. Biol. Sci.* 2023, *19*(4), 1178-1191. https://doi.org/10.7150/ijbs.79430.

296 de Mello, A.H.; Costa, A.B.; Engel, J.D.G.; Rezin, G.T. Mitochondrial dysfunction in obesity. *Life Sci.* 2018, *192*, 26-32. https://doi.org/10.1016/j.lfs.2017.11.019.

297 Pinti, M.V.; Fink, G.K.; Hathaway, Q.A.; Durr, A.J.; Kunovac, A.; Hollander, J.M. Mitochondrial dysfunction in type 2 diabetes mellitus: an organ-based analysis. *Am. J. Physiol. Endocrinol. Metab.* 2019, *316*(2), E268-E285. https://doi.org/10.1152/ajpendo.00314.2018.

298 Prasun, P.; Ginevic, I.; Oishi, K. Mitochondrial dysfunction in nonalcoholic fatty liver disease and alcohol related liver disease. *Transl. Gastroenterol. Hepatol.* 2021, *6*, 4. https://doi.org/10.21037/tgh-20-125.

299 Alizadeh, A.; Akbari, P.; Garssen, J.; Fink-Gremmels, J.; Braber, S. Epithelial integrity, junctional complexes, and biomarkers associated with intestinal functions. *Tissue Barriers* 2022, *10*(3), 1996830 https://doi.org/10.1080/21688370.2021.1996830.

300 König, J.; Wells, J.; Cani, P.D.; García-Ródenas, C.L.; MacDonald, T.; Mercenier, A.; Whyte, J.; Troost, F.; Brummer, R.J. Human Intestinal Barrier Function in Health and Disease. *Clin. Transl. Gastroenterol.* 2016, *7*(10), e196. https://doi.org/10.1038/ctg.2016.54.

301 Mohammad, S.; Thiemermann, C. Role of Metabolic Endotoxemia in Systemic Inflammation and Potential Interventions. *Front. Immunol.* 2021, *11*, 594150. https://doi.org/10.3389/fimmu.2020.594150.

302 Scheithauer, T.P.M.; Rampanelli, E.; Nieuwdorp, M.; Vallance, B.A.; Verchere, C.B.; van Raalte, D.H.; Herrema, H. Gut Microbiota as a Trigger for Metabolic Inflammation in Obesity and Type 2 Diabetes. *Front. Immunol.* 2020, *11*, 571731. https://doi.org/10.3389/fimmu.2020.571731.

303 Kustrimovic, N.; Balkhi, S.; Bilato, G.; Mortara, L. Gut Microbiota and Immune System Dynamics in Parkinson's and Alzheimer's Diseases. *Int. J. Mol. Sci.* 2024, *25*, 12164. https://doi.org/10.3390/ijms252212164.

304 Wu, H.J.; Wu, E. The role of gut microbiota in immune homeostasis and autoimmunity. *Gut Microbes* 2012, *3*(1), 4-14. https://doi.org/10.4161/gmic.19320.

