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Gastrointestinal tissue as a "new" target of pollution exposure

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Abstract

Airborne pollution has become a leading cause of global death in industrialized cities and the exposure to environmental pollutants has been demonstrated to have adverse effects on human health. Among the pollutants, particulate matter (PM) is one of the most toxic and although its exposure has been more commonly correlated with respiratory diseases, gastrointestinal (GI) complications have also been reported as a consequence to PM exposure. Due to its composition, PM is able to exert on intestinal mucosa both direct damaging effects, (by reaching it either via direct ingestion of contaminated food and water or indirect inhalation and consequent macrophagic mucociliary clearance) and indirect ones via generation of systemic inflammation. The relationship between respiratory and GI conditions is well described by the lung-gut axis and more recently, has become even clearer during coronavirus disease 2019 (COVID-19) pandemic, when respiratory symptoms were associated with gastrointestinal conditions. This review aims at pointing out the mechanisms and the models used to evaluate PM induced GI tract damage.

KEYWORDS

4HNE, COVID19, oxidative damage, particulate matters

1 | BACKGROUND

A recent study published by Lelieveld et al.[1] has reported that air pollution is a leading cause of global death, surpassing by a large margin the number of deaths occurring because of HIV/AIDS, malaria and other parasitic diseases, vector-borne and various infectious disorders.

This new research confirms the alarming data from the World Health Organization (WHO) estimating that 91% of the urban world's population breathes polluted air

Abbreviation: 4HNE, 4-hydroxynonenal; 8-oxodG, 7-hydro-8-oxo-2′-deoxyguanosine; ACE2, angiotensin converting enzyme 2; AED, aerodynamic equivalent diameter; AhR, aryl hydrocarbon receptor; AIDS, acquired immunodeficiency syndrome; AP-1, activator protein 1; Cat, catalase; CO, carbon monoxide; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CXCLs, chemokines; ERK, extracellular-signal-regulated kinase; FGFR4, fibroblast growth factor receptor 4; GI, gastrointestinal; GPCRs, G-protein-coupled receptors; GPX, glutathione peroxidase; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; IFNγ, interferon γ; IL-10, interleukin 10; IL-17, interleukin 17; IL-18, interleukin 18; IL-6, interleukin 6; IL-1β, interleukin 1β; IL, interleukin; JNK, c-Jun N-terminal kinase; KO, knockout; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MLCK, myosin light chain kinase; MP, microplastics; NFkB, nuclear factor-kappa-B; NO, nitric oxide; NO2, nitrogen dioxide; Nrf2, nuclear factor erythroid-2-related factor 2; O3, ozone; PAHs, polycyclic aromatic hydrocarbons; PI3K, phosphatidylinositol-3-kinase; PM, particulate matter; RNS, reactive nitrogen species; ROS, reactive oxygen species; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SARS, severe acute respiratory syndrome; SCFA, short chain fatty acids; SO2, sulfur dioxide; SOD, superoxide dismutase; TEER, trans-endothelial electrical resistance; TMPPSS2, transmembrane serine protease 2; TMRPSS4, transmembrane serine protease 4; TNF-α, tumor necrosis factor α; TXNRD, thioredoxin reductase; UFP, ultrafine particles; UVA, ultraviolet A-rays; WHO, World Health Organization; WT, wild-type; ZO-1, zona-occludin-1.

and that 4.2 million deaths occur every year as a result of exposure to ambient air pollution.[2]

Ambient air pollution is a mixture of different gaseous (nitrogen dioxide –NO_2–, nitric oxide –•NO–, sulfur dioxide –SO_2–, carbon monoxide –CO–, and ozone –O_3) and particulate matter (PM) components and the latter can be very heterogeneous in composition, by containing in turn solid, liquid and mixed-phase organic, inorganic and organometallic components (endotoxins, transition metals and polycyclic aromatic hydrocarbons -PAHs-).[3–5] Pollution composition varies not only based on the different gaseous and solid combination, but it results also from the kind of source; either natural (soil, forest fires, volcanic emission, and soil) or anthropogenic (particulate matter, vehicle and industry emissions, oil refineries and coal combustion).[6,7] In addition, airborne pollutants can be classified as primary pollutants when directly emitted in the air by fossil fuel combustion (soot, particulates, CO, nitrogen oxide, and sulfur oxide) or as secondary pollutants, when formed by chemical reactions in the atmosphere (hydrocarbons, O_3, NO_2, and acid rain).[8] It should be mentioned that, among the different anthropogenic-generated air pollutants, PM is considered one of the most toxic to human health and it has been indeed correlated with global increased mortality and morbidity.[9,10]

The ability of PM to affect health is mainly due to its complex and diversified composition (which varies based on the geographical area and seasons)[11,12] as well as its size. Based on aerodynamic equivalent diameter (AED), PM can be divided into three different fractions that influence their lung absorption: coarse particles of circa 10 μm diameter are filtered by the proximal airway; fine particles ranging between 2.5 and 0.1 μm can be inhaled into the gas exchange area of peripheral airway[13]; and ultrafine particles (UFP) with an AED of 0.1 μm. The micrometric size of UFPs increases their ability to absorb toxins, microorganisms, and spores (pathobionts) on their surface and allows them to translocate through alveolar epithelial cells and enter the systemic circulatory system where they can cause damage to distal tissues and cells and where the presence of absorbed reactive substances can further stimulate immune cell reactivity.[14,15] In particular, PM exposure has been associated with general adverse health effects and the development/exacerbation of organic-specific disorders: for example, in lungs (decreased lung function, asthma and general worsening of respiratory problems),[10,16] in the heart (cardiac arrhythmia and heart attack),[9,17,18] in the skin (psoriasis, atopic dermatitis, acne)[19–21] and in the eyes (dry eyes, conjunctiva disorders).[22,23]

Only relatively recently, the scientific community has been interested in investigating the harmful effects of PM on the gastrointestinal (GI) tract, linking the pollutant exposure to the triggering or exacerbation of inflammatory bowel disorders such as inflammatory bowel disease (IBD), Crohn's disease and colorectal cancer.[24,25] Recent studies have shown that alteration of tight junctions by PM could increase the risk of colorectal cancer and inflammatory bowel disease[26] or even that the translocation of the pathogen *Mycobacterium tuberculosis* from the macrophagic phagosomes into the cytosol can induce host cellular death,[27,28] increasing the risk of granulomatous diseases such as intestinal tuberculosis and Crohn's disease.[29]

PM is the only pollutant able to exert on intestinal mucosa both direct effects (by reaching it from food ingestion or by particles macrophagic mucociliary clearance) and indirect effects via the generation of systemic inflammation.

In this context, considering the growing literature on this topic and the different models used to evaluate the effect of PM in GI tract, the current review aims to summarize the actual state of the art on the gastrointestinal toxicity of PM linking to the possible molecular mechanisms involved in PM noxious GI tract effect.

1.1 | Gastrointestinal tract anatomy

The gastrointestinal tract is an extensive organ (9 m long) responsible for the digestion, absorption, transportation and excretion of nutrients, it is anatomically divided in two sections: the upper part formed by the mouth, pharynx, esophagus and stomach; and the lower part consisting of the small and large intestine. The small intestine is, in turn, organized in duodenum, jejunum and ileum, while the large intestine is composed of three segments: cecum, colon and rectum.

A layer of polarized simple columnar epithelial cells is found all over the length of the GI tract; this epithelium is supported by connective tissue (lamina propria) and underlying smooth muscle.

Among the columnar epithelial cells of the GI tract are distinguishable absorptive cells (enterocytes), hormone producing cells (Paneth cells and enteroendocrine cells) and mucus producing cells (goblet cells); where Paneth and goblet cells have a gut defensive function via the production and release of antimicrobial peptides (Paneth cells) and by secreting mucous to prevent the pathogens invasiveness (goblet cells).

To prevent the leakage of intestinal content, circa 1.5 L,[30] into the bloodstream, the intestinal epithelium acts as a selectively permeable barrier thanks to the presence of tight junctions, adherens junctions and desmosomes.[31]

The health of the GI tract is guaranteed also by the gut microbiome, which consists of a variety (10^{13}–10^{14}) of

commensal bacteria, protozoa and viruses[32] with Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria being the bacteria predominantly present.[33]

The gut microbiome is fundamental for different functions for the host such as immunity and metabolism (vitamins production and nutrients absorption) and the cardinal products responsible for these beneficial effects are short chain fatty acids (SCFA), like propionate, acetate and butyrate and to a lesser extent neurotransmitters, hormones and other secreted factors.[34] The metabolism and fermentation of dietary nondigestible fibers are at the base of SCFA production which from the intestine are able to travel to the peripheral circulation and with paracrine and endocrine actions, through the binding to G-protein-coupled receptors (GPCRs), are able to modulate the nearby intestine as well as different organs and their immunological functions (liver, skin, brain, and lungs).[35–39]

The amount and the rate of SCFA production is related to the richness and the composition of the microflora present in the colon, the intestinal transit time and the substrate source transitioning in the GI tract.[35]

Of note, commensal microbiota can modulate the generation of Reactive Oxygen Species (ROS) and other growth factors responsible for the proliferative and migratory activities of intestinal epithelial cells[40]; therefore, the alteration of the eubiosis induced by outdoor stressors[41] could potentially impact GI tract cellular turnover.[42]