305 Mousa, W.K.; Chehadeh, F.; Husband, S. Microbial dysbiosis in the gut drives systemic autoimmune diseases. *Front. Immunol.* 2022, *13*, 906258. https://doi.org/10.3389/fimmu.2022.906258.
306 Wiertsema, S.P.; van Bergenhenegouwen, J.; Garssen, J.; Knippels, L.M.J. The Interplay between the Gut Microbiome and the Immune System in the Context of Infectious Diseases throughout Life and the Role of Nutrition in Optimizing Treatment Strategies. *Nutrients* 2021, *13*(3), 886. https://doi.org/10.3390/nu13030886.
307 Wang, S.; Ju, D.; Zeng, X. Mechanisms and Clinical Implications of Human Gut Microbiota-Drug Interactions in the Precision Medicine Era. *Biomedicines* 2024, *12*, 194. https://doi.org/10.3390/biomedicines12010194.
308 Al-Habsi, N.; Al-Khalili, M.; Haque, S.A.; Elias, M.; Olqi, N.A.; Al Uraimi, T. Health Benefits of Prebiotics, Probiotics, Synbiotics, and Postbiotics. *Nutrients* 2024, *16*(22), 3955. https://doi.org/10.3390/nu16223955.
309 Chandrasekaran, P.; Weiskirchen, S.; Weiskirchen, R. Effects of Probiotics on Gut Microbiota: An Overview. *Int. J. Mol. Sci.* 2024, *25*(11), 6022. https://doi.org/10.3390/ijms25116022.
310 Slavin, J. Fiber and prebiotics: mechanisms and health benefits. *Nutrients* 2013, *5*(4), 1417-1435. https://doi.org/10.3390/nu5041417.
311 Davani-Davari, D.; Negahdaripour, M.; Karimzadeh, I.; Seifan, M.; Mohkam, M.; Masoumi, S.J.; Berenjian, A.; Ghasemi, Y. Prebiotics: Definition, Types, Sources, Mechanisms, and Clinical Applications. *Foods* 2019, *8*(3), 92. https://doi.org/10.3390/foods8030092.
312 Nogal, A.; Valdes, A.M.; Menni, C. The role of short-chain fatty acids in the interplay between gut microbiota and diet in cardio-metabolic health. *Gut Microbes* 2021, *13*(1), 1-24. https://doi.org/10.1080/19490976.2021.1897212.
313 Sánchez Macarro, M.; Ávila-Gandía, V.; Pérez-Piñero, S.; Cánovas, F.; García-Muñoz, A.M.; Abellán-Ruiz, M.S.; Victoria-Montesinos, D.; Luque-Rubia, A.J.; Climent, E.; Genovés, S.; Ramon, D.; Chenoll, E.; López-Román, F.J. Antioxidant Effect of a Probiotic Product on a Model of Oxidative Stress Induced by High-Intensity and Duration Physical Exercise. *Antioxidants (Basel)* 2021, *10*(2), 323. https://doi.org/10.3390/antiox10020323.
314 Chen, W.; Ma, Q.; Li, Y.; Wei, L.; Zhang, Z.; Khan, A.; Khan, M.Z.; Wang, C. Butyrate Supplementation Improves Intestinal Health and Growth Performance in Livestock: A Review. *Biomolecules* 2025, *15*(1), 85. https://doi.org/10.3390/biom15010085.
315 Shah, A.B.; Baiseitova, A.; Zahoor, M.; Ahmad, I.; Ikram, M.; Bakhsh, A.; Shah, M.A.; Ali, I.; Idress, M.; Ullah, R.; Nasr, F.A.; Al-Zharani, M. Probiotic significance of *Lactobacillus* strains: a comprehensive review on health impacts, research gaps, and future prospects. *Gut Microbes* 2024, *16*(1), 2431643. https://doi.org/10.1080/19490976.2024.2431643.
316 Bié, J.; Sepodes, B.; Fernandes, P.C.B.; Ribeiro, M.H.L. Polyphenols in Health and Disease: Gut Microbiota, Bioaccessibility, and Bioavailability. *Compounds* 2023, *3*, 40-72. https://doi.org/10.3390/compounds3010005.
317 Perler, B.K.; Friedman, E.S.; Wu, G.D. The Role of the Gut Microbiota in the Relationship Between Diet and Human Health. *Annu. Rev. Physiol.* 2023, *85*, 449-468. https://doi.org/10.1146/annurev-physiol-031522-092054.
318 Hijová, E. Postbiotics as Metabolites and Their Biotherapeutic Potential. *Int. J. Mol. Sci.* 2024, *25*(10), 5441 https://doi.org/10.3390/ijms25105441.
319 Quaranta, G.; Guarnaccia, A.; Fancello, G.; Agrillo, C.; Iannarelli, F.; Sanguinetti, M.; Masucci, L. Fecal Microbiota Transplantation and Other Gut Microbiota Manipulation Strategies. *Microorganisms* 2022, *10*, 2424. https://doi.org/10.3390/microorganisms10122424.
320 Cheng, Y.W.; Fischer, M. Fecal Microbiota Transplantation. *Clin. Colon Rectal Surg.* 2023, *36*(2), 151-156. https://doi.org/10.1055/s-0043-1760865.
321 Koo, H.L.; DuPont, H.L. Rifaximin: a unique gastrointestinal-selective antibiotic for enteric diseases. *Curr. Opin. Gastroenterol.* 2010, *26*(1), 17-25. https://doi.org/10.1097/MOG.0b013e328333dc8d.
322 DuPont, HL. Review article: the antimicrobial effects of rifaximin on the gut microbiota. *Aliment. Pharmacol. Ther.* 2016, *43* Suppl. 1, 3-10. https://doi.org/10.1111/apt.13434.
323 Schupack, D.A.; Mars, R.A.T.; Voelker, D.H.; Abeykoon, J.P.; Kashyap, P.C. The promise of the gut microbiome as part of individualized treatment strategies. *Nat. Rev. Gastroenterol. Hepatol.* 2022, *19*(1), 7-25. https://doi.org/10.1038/s41575-021-00499-1.