1.2 | Effect of particulate matter on GI tract

Among the different airborne pollutants, PM is the only one able to reach the intestine and therefore, exert damaging effects on the intestinal mucosa. Indeed, the gut can be exposed to particles either directly from ingestion of contaminated food and water (in a typical western diet a person can ingest up to 10^{12}–10^{14} particles daily[43,44]) or indirectly from inhalation. When in the lungs, PM can be cleared by the mucus layer covering the lower airways and be taken up by alveolar macrophages which, via mucociliary clearance, carry PM to the oropharynx, where particles can be swallowed and reach the intestinal lumen (Figure 1). In the bowels, PM can directly affect the epithelial mucosa and be metabolized by intestinal microbiota causing release of the adsorbed toxins[15] and ultimately be excreted in the fecal matter.[45–47] Shockingly, some studies demonstrated that particles can be found in fecal matter up to 6 months after inhalation.[46]

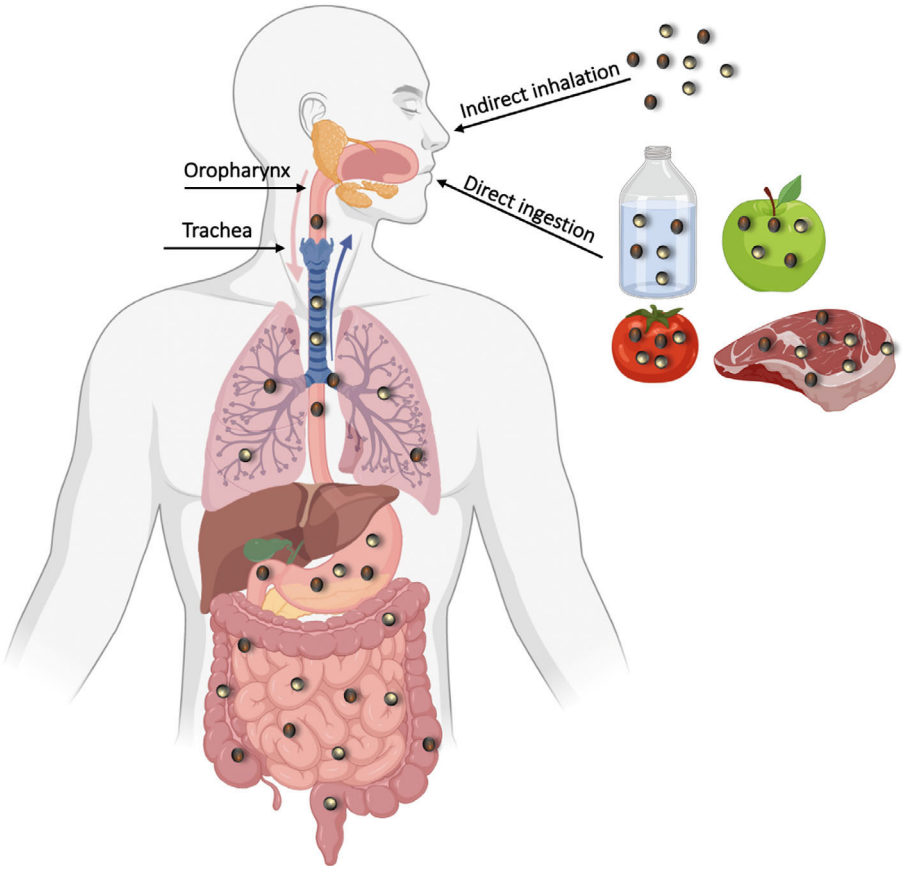

FIGURE 1 Routes of access of PM to the gastrointestinal tract. PM can reach the GI tract directly via ingestion of contaminated food or water and via indirect inhalation of particles. PM can be cleared by the mucus covering the conducting airways of the lungs and be taken up by alveolar macrophages. During mucociliary clearance, the mucus and its macrophagies-containing PM are swept by cilliary action from the lower to the proximal airways (blue arrow). In this way, PM is carried to the oropharynx where particles are swallowed (pink arrow) and reach the gastrointestinal tract

While mucociliary clearance is possible for particles smaller than 5 μm, larger particles are promptly sequestered by the lungs and they can only reach the GI tract by direct ingestion[46] where about 40% to 60% of transition metals present in PM can be absorbed across the intestinal epithelium.[48,49]

The composition of PM and more importantly the presence of transition metals, represents the potential cause of PM-induced intestinal damage. In fact, although the exact mechanisms have not been identified yet, the effects of PM exposure could be attributed to redox homeostasis disturbance, inflammation and genotoxicity.[50] In general, the pathways involved in PM-induced toxicity are: (1) generation of oxidative molecules and reactive electrophilic metabolites on the surface of the particles, (2) release of organic molecules and transition metals from the particles, (3) ability of the particles to activate an inflammatory cascade, and (4) positive feedback loop in which ROS-activated inflammatory cells generate more reactive oxygen (ROS) and nitrogen (RNS) species.[34] Intracellular ROS, identified as the crucial mediator of PM-induced toxicity, can be generated via redox cycling and metabolic activation when particles are taken up and phagocytosed by macrophages.[51–56] This mechanism can be enhanced by the presence of transition metals coating the surface of the particles (such as free iron, copper, zinc, and vanadium),[34] able to participate in Fenton-like reactions and eventually activate the aryl hydrocarbon receptor (AhR) which regulates the cytochrome P450 enzyme CYP1a1b involved in the conversion of PAHs into redox active quinones (Figure 2).[57]

Although, ROS and RNS during an acute response favor the resolution of the PM-induced damage by initiating an inflammatory response; in a long run these effectors represent a double-edged sword. In fact, the chronic production of ROS and RNS, due to their unstable and reactive nature, can initiate a harmful cascade of events, for example the oxidation of cellular biomolecules such as lipids, proteins, and DNA (via enhancement of strand breaks and increased levels of 7-hydro-8-oxo-2′-deoxyguanosine (8-oxodG) and endonuclease III[50]). The damage to different cellular components can lead to the deterioration of epithelial cells,

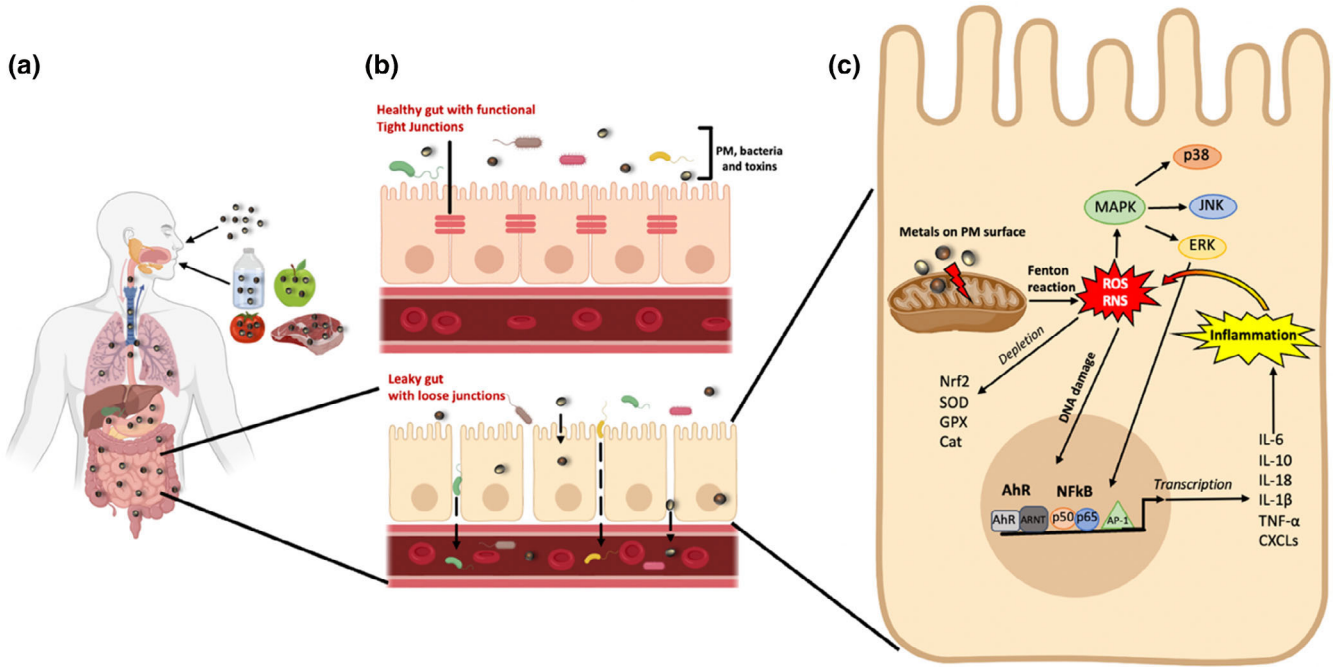

FIGURE 2 Legend on next page.

activation of transcription factors (eg, NFkB, AP-1, c-Jun) and intracellular protein kinases (like ERK and MAPK), which in turn yields to the production of proinflammatory and oxidative mediators (malondialdehyde -MDA- and myeloperoxidase), chemokines (CXCLs) and cytokines such as interleukin (IL)-6, IL-10, IL-18, IL-1β, and tumor necrosis factor α (TNF-α).[58] The chronic oxidative stress induced by the constant generation of ROS can finally lead to the depletion of the naturally present cellular defenses like the nuclear factor erythroid-2-related factor 2 (Nrf2),[59] superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (Cat).[60]

The study of these effects has gradually drawn more attention in recent years, and different models such as *2D* cell lines, *3D* human intestinal and in vivo models have been taken into consideration to evaluate the single and cumulative damaging mechanisms and adverse health outcomes of PM exposure. All these models present benefits and limitations, although when taken together they can provide a representative idea of the GI tract response to PM exposure.