324 Riaz Rajoka, M.S.; Thirumdas, R.; Mehwish, H.M.; Umair, M.; Khurshid, M.; Hayat, H.F.; Phimolsiripol, Y.; Pallarés, N.; Martí-Quijal, F.J.; Barba, F.J. Role of Food Antioxidants in Modulating Gut Microbial Communities: Novel Understandings in Intestinal Oxidative Stress Damage and Their Impact on Host Health. *Antioxidants (Basel)* 2021, *10*(10), 1563 https://doi.org/10.3390/antiox10101563.

325 Kurutas, E.B. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. *Nutr. J.* 2016, *15*(1), 71. https://doi.org/10.1186/s12937-016-0186-5.

326 Tkaczenko, H.; Kurhaluk, N. Antioxidant-Rich Functional Foods and Exercise: Unlocking Metabolic Health Through Nrf2 and Related Pathways. *Int. J. Mol. Sci.* 2025, *26*, 1098. https://doi.org/10.3390/ijms26031098.

327 Di Vincenzo, F.; Del Gaudio, A.; Petito, V.; Lopetuso, L.R.; Scaldaferri, F. Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review. *Intern. Emerg. Med.* 2024, *19*(2), 275-293. https://doi.org/10.1007/s11739-023-03374-w.

328 Xavier, L.E.M.d.S.; Reis, T.C.G.; Martins, A.S.d.P.; Santos, J.C.d.F.; Bueno, N.B.; Goulart, M.O.F.; Moura, F.A. Antioxidant Therapy in Inflammatory Bowel Diseases: How Far Have We Come and How Close Are We? *Antioxidants* 2024, *13*, 1369. https://doi.org/10.3390/antiox13111369.

329 Mohseni, A.H.; Casolaro, V.; Bermúdez-Humarán, L.G.; Keyvani, H.; Taghinezhad, S.S. Modulation of the PI3K/Akt/mTOR signaling pathway by probiotics as a fruitful target for orchestrating the immune response. *Gut Microbes* 2021, *13*(1), 1-17. https://doi.org/10.1080/19490976.2021.1886844.

330 Zhang, Z.; Jia, Y.; Zhang, C.; Zhang, Z.; Jin, F.; Pan, D.; Li, D.; Wu, X. Efficacy of epigallocatechin gallate (EGCG) and its underlying mechanism in preventing bisphenol-A-induced metabolic disorders in mice. *J. Hazard. Mater.* 2024, *469*, 134098. https://doi.org/10.1016/j.jhazmat.2024.134098.

331 Mohsenzadeh, M.S.; Razavi, B.M.; Imenshahidi, M.; Tabatabaee Yazdi, S.A.; Mohajeri, S.A.; Hosseinzadeh, H. Potential role of green tea extract and epigallocatechin gallate in preventing bisphenol A-induced metabolic disorders in rats: Biochemical and molecular evidence. *Phytomedicine* 2021, *92*, 153754. https://doi.org/10.1016/j.phymed.2021.153754.

332 Lombó, M.; González-Rojo, S.; Fernández-Díez, C.; Herráez, M.P. Cardiogenesis impairment promoted by bisphenol A exposure is successfully counteracted by epigallocatechin gallate. *Environ. Pollut.* 2019, *246*, 1008-1019. https://doi.org/10.1016/j.envpol.2019.01.004.