1.3 | 2D models

As mentioned above, the main player considered responsible for the PM-induced tissue damage is the altered redox homeostasis.[51,52] Therefore, to investigate the molecular mechanisms at the base of the GI tract responses to PM, and in particular its possible oxidative/inflammatory damage, few researcher groups performed studies with intestinal cell lines (*2D* models). Mutlu et al.[61] confirmed the oxidative-damage hypothesis by demonstrating that the PM exposure of Caco-2 cell monolayers (cells derived from small and large intestinal epithelium) increased the production of ROS and consequently the activation of the transcription factor nuclear factor-kappa-B (NFkB) which, among its various functions, also regulated the transcription of the myosin light chain kinase (MLCK),[62] involved in the structure reorganization and colocalization of actin and tight junctions (occludin, ZO-1).[63] Moreover, to confirm that this cascade of events can compromise the intestinal structure, permeability and function, Mutlu et al.[61] investigated the trans-endothelial electrical resistance (TEER) and found it decreased in intestinal epithelial cells after PM exposure; confirming the hypothesis that PM can induce leaky gut syndrome.

In addition, Li et al.[64] observed that the short-term exposure of Caco-2 cells to 25 and 50 μg/ml of ultrafine particles (UFP) induced a dose-dependent increase in permeability, validating the results of Salim et al.[15] who demonstrated in vitro that PM_{10} exposure indirectly increases intestinal permeability, through the increased production and secretion of TNF-α from macrophagic immune cells.

1.4 | 3D models

Although *2D* models allow for the investigation of the molecular aspects of cellular responses, they present some limitations, for example, the inability to represent the whole intestinal system and its complexity in terms of cellular cross talk, cytokines production and the expression of specific receptors and transporters associated with the different cells present in the tissue.[65–67] Other models can provide a more complete picture of the GI tract response to PM, like the *3D* Epintestinal: an in vitro model that better represents the human intestinal tissue. Our laboratory has recently used this approach (*3D* Epi-Intestinal tissues from MatTek Life sciences) to evaluate PM-induced GI tract damage by exposing *3D* intestinal models to different doses (50, 100, 150, 250, and 500 $\mu g/cm^2$) of urban atmospheric particulate matter (collected in St. Louis, Missouri between 1976 and 1977) for 1 and 2 weeks.

Our analysis showed no differences in terms of permeability measured via TEER confirming the previous in vivo data of Li et al.[64] who, after exposing mice to 10 weeks of PM (three times/week) did not observe any effect of PM on intestinal permeability. Moreover, our study demonstrated increased levels of 4-hydroxynonenal (4HNE) protein adducts, and decreased protein expression of intestinal structure markers and tight junctions such as zona-occludin-1 (ZO-1), claudin-1, and desmocollin. Therefore, the *3D* model was able to confirm the ability of PM to induce oxidative stress and the damage to intestinal structure and functions thus, linking the exposure of PM to GI conditions such as Crohn's disease, inflammatory bowel syndrome, and colorectal cancer, which all have as a common denominator a "leaky gut" clinical feature.[68] In this context, the bioactive product of lipid peroxidation 4-hydroxynonenal (4HNE) represents an important player and marker in the pathogenesis of GI conditions: it has been shown that the formation of conjugates and adducts with glutathione and aminoacidic residues (lysine, histidine, and cysteine) in proteins, can lead to the loss of function or degradation of these modified biomolecules, shifting the intestinal redox balance, already altered by the direct harmful effects of PM, even further to a pro-oxidant status.[69–72] Evaluation of the 4HNE levels not only provides insights regarding the redox balance of the cells but also their inflammatory status, since 4HNE is able to modulate the redox-sensitive transcription factor NFkB which is

involved in the regulation and generation of pro-inflammatory mediators like cytokines, chemokines, and adhesions molecules.[73,74]

1.5 | In vivo models

The most common in vivo model used to investigate PM-induced intestinal damage is represented by the murine approach although, it still does not completely resemble the human intestine because mice share different microbiome composition and bowel stricture (lack of mucosal folds and longer villi).[75]

Mutlu and his group confirmed in mice his previous in vitro findings by exposing (via gastric gavage) C57BL/6 mice to high doses (200 μg/mouse) of urban particulate matter; they showed increased intestinal permeability and IL-6 transcripts levels and consequent decreased colocalization and expression of the tight junction protein ZO-1, in both small intestine and colon in addition to increased apoptosis in the colonic mucosa.[61]

The generation of an inflammatory status in the intestine induced by PM, in terms of pro-inflammatory cytokine production and increased lymphocyte adhesion and migration was confirmed by Kish et al.,[76] by demonstrating in wild-type (WT) 129/SvEv and IL-10 knockout (KO) mice that 1, 2, and 5 weeks of PM_{10} exposure (via gastric gavage) increased colon production of IFNγ and costimulatory molecules. The acute PM exposure of 7 days up-regulated small intestinal expression of CXCL1, IL-1β, and IL-10, while extending the time of PM-exposure (2-fold) led to the increase of bowel permeability, microbial dysbiosis, and altered SCFA concentration.[76]Similar results were observed after PM_{10} exposure, in neonatal IL-10/KO mice's small intestine and colon by Salim's group. In their study, Salim et al. demonstrated higher levels of lipopolysaccharide (LPS) and pro-inflammatory cytokines such as IL-1β and TNF-α and decreased IL-17A levels.

Different experimental and PM exposure settings led to similar conclusions, for example Vignal et al. performed a PM inhalation study and confirmed the ability of PM to induce an oxinflammatory status (oxidative stress and inflammation)[77,78] by increasing serum levels of MDA, myeloperoxidase activity and pro-inflammatory cytokines (TNF-α, CXCL10, and IFNγ) in the animal's colons.[79]

High intestinal levels of TNF-α and other pro-inflammatory mediators like prostaglandin D_2 and arachidonic acid were also detected by Li et al.[80] in Ldlr/KO mice after inhalation of UFPs. Moreover, Li's group discovered that mice exposed to UFPs showed a striking reduction in villi length and this effect is linked to reduced nutrient absorption. Two years later, the same group performed an oral gavage-type of study in the Ldlr/KO and observed that mice fed with high-fat diet and exposed to UFPs had increased intestinal macrophagic and neutrophilic infiltration and higher plasmatic levels of TNF-α and the monocyte chemoattractant MCP-1.[64] Another group observed that the PM chronic exposure (12 months) of mice resulted in increased migration of immune cells in murine colons and epithelial lesions.[81] Moreover, the same group exposed human colon epithelial cells (NCM460) to PM for 48 to 72 hr, showing increased levels of the colonic cancer marker fibroblast growth factor receptor 4 (FGFR4) and in a follow up study demonstrated that by knocking out FGFR4 mice were more resistant to develop PM-induced colorectal cancer due to a decreased activation of the phosphatidylinositol-3-kinase (PI3K)/Akt pathway via FGFR4.[81] A panel study conducted by Li et al.[81] on 44 (24 males and 20 females) corroborated the association between air pollutants exposure and inflammatory response, in fact, they demonstrated that breathing air with concentrations of $PM_{2.5}$ and PM_{10} that exceed the WHO standards increased the fecal presence of white blood cells but no correlation was identified in terms of plasma IL-6 levels.

Finally, it should be mentioned that an even more close to reality approach to understand the effect of pollution to living organisms could be to conduct a wildlife research in free-living animals in their natural habitat or with wild-caught animals in various captive settings, but the costs and the not quantifiable variables make this model very rare to be used.

1.6 | Gut-lung axis

Although more reports associate long-term PM exposure to pulmonary and respiratory diseases (eg, chronic obstructive pulmonary disease -COPD- and asthma), in the last few years damaging effects of PM on intestinal tract have been extrapolated considering that both intestinal and respiratory tissues share the same embryonic origin, many microbial phyla (*Bacteroidetes, Firmicutes*, and *Proteobacteria*) and are composed of epithelial cells with active and conserved inflammatory pathways. The gut-lung axis describes this double crosstalk between the GI tract and the respiratory system. A study performed on nonsmokers, observed that patients with lung disorders (chronic bronchitis, bronchiectasis, and obstructive pulmonary dysfunction) concomitantly showed the development of inflammatory bowel disease, although no exact pathogenic mechanisms were established.[82] Other studies corroborated the same relationship demonstrating that 57.6%

of ulcerative colitis patients presented also impaired lung functions compared to healthy controls[83] or that asthma development in children can be associated with the higher abundance of intestinal *Clostridia* compared to *Bifidobacteria*.[84]

Indeed, more pulmonary disorders have been linked to the increased risk of gastrointestinal complications from exposure to airborne pollution: a recent review showed that respiratory diseases (asthma, COPD) that can be triggered/exacerbate by environmental pollution induce microbial dysbiosis in both lungs and intestine, assessed by the outgrowth of *Proteobacteria* and *Firmicutes* and the reduction of *Bacteroidetes*.[85]