333 Chen, J.; Jin, Y.; Yang, Y.; Wu, Z.; Wu, G. Epithelial Dysfunction in Lung Diseases: Effects of Amino Acids and Potential Mechanisms. *Adv. Exp. Med. Biol.* 2020, *1265*, 57-70. https://doi.org/10.1007/978-3-030-45328-2_4.

334 Anderson, G.; Rodriguez, M.; Reiter, R.J. Multiple Sclerosis: Melatonin, Orexin, and Ceramide Interact with Platelet Activation Coagulation Factors and Gut-Microbiome-Derived Butyrate in the Circadian Dysregulation of Mitochondria in Glia and Immune Cells. *Int. J. Mol. Sci.* 2019, *20*(21), 5500 https://doi.org/10.3390/ijms20215500.

335 Emanowicz, P.; Średnicka, P.; Wójcicki, M.; Roszko, M.; Juszczuk-Kubiak, E. Mitigating Dietary Bisphenol Exposure Through the Gut Microbiota: The Role of Next-Generation Probiotics in Bacterial Detoxification. *Nutrients* 2024, *16*(21), 3757. https://doi.org/10.3390/nu16213757.

336 Sun, B.; Liu, M.; Tang, L.; Hu, C.; Huang, Z.; Zhou, X.; Chen, L. Probiotic supplementation mitigates the developmental toxicity of perfluorobutanesulfonate in zebrafish larvae. *Sci. Total Environ.* 2021, *799*, 149458. https://doi.org/10.1016/j.scitotenv.2021.149458.

337 Fang, D.; Xu, T.; Sun, J.; Shi, J.; Li, F.; Yin, Y.; Wang, Z.; Liu, Y. Nicotinamide Mononucleotide Ameliorates Sleep Deprivation-Induced Gut Microbiota Dysbiosis and Restores Colonization Resistance against Intestinal Infections. *Adv. Sci. (Weinh)* 2023, *10*(9), e2207170. https://doi.org/10.1002/advs.202207170.

338 Pérez-Burillo, S.; Navajas-Porras, B.; López-Maldonado, A.; Hinojosa-Nogueira, D.; Pastoriza, S.; Rufián-Henares, J.Á. Green Tea and Its Relation to Human Gut Microbiome. *Molecules* 2021, *26*(13), 3907. https://doi.org/10.3390/molecules26133907.

339 Pires, L.; González-Paramás, A.M.; Heleno, S.A.; Calhelha, R.C. Exploring Therapeutic Advances: A Comprehensive Review of Intestinal Microbiota Modulators. *Antibiotics (Basel)* 2024, *13*(8), 720. https://doi.org/10.3390/antibiotics13080720.

340 Ruiz-Malagón, A.J.; Rodríguez-Sojo, M.J.; Hidalgo-García, L.; Molina-Tijeras, J.A.; García, F.; Pischel, I.; Romero, M.; Duarte, J.; Diez-Echave, P.; Rodríguez-Cabezas, M.E.; Rodríguez-Nogales, A.; Gálvez, J. The Antioxidant Activity of *Thymus serpyllum* Extract Protects against the Inflammatory State and Modulates Gut Dysbiosis in Diet-Induced Obesity in Mice. *Antioxidants (Basel)* 2022, *11*(6), 1073. https://doi.org/10.3390/antiox11061073.

341 Xu, X.; Liu, A.; Hu, S.; Ares, I.; Martínez-Larrañaga, M.R.; Wang, X.; Martínez, M.; Anadón, A.; Martínez, M.A. Synthetic phenolic antioxidants: Metabolism, hazards and mechanism of action. *Food Chem.* 2021, *353*, 129488. https://doi.org/10.1016/j.foodchem.2021.129488.

342 Tenório, M.C.D.S.; Graciliano, N.G.; Moura, F.A.; Oliveira, A.C.M.; Goulart, M.O.F. N-Acetylcysteine (NAC): Impacts on Human Health. *Antioxidants (Basel)* 2021, *10*(6), 967. https://doi.org/10.3390/antiox10060967.