The potential mechanism at the base of this two-way organ interaction is the presence of metals and pathobionts on PM's surface that can get deposited into the lungs where they induce oxinflammation and toxins release, damaging the respiratory epithelium and microbiota. Moreover, these harmful components can get absorbed through endothelial cells and reach the systemic circulation translocating to different distal organs, like the GI tract. In the intestine, microorganisms and metals can induce dysbiosis and compromise the intestinal structure and functions via oxidative stress and inflammation. Moreover, the inflammatory responses induced by PM collected in the lungs induces extravasation of activated immune cells that can reach other organs, like intestine, via blood and/or lymphatic circulation, transforming a local inflammatory response into a systemic inflammation. In turn, the inflammatory process can further compromise the tight junction's function and induce a systemic release of gut-derived metabolites facilitating the recruitment of immune cells in the tissues, therefore worsening the inflammatory state.[86]

1.7 | PM and COVID-19

The interconnection of gut and lung has been confirmed even more strongly during the 2019 pandemic era, when increasing reports of patients with coronavirus disease 2019 (COVID-19) concomitantly showed gastrointestinal symptoms and on the other hand, the poor air quality has been associated with increased risk of COVID-19 infection and rapid spreading.[87]

As of May 2021, COVID-19 pandemic led to over 3.4 million victims and more than 165 million infected individuals reporting mostly respiratory symptoms[88] due to infection and replication of the virus in the pulmonary epithelium. This pathological mechanism of replication induces cytokines and chemokines release which progresses into the development of severe acute respiratory syndrome.[89] After a few months post COVID-19 outbreak, more extrapulmonary symptoms had been reported, in particular the ones coming from the GI tract.[90]

The explanation for this dual symptoms is that SARS-CoV-2 can enter the small intestine via transmembrane protease serine 2 receptors (TMPPSS2 and TMRPSS4) compromising enterocyte's functions and intestinal permeability[87,91–93] and moreover, the virus has been shown to be able to activate the angiotensin converting enzyme 2 (ACE2) inducing diarrhea and general enteritis.[94]

Of note is the positive correlation between COVID-19 severity and the concentration of airborne pollution in the same areas[95]: a nationwide cross-sectional study showed that an increase of 1 $\mu g/m^3$ of PM in the air corresponded to an 8% increase in COVID-19 deaths,[96] although the exact mechanism has not been elucidated yet.[87]

1.8 | Face masks and microplastics

Laboratory evidence[97] and ecological studies[98] demonstrated that wearing face masks reduces SARS-CoV-2 transmission and spreading and parallel investigations have shown that face masks are also effective against $PM_{2.5}$, making them a potential remedy to reduce primary gastrointestinal disorders induced by COVID-19, as well as the ones generated or worsen by daily PM exposure.[99–101]

Multiple studies demonstrated that different types of face masks, correctly worn, can block up to 60% to 90% of the particles,[99–101] although "real-life" filtration may be reduced due to poor facial fit.[102]

Although wearing face masks has been proven a possible remedy in reducing PM inhalation and therefore intestinal and systemic inflammation and oxidative stress, face masks could represent a double-edged sword because of their possible release of microplastics (MP). MP, as the word suggests, are plastics of millimetric or sub-millimetric size and different shapes (fragments, films and fibers) produced for cosmetics and clothes, however they can also originate from the breakdown of larger plastic detritus. MP have become an emerging concern in the last few decades[103,104] due to the increased demand for synthetic fibers for clothing and house industries, as well as higher degradation of macroplastics and waste incineration.[105,106]

Marine MP pollution has been well documented over the years but recently new insights have come to light regarding human health since, like PM, MP possible intestinal gateways could be the direct ingestion of contaminated food and water and the indirect inhalation of MP.[105,107,108]

Of note, another aspect that MP share with PM is that pathogens, transition metals and organic contaminants can be absorbed on their surface.[109] Furthermore, it has been shown that exposure to airborne UV radiation (UVA or greater >320 nm) and thermo-oxidation can increase the rate and the extent of plastic photo- and thermo-oxidative degradation, therefore increasing the release of MP and potentially the toxicity level when in contact with tissues and organs.[110–112]

Fighting the COVID-19 pandemic indirectly induced a striking increase in the production and waste of plastic individually packed groceries, disposable utensils and sanitary equipment like gloves, face masks and shields. Since the COVID-19 outbreak, China solely has produced over 14.8 million face masks per day and an inadequate disposal of these plastic materials could become a threat to aqueous environment, soils and potentially the air we breathe.[108]

As the COVID-19 pandemic started many masks have been observed on shorelines, and in water basins like rivers and lakes.[113,114] While masks themselves pose a direct risk to the environment, their plastic and fiber materials can worsen the problem.