343 Tieu, S.; Charchoglyan, A.; Paulsen, L.; Wagter-Lesperance, L.C.; Shandilya, U.K.; Bridle, B.W.; Mallard, B.A.; Karrow, N.A. N-Acetylcysteine and Its Immunomodulatory Properties in Humans and Domesticated Animals. *Antioxidants* 2023, *12*, 1867. https://doi.org/10.3390/antiox12101867.

344 Wang, X.; Qi, Y.; Zheng, H. Dietary Polyphenol, Gut Microbiota, and Health Benefits. *Antioxidants (Basel)* 2022, *11*(6), 1212. https://doi.org/10.3390/antiox11061212.

345 Kim, B.; Song, A.; Son, A.; Shin, Y. Gut microbiota and epigenetic choreography: Implications for human health: A review. *Medicine (Baltimore)* 2024, *103*(29), e39051. https://doi.org/10.1097/MD.0000000000039051.

346 Lin, X.; Han, H.; Wang, N.; Wang, C.; Qi, M.; Wang, J.; Liu, G. The Gut Microbial Regulation of Epigenetic Modification from a Metabolic Perspective. *Int. J. Mol. Sci.* 2024, *25*, 7175. https://doi.org/10.3390/ijms25137175.

347 Sohail, M.U.; Yassine, H.M.; Sohail, A.; Thani, A.A.A. Impact of Physical Exercise on Gut Microbiome, Inflammation, and the Pathobiology of Metabolic Disorders. *Rev. Diabet. Stud.* 2019, *15*, 35-48. https://doi.org/10.1900/RDS.2019.15.35.

348 Varghese, S.; Rao, S.; Khattak, A.; Zamir, F.; Chaari, A. Physical Exercise and the Gut Microbiome: A Bidirectional Relationship Influencing Health and Performance. *Nutrients* 2024, *16*(21), 3663. https://doi.org/10.3390/nu16213663.

349 Shukla, V.; Singh, S.; Verma, S.; Verma, S.; Rizvi, A.A.; Abbas, M. Targeting the microbiome to improve human health with the approach of personalized medicine: Latest aspects and current updates. *Clin. Nutr. ESPEN* 2024, *63*, 813-820. https://doi.org/10.1016/j.clnesp.2024.08.005.

350 Aguiar-Pulido, V.; Huang, W.; Suarez-Ulloa, V.; Cickovski, T.; Mathee, K.; Narasimhan, G. Metagenomics, Metatranscriptomics, and Metabolomics Approaches for Microbiome Analysis. *Evol. Bioinform. Online* 2016, *12*(Suppl. 1), 5-16. https://doi.org/10.4137/EBO.S36436.

351 Go, D.; Yeon, G.H.; Park, S.J.; Lee, Y.; Koh, H.G.; Koo, H.; Kim, K.H.; Jin, Y.S.; Sung, B.H.; Kim, J. Integration of metabolomics and other omics: from microbes to microbiome. *Appl. Microbiol. Biotechnol.* 2024, *108*(1), 538. https://doi.org/10.1007/s00253-024-13384-z.

352 Yaqub, M.O.; Jain, A.; Joseph, C.E.; Edison, L.K. Microbiome-Driven Therapeutics: From Gut Health to Precision Medicine. *Gastrointest. Disord.* 2025, *7*, 7. https://doi.org/10.3390/gidisord7010007.

353 Hitch, T.C.A.; Hall, L.J.; Walsh, S.K.; Leventhal, G.E.; Slack, E.; de Wouters, T.; Walter, J.; Clavel, T. Microbiome-based interventions to modulate gut ecology and the immune system. *Mucosal Immunol.* 2022, *15*(6), 1095-1113. https://doi.org/10.1038/s41385-022-00564-1.

354 Kang, M.; Choe, D.; Kim, K.; Cho, B.K.; Cho, S. Synthetic Biology Approaches in The Development of Engineered Therapeutic Microbes. *Int. J. Mol. Sci.* 2020, *21*(22), 8744. https://doi.org/10.3390/ijms21228744.