A new research study published in May 2021 demonstrated that a single mask can release over 1.5 million microplastics to the marine environment and that the physical contact with sand produces abrasions and biodegradation which further worsen the release of particles reaching over 16 million MP liberated from each mask.[115]

Unsurprisingly, many studies have demonstrated the presence of MP in plankton, fish and birds[116] and few of them already showed the accumulation of MP in human intestine[117] and shockingly in human placenta.[118] Although it is still not clear the mechanism by which MP reach human body the possible routes are ingestion from contaminated food and water and the inhalation of MP from the air. Moreover, to date, it is not clear if, while wearing face masks, people can directly inhale MP coming from the fabric of the mask itself; however, as previously mentioned, photo- and thermo-oxidative degradation accelerate MP release from plastics, potentially even from face masks, making this the possible missing link between the usage of not frequently changed masks and MP inhalation.

MP toxicity in humans is still unclear due to limited data, however occupational risk studies suggest a possible positive correlation between plastics exposure and development of colorectal cancer.[119,120] Moreover, evidence from in vitro studies assessed with human cell lines, corroborated the harmful effect of MP, nanoplastics and polystyrene, especially at high concentration and with small size particles.[121–123] Further possible extrapolation can be done from ecotoxicology studies performed on marine species which demonstrated that MP can induce intestinal permeability, oxidative stress, inflammation and dysbiosis.[124]

Protective effects of face masks have been confirmed against both COVID-19 infection and PM inhalation, on the other hand, although MP-induced toxicity on humans is still scarce, the damaging effects of improper disposal of masks on aquatic kingdom and environment are well known and established. Since wearing masks has become a reality that potentially will endure even after the pandemic era, appropriate waste management and environmental awareness need to be taken into profound consideration to protect the habitat and human health.

1.9 | Balanced nutrition to prevent PM-induced intestinal damage

Multiple studies have confirmed how a balanced diet can restore the intestinal functions and structure, as well as eubiosis and homeostatic permeability capabilities.

A healthy diet provides important antioxidants micronutrients such as Vitamin E, Vitamin C and carotenoids that counteract PM-induced oxidative stress, respectively, by scavenging hydroxyl radicals and quenching singlet oxygen, via the donation of protons and transformation into nonreactive radicals which can be further detoxified by glutathione, enzymes or ascorbate itself[125] with the latter able not only to prevent oxinflammation but also to improve intestinal wound healing.[126]

Healthy nutrition is the only provider of other essential vitamins, amino acids and trace minerals fundamental as necessary cofactors for the regeneration of PM-depleted antioxidant defenses such as cysteine for glutathione synthesis, copper, zinc, and manganese for different cellular isoforms of SOD, selenium and cysteine for GPXs and thioredoxin reductase (TXNRD) synthesis.[127]

The introduction of the recommended amounts of fibers and probiotics (like *Lactobacilli spp*. and *Bifidobacterium spp*.) in the diet has been shown to improve intestinal microbiota and prevent PM-induced dysbiosis. In fact, different studies demonstrated that the supplementation of dietary fibers can reduce lesions of the epithelial mucosa during the course of IBD, through the increased luminal production of SCFA which in turn positively modulate the immune system, accelerate the regenerative intestinal processes and lower the colonic pH thereby inhibiting the growth of pathogenic microflora and stimulating the growth of commensal ones.[128,129]

2 | CONCLUSIONS

Particulate matter can enter the intestinal mucosa directly (via ingestion of contaminated food and water) or indirect (via mucociliary clearance) and locally induce the production of ROS and inflammatory mediators which, in a vicious cycle, generate chronic damage on intestinal mucosa, affecting its permeability, structure, function and microflora content. Concomitantly, PM, with the same harmful mechanisms can negatively affect other organs (lungs, heart, skin, eyes, etc.) which in turn lead to systemic oxinflammation thereby worsening GI tract condition.

It should be mentioned that at this stage it is hard to distinguish between the direct inflammation derived from the local effects of PM on intestinal mucosa and from an indirect effect of systemic inflammation produced by general PM exposure.

The dual interrelationship between lungs and intestine is explained by the existence of the gut-lung axis and this crosstalk grew clearer during the COVID-19 pandemic when respiratory symptoms were associated with gastrointestinal ones.

COVID-19 spreading has been significantly reduced by wearing face masks, and the same use has been demonstrated crucial to prevent inhalation of $PM_{2.5}$. Unfortunately, the high demand of plastic-products and masks during the pandemic brought to light a growing problem which is the microplastics presence in the environment. MP gateway to the human intestine can be through the food chain (ingestion of contaminated food and water) or indirectly from inhalation of MP present in air or potentially even from the fabric of the masks themselves.

Although wearing masks could still be an important remedy to prevent the inhalation of PM that can damage intestine and other organs, a balanced diet should be the first choice to protect our GI tract against the oxinflammation induced by PM exposure.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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